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SPECIAL SECTION

KIDNEY STONE DISEASE

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

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Kidney Stone Disease – Clinical Perspectives

JIE TANG, MD, MPH
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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

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

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

ABSTRACT

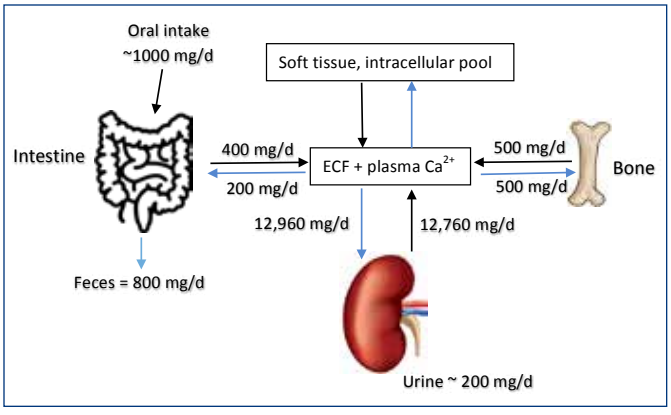
Idiopathic hypercalciuria is defined as excessive urine calcium excretion in the absence of an identifiable cause. It has been strongly associated with the risk of calcium kidney stone formation. Animal and human studies have suggested excessive bone mineral loss or increased gastrointestinal calcium 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 $1,25(OH)_2D$ 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

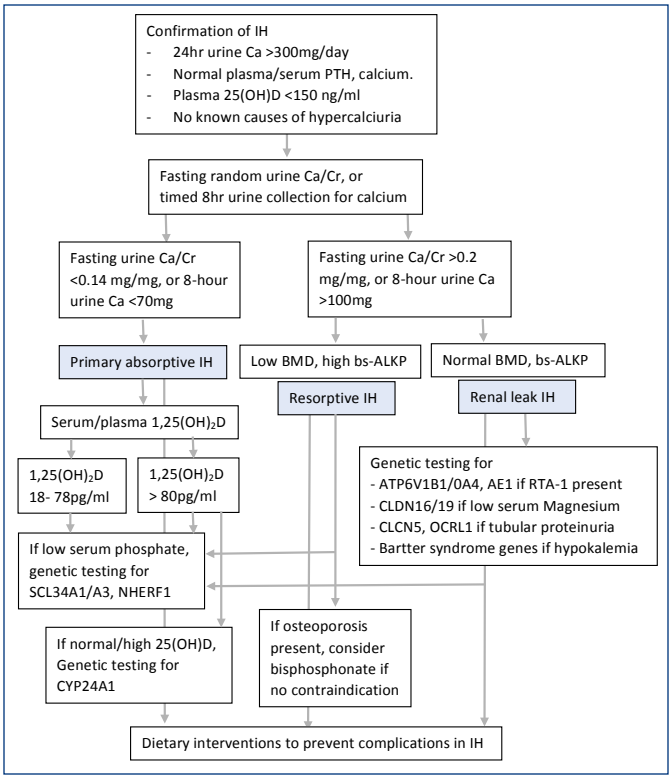
ADHH: autosomal dominant hypocalcemic hypercalciuria. HHRH: hereditary hypophosphatemic rickets with hypercalciuria. FHH: familial hypomagnesemia with hypercalciuria. AD: autosomal dominant. AR: autosomal recessive. CLC-5: chloride/proton antiporter 5. OCRL1: oculocerebrorenal-1 gene. NKCC2: Na–K–Cl 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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Hyperoxaluria – A Major Metabolic Risk for Kidney Stone Disease

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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

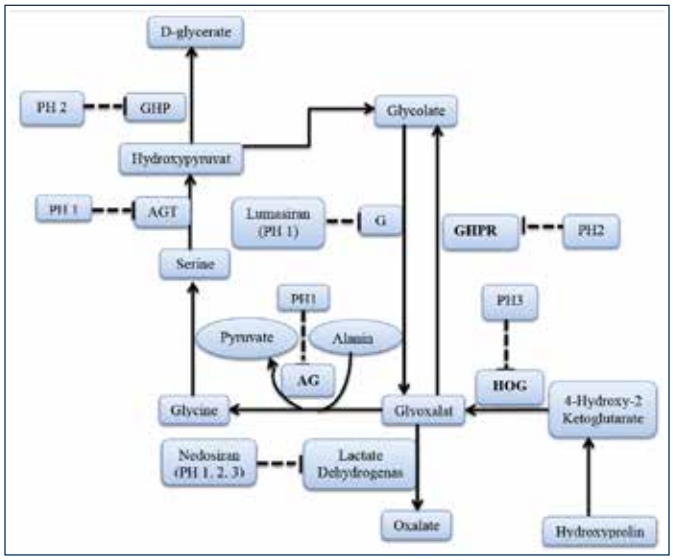
INTRODUCTION

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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Conflict of Interest

Authors declare that they have no competing interests

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

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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.

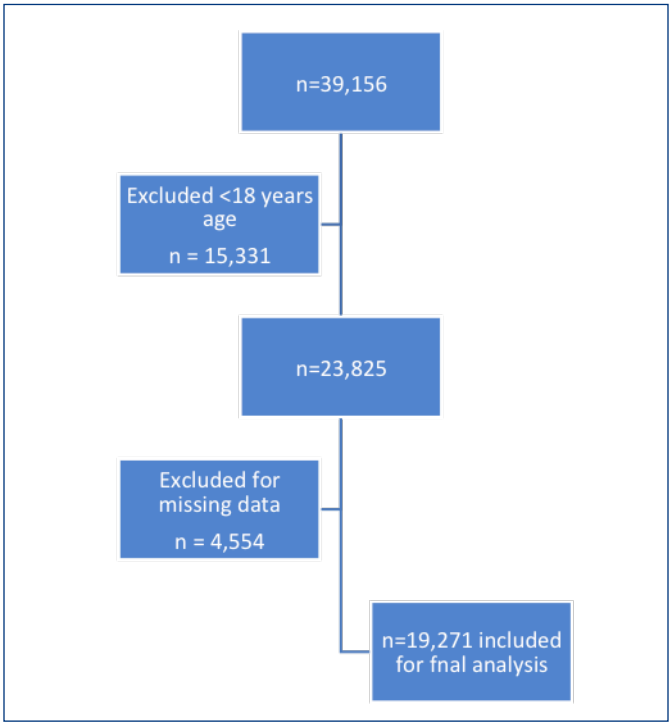
Here, we used a large US population survey database, the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2018, to examine the independent association between DMI with KS disease.

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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Conflict of Interest

Authors declare that they have no competing interests.

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Diet Interventions for Calcium Kidney Stone Disease

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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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Renal Imaging in Stone Disease: Which Modality to Choose?

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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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The Surgical Management of Urolithiasis: A Review of the Literature

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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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Disclosures

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To Lick One's Wounds: A Case of *Pasteurella canis oralis* Osteomyelitis and *Neisseria animaloris* Infection from Canine Saliva

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ABSTRACT

The complications of wound infections caused by animal related trauma are well known and explored. Of the numerous polymicrobial etiologies, *Neisseria animaloris* and *Pasteurella canis oralis* have been reported only in a limited number of cases. This manuscript explores the rare finding of these species in the case of an 83-year-old male with a diabetic foot wound complicated by infection from the saliva of his pet dog. The case highlights the first instance of *P. canis oralis* without the setting of a penetrating animal bite, emphasizing the vulnerability of open lesions in patients whose comorbidities impair proper wound healing. These bacteria are susceptible to beta-lactams with beta-lactamase inhibitors and can be treated once identified. It is crucial to recognize rare pathogens and initiate appropriate treatment early, and to emphasize proper wound care, especially in the context of pet interactions.

KEYWORDS: animal bites, zoonotic pathogens, osteomyelitis, Pasteurella species, Neisseria species

INTRODUCTION

Animal bites and scratches are commonly complicated by wound infections that involve skin and soft tissues. These infections tend to be polymicrobial in nature due to contamination with a mixture of aerobic and anaerobic bacteria. However, *Pasteurella spp*. have demonstrated a predominance in infected dog and cat bites.[1,2] Additionally, a majority of reported *Pasteurella* infections have occurred secondary to not just bites, but also scratches and licks to open wounds from pets.[3,4] Another group of bacteria frequently isolated from gingiva and oral secretions of healthy canines and felines include the Centers for Disease Control and Prevention group Eugonic Fermenter-4 (CDC Group EF-4) bacteria, such as *Neisseria animaloris* and *Neisseria zoodegmatis*, that are rarely identified as human pathogens secondary to animal bites.[5]

CASE REPORT

An 83-year-old male with history of poorly controlled diabetes mellitus with peripheral neuropathy, hypertension, hyperlipidemia, peripheral vascular disease, and prior osteomyelitis of the right foot status post partial second- and third-toe amputations, presented from podiatry clinic due to a diabetic left foot infection and clinical suspicion of osteomyelitis and cellulitis with associated critical limb ischemia. The patient stated that his foot had been in this condition for three months prior to presentation. He noted that he would allow his dog to lick his lesions due to the perceived healing properties of saliva. Review of systems was positive for pain in the left hallux but negative for fevers, chills, or other constitutional symptoms. Physical exam of the left foot revealed a black eschar on the distal hallux and lateral fifth submetatarsal region. The hallux eschar was firm, dry, malodorous, probed to bone, and with bordering erythema. The fifth metatarsal eschar was loose and peeled away to expose malodorous, wet, yellow fibrotic tissue with probe to fifth metatarsal head, with peri-wound erythema. Pertinent lab findings included erythrocyte sedimentation rate of 82 mm/hr, C-reactive protein of 55.6 mg/L, and white blood count of 12.2 x 10^9/L. Radiograph of the left foot revealed diffuse osteoarthritis with no acute osseous abnormality. Due to cellulitis affecting tissue proximal to the lesions, the patient was started on piperacillin-tazobactam. Wound swab grew specimen on blood and chocolate agar, identified by MALDI biotyper as *Pasteurella canis oralis* and *N. animaloris*, both organisms which are present in canine oral flora. Per organism susceptibility, the antibiotic regimen was narrowed to ampicillin-sulbactam. Additionally, due to history of peripheral vascular disease, the patient underwent CT angiography of abdominal arteries with runoff, which demonstrated calcific aortoiliac disease with calcifications in external iliac, common femoral, deep femoral, and superficial femoral arteries, and occlusion of the left arterial tibial artery. Due to necessity of revascularization prior to any podiatric procedures, the patient was planned for femoral endarterectomy and amputation of left hallux and fifth toe and metatarsal for source control. On hospital day nine, the patient's cellulitis had resolved, with reduced erythema surrounding his eschars. The patient completed a nine-day course of ampicillin-sulbactam prior to amputation and was discharged with appropriate vascular surgery and podiatry follow-up.

DISCUSSION

Pasteurella spp. are easily identified in animal oral flora, and *Pasteurella multocida* has been recognized as the most prevalent zoonotic pathogen transmitted to humans, usually through bites or contact with nasal and oral secretions.[6] The most common manifestation of animal bite wounds is cellulitis developing within 24 hours with associated

erythema, tenderness, swelling, and serosanguinous to purulent drainage. Abscess and tenosynovitis are additional frequent local complications, although septic arthritis and osteomyelitis may also occur.[7] Non-injury infections tend to include open wounds that were contaminated by pet saliva. All cases in the literature have reported infections with P. multocida but very rarely with *P. canis oralis*, as isolated in our patient.[3] All prior cases of *P. canis oralis* infections in humans have been reported in the setting of penetrating dog bites,[4,8,9] in contrast to our patient who is suspected to have been infected via saliva on an open wound. Unlike *Pasteurella spp.*, *N. animaloris* is a rarer occurrence in humans following animal bites, with only 14 documented cases in the literature.[10] Infections from the above mentioned pathogens typically present with acute-onset cellulitis, with purulent discharge and regional lymphadenopathy, prompting immediate workup and treatment.[4,5] However, this patient's case was complicated by extensive peripheral vascular disease and diabetic neuropathy, and the patient presented to the ED months after the initial infection and subsequent osteomyelitis. Due to the rarity of the organisms identified in the wound, there were no standardized treatment guidelines; however, in a case review of 13 patients with *N. animaloris*, the most common antibiotic of choice was penicillin V for 10 days.[5] After review of available literature that reported susceptibility to amoxicillin-clavulanate in both *N. animaloris* and *P. canis oralis*,[4,10] the patient's infection was treated successfully with nine days of ampicillin-sulbactam prior to amputation.

While these pathogens are rare, they are imperative to recognize in the management of infected wounds in individuals who have close contact with animals. N. animaloris especially is expected to be severely underrecognized in animal-associated infections, and is often misidentified as *Pasteurella spp.* or contaminants.[5] As demonstrated in this report, both *N. animaloris* and *P. canis oralis* can grow promptly on blood and chocolate agar, thus they can be isolated from routine wound cultures. When diagnosis is delayed, there is the possibility of ineffective antibiotic coverage with an increased risk for exacerbation of infection that can lead to complications such as osteomyelitis, sepsis, and possibly death.

CONCLUSION

There is a limited number of published cases on *N. animaloris* or *P. canis oralis* infections isolated from penetrating animal bites, and this appears to be the first reported case of *N. animaloris* and *P. canis oralis* infection transmitted by canine saliva on an open wound. In patients with open lesions complicated by poor wound healing, it is important to emphasize proper wound care especially in the context of house pets. Ultimately, while these bacteria are rare causes of animal-associated infection, they are susceptible to beta-lactamase inhibitors and can be treated appropriately once identified.

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Revision Total Knee Arthroplasty for Catastrophic Tibial Post Failure: Rare Complication of Total Knee Replacement

JONATHAN LIU, MD; LAUREN LUTHER, MD; NATHANIEL SMITH, MD; DEREK R. JENKINS, MD

ABSTRACT

Tibial post failure is a rare but serious complication of posterior-stabilized total knee arthroplasty that requires revision surgery. Although tibial post fracture has previously been reported, this case involves an implant with a design feature that may predispose patients to the complication. The fracture also occurred later than observed in most other reports. A 72-year-old male who had undergone a posterior stabilized total knee arthroplasty seven years prior presented with knee pain and instability after a fall from standing. Although plain radiographs were not diagnostic, history and physical exam suggested failure of the tibial polyethylene post. This was confirmed during surgery when the fractured component was identified in the suprapatellar pouch. Given absence of malrotation or malalignment of the well-fixed femoral and tibial components, a polyethylene liner exchange was performed. Postoperatively, the patient had complete resolution of pain and instability with 0–120 degrees of stable ROM, which has persisted to latest follow-up at 6 months.

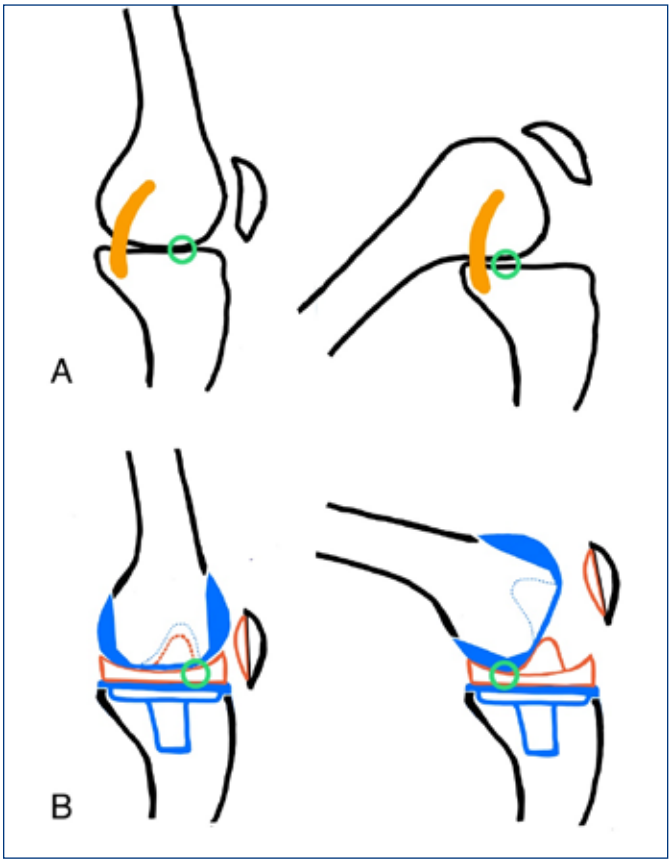
KEYWORDS: total knee revision arthroplasty, post fracture, polyethylene failure, posterior stabilized

INTRODUCTION

Activity-limiting knee pain is a frequent presentation to primary care physicians. Total knee arthroplasty (TKA) is one of the most common elective orthopedic procedures and an effective method of relieving pain and restoring function in patients with end-stage osteoarthritis.[1] The posterior cruciate ligament (PCL) permits deep knee flexion by limiting posterior subluxation of the tibia (**Figure 1A**). Frequently, however, excision of the cruciate ligaments during TKA may be required to allow for deformity correction and greater surgical exposure.[2] To compensate for an absent PCL, posterior stabilized (PS) TKA implants rely on a post incorporated in the tibial polyethylene liner that prevents posterior tibial subluxation and allows deep flexion (**Figure 1B**).[3,4]

The tibial post resulted in increased functionality in PS TKA compared with previous total condylar prosthesis designs and demonstrated greater than 95% survivorship at ten years.[2,5,6] However, it also created a new source of complications at both the patellofemoral and the femoral-post articulations.[7,8] We present a case of tibial post fracture occurring seven years after index TKA using Foundation-500 series PS components (DJO Surgical, Lewisville, TX). Although reports of both chronic wear and acute fracture of polyethylene tibial posts exist in the literature, this case involves an implant with a design feature that may predispose patients to the complication. Additionally, the tibial post fracture in this case occurred seven years after the index surgery, longer than the average elapsed time reported in other studies.

Figure 1A,B. [**A**] Femoral rollback, posterior shift in femoral-tibial contact (green circle) that occurs during native knee flexion with PCL (orange). [**B**] Femoral rollback (green circle) in prosthetic knee facilitated by tibial post (orange hashed line) articulation with femoral component (blue dotted line).



CASE HISTORY

A 72-year-old male with history of left total knee arthroplasty (TKA) in 2014 presented with left knee pain and instability after fall from standing. Of note, he had a periprosthetic infection found to be *Streptococcus mitis/oralis* approximately two months after the original surgery that was treated with open irrigation and debridement, polyethylene liner exchange and six weeks of intravenous vancomycin. Otherwise, he had been doing well clinically with no complaints regarding his prosthesis until this traumatic event. On exam, he had normal range of motion (ROM) but had significant anteroposterior subluxation with a positive posterior drawer test. Plain radiographs showed acceptable alignment of prior TKA with no evidence of hardware failure (**Figure 2**). Computed tomography (CT) scan showed a large joint effusion but stable arthroplasty components (**Figure 3**). His knee was aspirated with results not suspicious for infection. Because of his markedly abnormal physical exam findings, and severe limitations in ambulation due to feelings of instability, he was indicated for revision surgery. At the time of revision surgery, a large knee effusion was noted with significant detritic synovitis. The polyethylene bearing post was found to be sheared off and located in the suprapatellar pouch (**Figure 4**). The bearing was removed with evidence of severe delamination and oxidative degradation of the polyethylene. A new posterior-stabilized (PS) bearing with screw was placed. Due to his history of infection, he was discharged on a seven-day course of cefadroxil per previously published protocols.[9] Post-operative radiographs showed well-aligned femoral and tibial components status post polyethylene exchange (**Figure 5**). Post-operatively the patient's inpatient course was uncomplicated and he was discharged home with services on post-operative day one. On latest office follow-up, at more than six months after

Figure 2. Pre-operative plain radiographs of the left knee including AP (left), lateral (right) views showing no acute fractures or evidence of hardware failure.

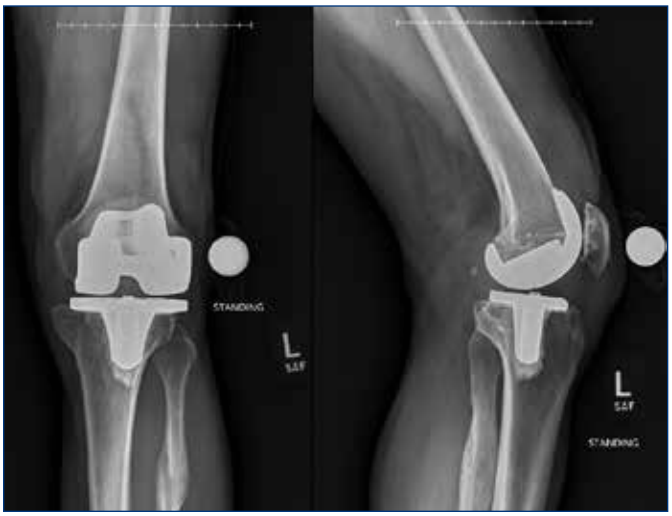


Figure 3. Representative coronal cut from pre-operative computed tomography (CT) imaging of the left knee showing stable tibial and femoral implant components.

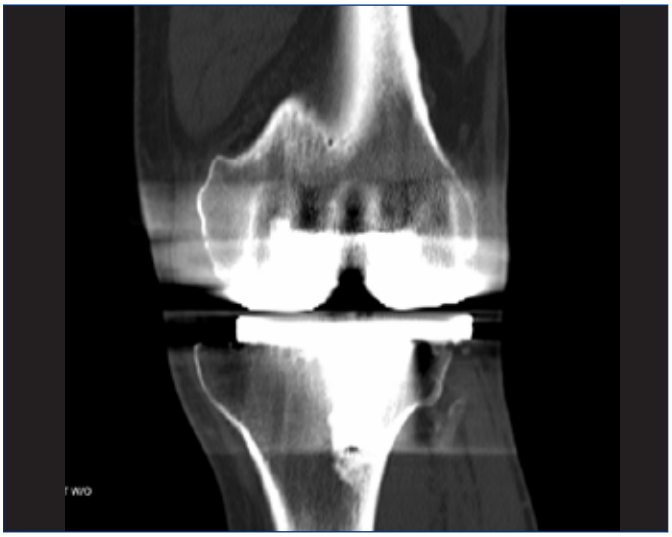


Figure 4. Intra-operative clinical photos showing the post of the polyethylene liner.

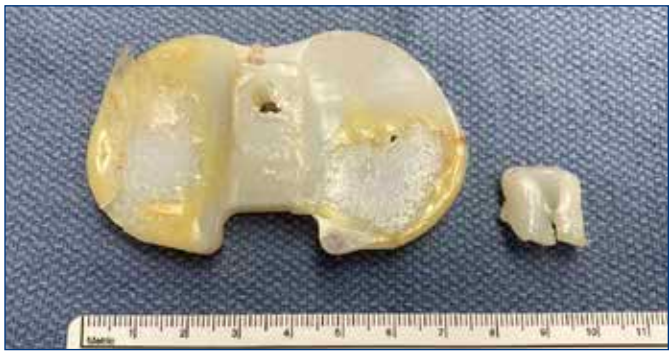
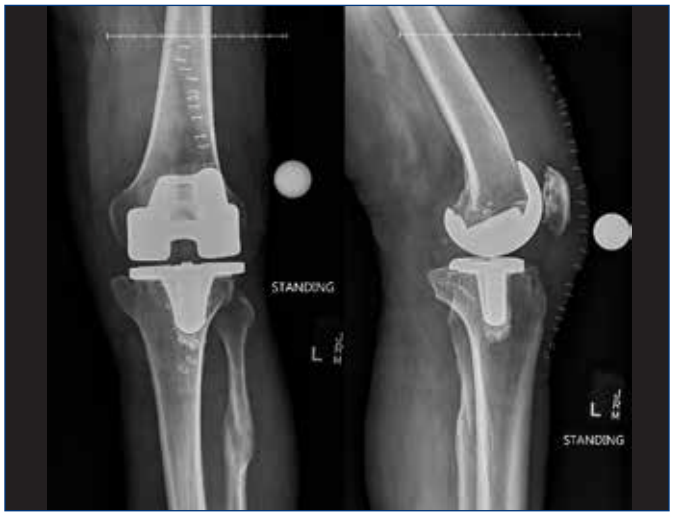


Figure 5 Post-operative plain radiographs of the left knee AP (left) and lateral (right) views showing stable alignment after polyethylene exchange.



revision, he presented with resolved symptoms of instability, with no complaints or episodes of femoro-tibial sublluxation. He had no clinical signs or symptoms of infection. Radiographs demonstrated no signs of loosening or wear.

DISCUSSION

We present the case of a fractured polyethylene tibial post seven years after initial posterior-stabilized (PS) total knee arthroplasty (TKA) utilizing Foundation components (DJO Surgical Lewisville, TX). The limited literature on this complication contains only case series, the majority of which describe tibial post fractures occurring soon after index arthroplasty.[3,7,8,10] Additionally, failure of the implant model used in this case has not been previously reported. The tibial post common to PS knee prostheses provides a substitute for the posterior cruciate ligament (PCL) that allows for increased knee flexion and more closely mimics native knee mechanics than previous prosthesis designs.[2,5,6,10] However, the additional articulation in PS knee prosthesis creates a potential mechanism of implant failure – tibial post fracture, a serious complication of PS TKA that necessitates revision surgery.

Tibial post failure is an uncommon late complication of PS TKA. The majority of reported cases occurred between two to four years after the index arthroplasty.[11] The incidence of tibial post-fractures is reported to range from 0.5–1.2%. Some implant designs seem to be more prone to this complication however. A retrospective study of 564 patients performed by Bal et al in 2008 found 70 (12%) cases of tibial post fracture requiring revision surgery.[11,12] Interestingly, all of the procedures in the study by Bal et al utilized Foundation-100 series Total Knee System (DJO Surgical Lewisville, TX), an earlier version of the components that fractured in our case.[12] The design of the tibial polyethylene in the Foundation-100 series features a screw hole in the center of the of the tibial post that was hypothesized to result in a stress riser and, thereby, increase risk of tibial post failure.[7,12] Despite other updates to the implant, the Foundation-500 series continues to feature a screw hole in the center of the tibial post, which may have contributed to the fracture observed in our case. Other risk factors for tibial post fracture related to implant design include a taller tibial post, which leads to a longer lever arm during knee flexion when the femur exerts a tensile lift-off force on the post, and a highly conforming implant, in which the post also acts to provide medial and lateral constraint leading to greater experienced force.[13–16] Implants with more anterior post placement have also demonstrated increased wear damage of the tibial post in retrieval studies.[4,17] Sterilization during implant manufacturing may also play a role in tibial post fracture since historical γ irradiation in air can lead to oxidative degradation of the polyethylene implant during storage.[18] The current practice of γ sterilization in an inert environment combined with barrier packaging reduces pre-implantation degradation but still produces free radicals within the polymer that make it susceptible to in-vivo oxidation.[18] Given that tibial post fractures have been reported in in γ inert sterilized components, further research is needed to determine the impact sterilization method has on tibial post failure.[3,19,20]

In addition to implant characteristics, factors related to surgical technique and individual anatomy have also been implicated in elevated risk for tibial post failure. Surgical techniques that result in anterior tibial post impingement during knee extension, such as anterior positioning of the tibial tray or excessive femoral component flexion, have been found to result in increased tibial post damage.[4,13,21-25] In terms of patient related factors, medial laxity postoperatively may increase risk for post-fracture as Hendel et al described five patients with noted to have mild medial laxity two to three years after the index arthroplasty who went on to have tibial post fractures.[22] Patients with a large native anterior femoral bow may also be at risk for tibial post fracture due to the difficulty in properly positioning the intramedullary alignment guide so as to prevent femoral component flexion.[4,10] For these patients, the use of an alternative system, such as a cruciate-retaining device may be a better option to avoid tibial post fracture.[4]

Knee pain has been estimated to affect 25% of adults, and results in 4 million primary visits annually.[26,27,28] Although not all patients with knee pain require knee replacement, arthroplasty is one of the most common orthopedic procedures.[1] As the United States population ages, the demand for TKA is projected to approach 3.5 million procedures annually by 2030.[29] In some national registry studies, 10-year TKA implant survival without revision is over 95%, with risk of failure requiring revision decreasing with age of index surgery.[30] Despite the high success of TKA, from 2012 to 2019 over 500,000 revision surgeries were performed in the United States. Approximately 40% of revision TKA were performed for aseptic loosening and prosthetic joint infection with instability (11%) and bearing surface wear (2.3%) being less common indications.[31,32] As the number of primary TKA increases, the number of revision TKA is also projected to surpass 200,000 annually by 2030.[29] As a result, primary care physicians and other non-orthopedic clinicians can be expected to increasingly be caring for patients who will need TKA, or have undergone either primary or revision TKA.

It is important for clinicians who care for patients with TKA to be aware of tibial post fractures as patients will often present to primary care physicians with intermittent and non-specific symptoms. Most commonly reported symptoms in post fractures are pain, swelling, and instability; however, patients can present with more objective mechanical symptoms such as "clunking" during range of motion, a palpable mass, or knee dislocation.[3,7,8,11,22,33] Common mechanisms of failure include direct trauma to knee, standing from seated

position, or climbing stairs.[12,34] In addition to a thorough history, it is important to evaluate posterior stability at varying degrees of flexion as any residual post may confer stability at flexion angles less than 90 degrees.[12] Although the use of arthroscopy and CT arthrography has been reported, the diagnosis of tibial post failure relies on a detailed clinical history and physical exam because radiographs, as in this case, are typically non-specific.[11,35] High clinical suspicion should prompt evaluation by an arthroplasty specialist.

Standard treatment guidelines for tibial post fractures have not been established. In a 2011 review, Lachiewicz found the most common intervention performed was polyethylene liner exchange.[11] Only one (5%) of the patients treated with this method went on to require an additional revision surgery although limited follow up data was available. In our case, revision with a new posterior stabilized bearing of the same thickness as the initial implant provided optimal stability. The altered biomechanics of a knee with a fractured tibial post leads to increased wear and release of polyethylene debris which predisposes patients to osteolysis, aseptic loosening and reactive synovitis.[13] As a result, different operative treatments may be required depending on timing of diagnosis and patient specific characteristics.[22,36,37] Because delayed diagnosis can make revision more challenging, clinicians should maintain a high index of suspicion for tibial post fracture. In the absence of loss of implant fixation, ligamentous instability, or malalignment of the femoral or tibial components, polyethylene liner exchange is an appropriate initial intervention since it preserves bone stock and likely results in less patient risk, shorter operative times, faster rehabilitation, and lower cost.[38,39]

In summary, we present a patient with a posterior stabilized total knee arthroplasty complicated by late tibial post fracture. We suggest that surgeons and primary care providers should maintain a high index of suspicion for this uncommon complication when faced with patients reporting similar histories and physical exam findings, especially those with implants which may have a track record of tibial post fracture. Polyethylene exchange utilizing an implant of the same thickness was a successful intervention in this case but we suggest that appropriate revision surgery should be dictated by the unique characteristics of the patient at the time of failure. The authors suggest an area to direct further research would be to determine the potential increased risk of catastrophic implant failure in total knee designs utilizing a fixation screw through the post compared to those without this design feature.

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Solitary Eruptive Keratoacanthoma Developing at Site of COVID-19 Vaccine Injection

SARA YUMEEN; MD; LESLIE ROBINSON-BOSTOM, MD; ELNAZ F. FIROZ, MD

INTRODUCTION

Keratoacanthomas (KA) are cutaneous tumors which typically present as dome-shaped nodules with central keratin-filled crater.[1] Due to relative paucity of data, their epidemiology, classification, and management have remained somewhat controversial.[2,3] Most often, KAs are classified as a variant of cutaneous squamous cell carcinoma which may spontaneously regress, but rarely have the potential to behave in a more aggressive manner and metastasize.[2] Surgical excision with clear margins is the current standard of treatment.[4] KAs commonly occur in sun-exposed areas of the skin and in those with Fitzpatrick skin types I to III.[2] Thus, ultraviolet radiation has been postulated to play a role in their development.[2]

More rarely, KAs have been reported to occur in sites of iatrogenic or accidental trauma.[5] While the etiology of such KAs remains unknown, it is hypothesized to be associated with local wound-healing response. Development of KAs following injection of pneumococcal and smallpox vaccines has been previously reported[5]; however, KA occurring at the vaccination site after COVID-19 vaccination has not yet been described in the literature. Herein, we report a case of development of a solitary KA at the site of COVID-19 vaccine injection.

CASE REPORT

A 66-year-old male with past medical history of osteoarthritis presented for evaluation of a new, painful, solitary lesion on the right shoulder. The patient had received his first and second doses of the Moderna COVID-19 vaccine approximately nine and ten months prior to presentation (in February and March of 2021 respectively), both administered in the right arm. He had subsequently received his third booster dose of the Moderna COVID-19 vaccine in the right arm six weeks prior to presentation (October 2021). Within a week of receiving this third booster dose, the patient noted development of a new skin lesion in exactly the same location where the third shot had been injected. He did not note any bleeding or pruritus. There was no history of fevers, night sweats, fatigue, or weight loss. The patient had not experienced any other symptoms following administration of the vaccine. The patient had no other chronic medical conditions, no allergies, nor was he was not taking any medications. The patient did not have any prior history of skin cancer or inflammatory skin disease.

Figure 1. Lesion on initial presentation. Overlying the right deltoid there was a 1.5 cm firm, pink nodule with crateriform center.

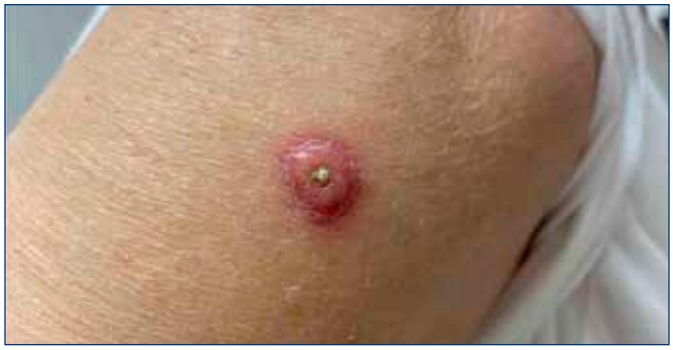
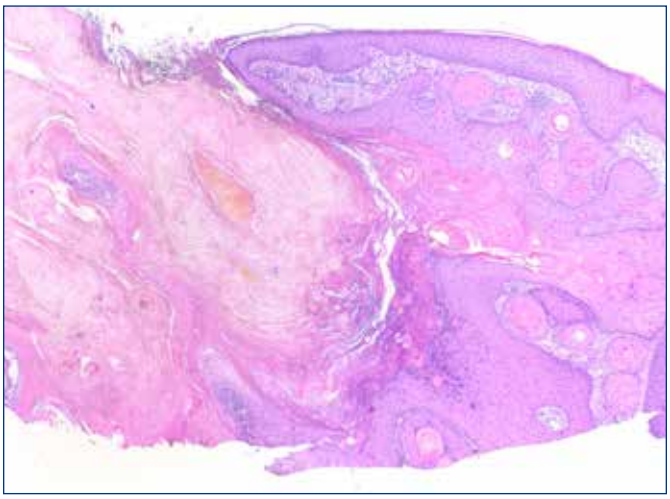
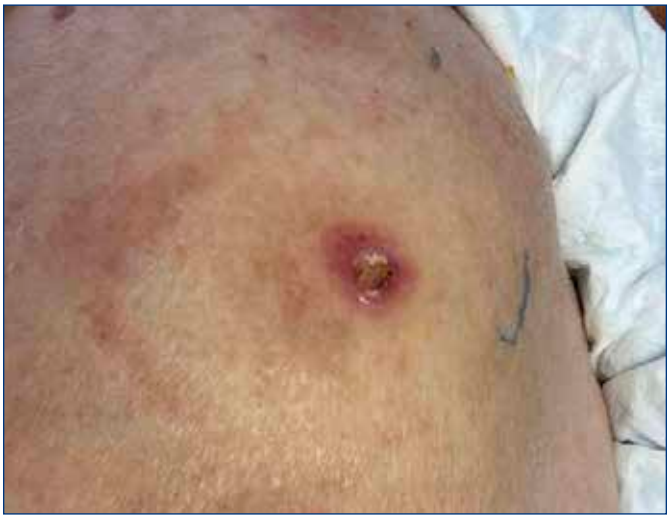


Figure 2. Histopathology, H&E 40x Magnification. Histologic examination shows a crateriform, atypical proliferation of keratinocytes with prominent pink, glassy cytoplasm, consistent with a squamous cell carcinoma, keratoacanthomatous type.



On examination, the patient had Fitzpatrick skin type II. Overlying the right deltoid was a 1.5 cm firm, pink nodule with crateriform center (**Figure 1**). Histologic examination of a skin biopsy at that time showed a crateriform, atypical proliferation of keratinocytes with prominent pink, glassy cytoplasm, consistent with a squamous cell carcinoma, keratoacanthomatous type (**Figure 2**).

Figure 3. Persistent lesion on examination one month following presentation.



The patient presented one month later for surgical excision of the KA. The lesion was persistent and had increased in size to 1.7 cm by 1.4 cm (**Figure 3).** The lesion was excised with 3–5 mm margins, and subsequent histologic examination confirmed complete excision of residual squamous cell carcinoma, keratoacanthomatous type.

DISCUSSION

Keratoacanthomas (KA) are squamous proliferations that are typically classified as a variant of squamous cell carcinoma.[2] They most often occur as solitary lesions, but disorders in which multiple KAs may arise have been reported, such as multiple self-healing squamous epithelioma (MSSE) and generalized eruptive keratoacanthomas of Grzybowski.[3] Factors postulated to predispose to KA development include chronic exposure to UV radiation, Fitzpatrick skin types I–III, exposure to chemical carcinogens, immunosuppression, certain viruses, and some genetic syndromes.[5] Trauma, iatrogenic or accidental, has also been described to result in occurrence of KAs.[5] The etiology of KAs occurring after trauma remains unknown but has been thought to be associated with wound-healing response, particularly in skin that has previously been exposed to carcinogens such as UV radiation.[3] Our case describes a rare occurrence of a KA in the site of COVID-19 vaccination.

Accidental traumatic insults reported to lead to development of KA have included injury with a thorn, dog scratch, cutaneous injuries incurred during a motor vehicle accident, and arthropod bites.[5] Iatrogenic insults previously described include cryotherapy, carbon dioxide laser resurfacing, fractional photothermolysis, skin grafting, Mohs micrographic surgery, and excisions.[5,6] There have also been multiple reports of KA following surgical excision of benign or malignant lesions.[7] KAs have also been described in association with skin diseases that cause cutaneous disruption, such as psoriasis, eczema, stasis dermatitis, milia, and rosacea.

Herein, we presented a case of occurrence of a solitary KA at the site of COVID-19 vaccine administration. While solitary cases of KAs following pneumococcal and smallpox vaccines have previously been described[8,9], development of KA following COVID-19 vaccination has not yet been reported. With emergence of the COVID-19 pandemic, and subsequent development of vaccinations for COVID-19, there has been a concerted effort for vaccination. It is important for both physicians and patients to be aware of adverse cutaneous reactions that can occur following COVID-19 vaccination, so that these can be appropriately diagnosed and managed. Local injection site reactions such as tenderness, erythema, pruritus, and edema have been described immediately following vaccination.[10] Delayed reactions, such as "COVID arm" – a tender indurated plaque developing at the injection site – have also been described.[10] Our case report adds to the literature by describing development of a malignant lesion that may occur following COVID-19 vaccination, and warrants prompt recognition and treatment.

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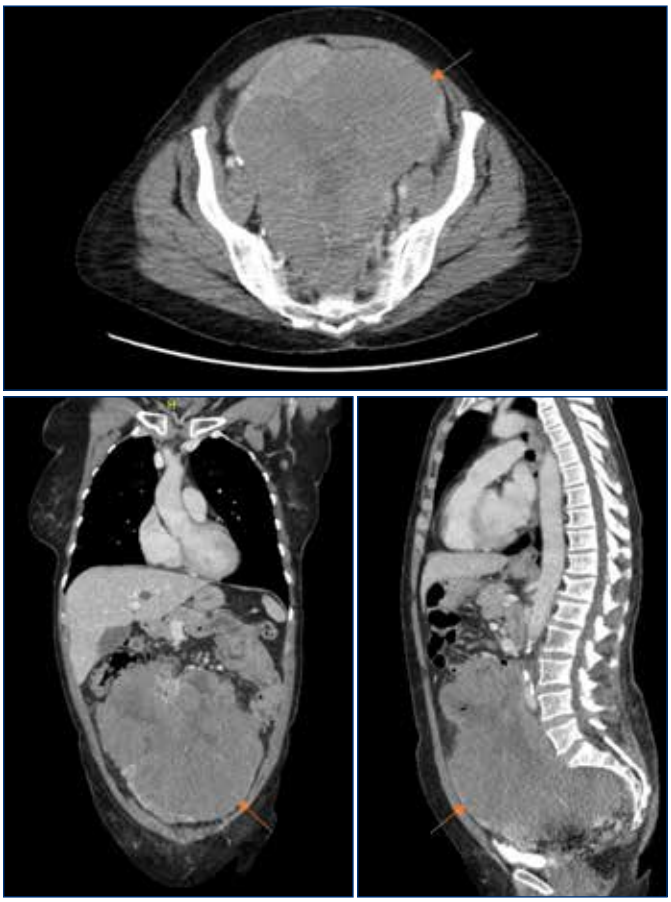
Large Gastrointestinal Stromal Tumor Presenting as Vascular Insufficiency

VIJAIRAM SELVARAJ, MD, MPH

CASE PRESENTATION

A 63-year-old woman with history of anxiety and hypertension presented with three weeks of atraumatic right ankle edema. The patient denied any trauma or prolonged immobility or travel, and did not have any fever, chills, or sweats. She did not take any medications. She denied having any fever, chills, or sweats. On presentation, her temperature was 98.1F, BP was 140/92 mm Hg, heart rate was 95 beats/min, and she was saturating well on ambient air. Physical exam revealed mild abdominal distension and tenderness to palpation, as well as decreased pulses in the lower extremities. A Computerized Tomography Angiography (CTA) study of the abdominal aorta with runoff was ordered to evaluate the arterial circulation. Exam also revealed decreased pulses in the lower extremities for which a CTA abdominal aorta runoff with and without contrast was ordered. The CTA abdomen showed a 19.7 x 10.0 x 21.9 cm heterogenous enhancing mass within the pelvis and abdomen, lobulated with vascular supply, communicating with the small bowel concerning for fistula and moderate bilateral hydroureteronephrosis (**Figures 1A,B,C**). X-ray of the right ankle/foot showed only soft tissue edema. She underwent biopsy of the mass with pathology report consistent with Gastrointestinal Stromal Tumor (GIST), spindle type. She was subsequently started on imatinib following oncologic consultation. The patient was discharged home with outpatient follow-up.

Figures 1A,B,C: [**A**] CT scan of abdomen and pelvis with axial, [**B**] coronal, and [**C**] sagittal views showing 19.7 x 10.0 x 21.9 cm heterogenous enhancing intra-abdominal mass.



DISCUSSION

GISTs are infrequent neoplasms, accounting for 1–2% of all GI malignancies. They were originally thought to arise from mesenchymal cells although later discovered to originate from the interstitial cells of Cajal. Most GISTs are discovered incidentally, hence their true prevalence is unknown.[,] Approximately 10–30% of GISTs progress to malignancy.[1,2] GISTs most commonly occur in the stomach (60%) or small intestine (20–30%). GISTs may also rarely occur in the omentum, mesentery, or retroperitoneum.[3-5] GISTs typically occur later in age, usually in the 60s, and occur equally between males and females. They present in different fashions: Gastrointestinal bleeding or signs and symptoms of mass effect caused by tumor such as abdominal discomfort, early satiety, etc. In 15–30% of the cases, GISTs are discovered incidentally. Tumors are often discovered through endoscopy, ultrasound, CT imaging or MRI.[4-6]

Three main histological patterns of GISTs exist: spindle cell type (70%), epithelioid cell type (20%), and mixed type (10%). Spindle cell type GISTs have cells arranged in short whirls or fascicles. In contrast, epithelioid cell GISTs have cells arranged in a nested or diffuse pattern. Mixed cell type GISTs combine both spindle cell and epithelioid cell histologic patterns. The immunohistochemical analysis represents the basis for the diagnosis of GIST. The most common markers are C-KIT or CD117 (95%) and anoctamin.

In KIT-negative tumors, staining for DOG-1 and CD34 can be used to confirm the diagnosis.[3,7]

Treatment depends on the size of the tumor and the extent of its spread. Surgical resection remains the standard of care for localized, resectable disease greater than 2 cm. For patients with locally advanced disease, where complete surgical resection may not be feasible, neoadjuvant imatinib may help reduce tumor burden prior to resection. In patients with high-risk or metastatic disease, therapy with tyrosine kinase inhibitors such as imatinib is recommended as first-line treatment.[8] There are several targeted therapies that have also improved survival in GIST patients after progression on imatinib. High-risk tumors should be monitored for recurrence with serial abdominal CT scans. GISTs may present in a variety of ways. The prognosis may depend on different characteristics, including tumor site, tumor size, and mitotic count. Once diagnosed, it's imperative to involve surgical and medical oncologists early in the illness.

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Pandemic Preparedness and the Workforce: Employer Experiences with Long COVID

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ABSTRACT

BACKGROUND: Although viral infections, including SARS-CoV-2, can cause persistent symptoms and functional limitations, the impact of post-viral syndromes on workplaces is uncertain.

METHODS: We conducted a cross-sectional study of workplaces in Rhode Island in the D&B Hoovers database (September–October 2022). Eligible workplaces had ≥1 contact with a valid email address and ≥2 paid employees. Participants completed a survey on the impact of Long COVID (post-viral syndrome of SARS-CoV-2) on their workplace.

RESULTS: Of 6,149 eligible workplaces, 484 (8%) participated. Awareness of Long COVID among workplace leaders was limited. Overall, 28% of workplaces had any employees report having Long COVID. Of those, 14% had ≥1 employee discontinue employment, 45% had ≥1 employee reduce their workload, and 22% had ≥1 employee request an accommodation due to having Long COVID; 80% of employers reported improvement in employee productivity with accommodations.

CONCLUSION: Pandemic preparations for the long-term impacts of post-viral syndromes should consider workplace settings.

KEYWORDS: Pandemic preparedness; occupational health; post-viral syndrome; COVID-19; Long COVID

INTRODUCTION

Many viral infections can lead to post-viral syndromes in some patients, including polio, dengue, Epstein-Barr, influenza, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among others. Though the symptoms of acute infection with each of these viruses can be distinctive, many of the long-term symptoms of their post-viral syndromes are similar, such as fatigue, exercise intolerance, flu-like symptoms, and neurological complications.[1,2] Post-viral syndromes can greatly impact people's quality of life and ability to work,[1] making anticipation of these long-term effects of infection an important component of pandemic preparedness.

During the Coronavirus Disease 2019 (COVID-19) pandemic, widespread recognition of the long-term impacts of acute SARS-CoV-2 infection was slow to emerge.[3] The post-viral syndrome known as Long COVID most commonly includes symptoms of fatigue, shortness of breath, chest pain, and cough.[4-7] As of February 2023, as many as one in 20 people in the United States (US) were estimated to have lingering effects of COVID-19,[8] with some experiencing severe impacts on their quality of life and function.[8-16] Consequently, there has been significant concern for not only the individual impacts of Long COVID, but the impacts on the workforce and economy. In 2022, as many as two to four million working-age adults in the US were estimated to be out of the workforce due to Long COVID.[17] Lost earnings, diminished quality of life, and increased medical spending associated with Long COVID may contribute to vast economic impacts. In one study, the cost of Long COVID in the US through 2021 was estimated at $3.7 trillion.[18,19]

While such studies provide a macroeconomic view on the impacts of Long COVID, less is known about the effects on workplaces and their employees. Emerging evidence has suggested that many people with Long COVID may not be able to return to work or may experience decreased productivity at work, even with accommodations such as telework and flexible hours.[20-22] However, the studies were conducted early in the pandemic and in Europe, highlighting the need for more recent data and information from other geographic settings with distinct health and social systems. Additionally, these previous studies focused on the impacts of Long COVID for individual employees; the impact on workplaces, including productivity and accommodations provided for employees, remains uncertain. To help fill these important gaps and prepare the workforce for future viral pandemics, we conducted a study of the impact of Long COVID on workplaces in the state of Rhode Island.

METHODS

We conducted a cross-sectional study of workplaces in Rhode Island. The study was not considered human subjects research because survey respondents were "key informants" on their workplace; therefore, the study did not meet criteria for review by the Brown University Institutional Review Board.[23]

Sample selection

The D&B Hoovers Web-based platform (Austin, Texas)[24] was used to identify a sample of 7,263 workplaces in Rhode Island. D&B Hoovers maintains a paid-access platform that provides searchable information (including employee contact information) on more than 330 million workplaces worldwide, which are identified using data from trade, registry, and other sources; millions of websites; and D&B Hoovers' vendors, partners, customers, and third parties.[25] For each workplace sampled, one professional was selected for invitation to participate in the study, with preferential selection of human resources professionals due our interest in the impact of Long COVID on employees at the workplace. The list of invitees was generated from August 8 to August 30, 2022.

To select the sample using the D&B Hoovers platform, the database was filtered to view and extract *all* employee contacts in Rhode Island who had an email address listed. Subsequently, SAS version 9.4 (Cary, North Carolina) was utilized to select the most suitable contact per workplace using a pre-specified hierarchy based on job function, job title, and seniority level. Briefly, the most senior human resources professional was considered to be the most suitable contact. If no human resources professionals were listed, then the most senior benefits and compensation executive was selected. If no benefits and compensation executives were listed, then the most senior employee was selected. One individual from each workplace was then randomly selected among all employees identified as being the most suitable contact. This process yielded a list of contact information for 7,263 unique professionals at 7,263 unique workplaces in Rhode Island.

Contacts with invalid email addresses were classified as ineligible. Additionally, a screening question at the beginning of the survey was used to determine whether the workplace had at least two employees paid by the organization. Respondents who reported fewer than two paid employees were classified as ineligible, as their responses would provide limited insight on workplace productivity and accommodations.

To check data quality of the contact list, a subset of 512 contacts was selected for verification through open-source intelligence (i.e., finding the contact and workplace on publicly available Web pages through a Google search). Of the 512 contacts, only 13% could not be validated, providing confidence in the quality of the contact list.

Survey data collection

The 7,263 professionals were invited to complete the Web-based Qualtrics study survey on September 28, 2022. Invitations were sent via email, and three reminder emails were sent to those who had not yet completed the survey. Invitees were provided with the option of sharing the email address of an alternative employee at the workplace who may be better able to complete the survey. Another unique email invitation was subsequently sent to any newly identified individuals. The survey closed on October 28, 2022. Respondents were offered a $20 electronic Amazon gift card as compensation for their time participating in the study.

The study survey, which is available in the **Supplementary Appendix** by emailing corresponding author, collected information regarding COVID-19 workplace policies and overall pandemic impact, the specific impact of Long COVID, and accommodations requested and granted for Long COVID. The World Health Organization's October 2021 definition of Long COVID[4] was included to provide standard terminology for those who may not be familiar with the condition. Productivity impacts were measured by the number of employees who had to reduce workloads or discontinue employment due to Long COVID. The survey questions on Long COVID accommodations were based on guidance regarding the Americans with Disabilities Act (ADA) of 1990 from the US Equal Employment Opportunity Commission[26] as of October 28, 2021.

Data management and analysis

Study data were managed and analyzed in SAS. The characteristics of workplaces were summarized by study participation status. Survey responses were summarized among workplaces that participated in the study. For each survey question summarized, participants who had discontinued the survey before reaching that question were excluded from the denominator. Additionally, counts of less than 10 along with associated percentages were suppressed to protect participants' confidentiality.

RESULTS

Survey response

Of 7,263 professionals at unique workplaces in Rhode Island who were invited to participate in the study, 893 (12%) were ineligible due to invalid email addresses, 136 (2%) were ineligible due to no longer being in the position, and 85 (1%) were ineligible due to having fewer than two employees paid by the organization. Of the remaining 6,149 professionals, 484 (8%) participated by responding to at least one survey question. Of 484 participants, 406 (84%) fully completed the survey, while 78 (16%) partially completed the survey.

Characteristics of invited workplaces

Of 7,263 invited workplaces, most (92%, n=6,669) were small organizations with fewer than 50 employees (**Table 1**). About half of workplaces (52%, n=3,776) were part of an industry where remote work is often feasible. Most were private (86%, n=6,232) and independent (80%, n=5,834) workplaces. Just over half of workplaces (55%, n=3,965) were located in Providence County, which is the county containing the state's capital city. The characteristics of workplaces that did and did not participate in the study were generally similar.

However, compared to workplaces that did not participate, those that participated were somewhat less likely to be part of an industry where remote work is often feasible (45% vs. 53%), somewhat more likely to be a non-profit organization (18% vs. 9%), and somewhat less likely to be a private company (76% vs. 88%). The characteristics of participating workplaces stratified by whether they partially or fully completed the survey are available in **Supplemental Table S1**, and their detailed industry classifications are available in **Supplemental Table S2**, by emailing corresponding author.

Table 1. Characteristics of invited workplaces, overall and by survey participation status

	Invited N=7,263		Did not participate* N=6,779		Participated N=484		p-value
	n	(%)	n	(%)	n	(%)	
Size							0.24
Small (0–49 employees)	6,669	(92)	6,225	(92)	444	(92)	
Medium (50–249 employees)	512	(7)	474	(7)	38	(8)	
Large (250 or more employees)	82	(1)	80	(1)	<10		
Industry where remote work is often feasible†							0.01
Yes	3,776	(52)	3,559	(53)	217	(45)	
No	2,818	(39)	2,611	(39)	207	(43)	
Unknown	669	(9)	609	(9)	60	(12)	
Ownership type							<0.01
Nonprofit	708	(10)	619	(9)	89	(18)	
Partnership	177	(2)	163	(2)	14	(3)	
Private	6,232	(86)	5,865	(88)	367	(76)	
Public	14	(<1)	14	(<1)	0	(0)	
Public sector	132	(2)	118	(2)	14	(3)	
Entity type							0.04
Branch	674	(9)	646	(10)	28	(6)	
Independent	5,834	(80)	5,426	(81)	408	(84)	
Parent	534	(7)	499	(7)	35	(7)	
Subsidiary	221	(3)	208	(3)	13	(3)	
County							0.74
Bristol	341	(5)	317	(5)	24	(5)	
Kent	1,228	(17)	1,152	(17)	76	(16)	
Newport	823	(11)	775	(12)	48	(10)	
Providence	3,965	(55)	3,692	(55)	273	(56)	
Washington	890	(12)	827	(12)	63	(13)	

* Includes N=1,114 workplaces that were ineligible due to the contact having an invalid email address (n=893), the contact no longer working in that position (n=136), or the workplace having fewer than two employees paid by the organization (n=85).

† Classified the National American Industry Classification System code for each workplace into these categories based on the Spring 2022 McKinsey American Opportunity Survey on remote-work availability by occupation and role, as well as the 2017 North American Industry Classification System descriptions of industries.

Table 2. COVID-19 workplace policies and pandemic impact

	n	(%)
Most strict masking policy (N=448)		
Required to wear a mask at all times	220	(49)
Required to wear a mask when working close to other people	127	(28)
Recommended to wear a mask at all times	21	(5)
Recommended to wear a mask when working close to other people	55	(12)
Not required or recommended to wear a mask	23	(5)
No response	<10	
Most strict testing policy for on-site staff (N=454)*		
Required for all staff	94	(21)
Required only for unvaccinated staff	24	(5)
Not required of any staff	311	(69)
No on-site staff	25	(6)
Current vaccination policy (N=468)		
Required for all staff	93	(20)
Required for all staff but with medical/religious exceptions	38	(8)
Required for certain staff (e.g., customer-facing)	<10	
Choice of vaccination or regular testing	12	(3)
Recommended but not required	223	(48)
No requirement or recommendation	87	(19)
Other	<10	
Current vaccination coverage - primary vaccination series (N=460)		
0-25%	12	(3)
26-50%	11	(2)
51-75%	44	(10)
75-100%	277	(60)
Don't collect vaccination information	68	(15)
Don't know	48	(10)
Ever reduced operations during pandemic (N=448)		
Yes	306	(68)
No	141	(31)
No response	<10	
Workplace productivity is back at pre-pandemic levels (N=446)		
Strongly agree	204	(46)
Agree	171	(38)
Disagree	59	(13)
Strongly disagree	11	(2)
No response	<10	

* Survey question asked about regular COVID-19 testing policies at any time during the pandemic.

COVID-19 workplace policies and pandemic impact

Among participating workplaces, nearly half (49%, n=220/448) had required employees to wear a mask at all times at some point during the pandemic (**Table 2**). Only 5% of workplaces (n=23/448) reported no mask requirement or recommendation at any point. More than two thirds of workplaces (69%, n=311/454) had not required testing for any employees at any point. At the time of the survey, nearly half of workplaces (48%, n=223/468) recommended but did not require vaccination among their employees; only 20% (n=93/468) required vaccination for all employees, while another 8% (n=38/468) required vaccination but with some medical or religious exemptions. The majority of workplaces (60%, n=277/460) reported that 75 to 100% of employees had completed the primary vaccination series. Most workplaces (68%, n=306/448) had reduced operations at some point during the pandemic, with 46% (n=204/446) strongly agreeing that productivity had returned to pre-pandemic levels. At nearly half of workplaces (46%, n=204/440), leaders had never discussed Long COVID as a condition that may affect employees. The largest number of workplaces (38%, n=164/437) had "very low" concern among leadership about the impact that Long COVID may have on productivity. Additionally, nearly half of workplaces (46%, n=192/422) disagreed or strongly disagreed that leadership was aware of ADA guidelines for Long COVID.

Table 3. Awareness of Long COVID among workplace leaders

	n	(%)
Frequency with which workplace leaders have discussed Long COVID as a condition that may affect employees (N=440)		
Never	204	(46)
1–2 times	121	(28)
3–5 times	28	(6)
>5 times	35	(8)
Don't know	50	(11)
No response	<10	
Level of concern among workplace leaders about the impact that Long COVID may have on work productivity (N=437)		
Very high	15	(3)
Above average	27	(6)
Average	117	(27)
Below average	40	(9)
Very low	164	(38)
Don't know	74	(17)
Workplace leaders are aware of the ADA guidelines for Long COVID (N=422)		
Strongly agree	56	(13)
Agree	172	(41)
Disagree	150	(36)
Strongly disagree	42	(10)
No response	<10	

* Survey question asked about regular COVID-19 testing policies at any time during the pandemic.

Impacts of Long COVID on the workplace and productivity

Overall, 56% of workplaces (n=224/436) indicated that none of their employees had reported having Long COVID, while 28% (n=122/436) had at least one employee report having the condition (**Table 3**). Most of the workplaces with any employees reporting having Long COVID indicated that one to five employees had the condition (92%, n=112/122). Among workplaces that may have had at least one employee with Long COVID (i.e., those that reported having an employee with Long COVID or did not respond to that question), 14% (n=17/120) had at least one employee discontinue employment because of Long COVID, and 45% (n=54/121) reported that at least one employee had to reduce their workload due to the condition.

Table 4. Impacts of Long COVID on the workplace and productivity

	n	(%)
At least one employee reported having Long COVID (N=436)		
No	244	(56)
Yes	122	(28)
Don't know	70	(16)
At least one employee discontinued employment due to having Long COVID (N=120)*		
No	96	(80)
Yes	17	(14)
Don't know	<10	
No response	<10	
At least one employee reduced their workload due to having Long COVID (N=121)*		
No	60	(50)
Yes	54	(45)
Don't know	<10	
No response	<10	
At least one employee requested accommodations for Long COVID (N=118)*		
No	85	(72)
Yes	26	(22)
Don't know	<10	
At least one employee reduced their workload due to caring for a family member or friend with Long COVID (N=433)		
No	327	(76)
Yes	37	(9)
Don't know	69	(16)

* Among workplaces where at least one employee reported having Long COVID and workplaces that did not respond to that ques tion.

Accommodations for Long COVID

Among workplaces that may have had at least one employee with Long COVID, 22% (n=26/118) reported that at least one employee had requested job accommodations for Long COVID (**Table 4**). At workplaces where accommodations had been requested, the two most requested and granted accommodations were adjustments to work schedules (85%, n=22/26 requested and granted) and permission for remote work (58%, n=15/26 requested and granted). Most workplaces that had granted accommodations for Long COVID (80%, n=20/25) reported that the accommodations had an effect on returning the employee to their pre-Long COVID productivity level. Of those reporting any effect on productivity, most (85%, n=17/20) reported a minor or moderate effect. Among all workplaces, 47% (n=196/418) reported that they would modify work schedules, and 35% (n=148/418) reported that they would grant permission for remote work, if requested by an employee with Long COVID.

DISCUSSION

Among a sample of workplaces from across Rhode Island, respondents at nearly half of workplaces reported that workplace leaders had below average concerns for Long COVID (47%), had never discussed Long COVID as a condition that may impact employees (46%), and were not aware of ADA guidelines for Long COVID (46%). In contrast, workplace adaptations for acute COVID-19 were more common (e.g., 77% had ever required employees to mask at all times or when working close to other people). Most workplaces indicated that no employees had reported having Long COVID (56%) or that they did not know if any employees had reported having Long COVID (16%); only 28% had any employees report that they had the condition. Among workplaces that may have had an employee with Long COVID, 14% had at least one employee discontinue employment, 45% had at least one employee reduce their workload, and 22% had at least one employee request an accommodation for the condition. Most accommodations requested for Long COVID were granted, with the most common requests being work schedule adjustments and remote work options.

Table 5. Workplace accommodations for employees with Long COVID

	n	(%)
Accommodations requested by an employee (N=26)†		
Modifying equipment and/or devices	<10	
Restructuring roles	<10	
Modifying work schedules	22	(85)
Reassigning to a vacant position	<10	
Adjusting or modifying examinations, training materials, or policies	0	(0)
Providing readers and interpreters	0	(0)
Making the workplace more readily accessible and usable	<10	
Granting remote-work options (if in-person work is typically required)	15	(58)
Other	<10	
None	<10	
Accommodations granted to an employee (N=26)†		
Modifying equipment and/or devices	<10	
Restructuring roles	<10	
Modifying work schedules	22	(85)
Reassigning to a vacant position	<10	
Adjusting or modifying examinations, training materials, or policies	0	(0)
Providing readers and interpreters	0	(0)
Making the workplace more readily accessible and usable	<10	
Granting remote-work options (if in-person work is typically required)	15	(58)
Other	0	(0)
None	<10	
Accommodations likely granted if requested by an employee (N=418)		
Modifying equipment and/or devices	59	(14)
Restructuring roles	116	(28)
Modifying work schedules	196	(47)
Reassigning to a vacant position	58	(14)
Adjusting or modifying examinations, training materials, or policies	37	(9)
Providing readers and interpreters	15	(4)
Making the workplace more readily accessible and usable	70	(17)
Granting remote-work options (if in-person work is typically required)	148	(35)
Other	27	(6)
None	122	(29)
No response	<10	
Effect of accommodations on employee productivity (N=25)		
No effect	<10	
Any effect	20	(80)
There have not been any modifications	<10	
No response	<10	

† Among workplaces where at least one employee had requested an accommodation for Long COVID and workplaces that did not respond to that question.

Most workplaces (80%) reported some improvement in productivity with accommodations.

The finding that only 28% of employers reported having an employee with Long COVID suggests a mismatch with the suspected population burden of Long COVID. Given that roughly 15% of the adult population reports ever having had Long COVID,[8] this may suggest that many people with Long COVID do not consider their symptoms to be of sufficient severity and/or to have a sufficient impact on their work responsibilities to warrant reporting to their employer. A prior study found that 22% of workers with Long COVID did not ask for accommodations because they felt that their symptoms were not severe enough.[27] However, it is also possible that some people with Long COVID who would benefit from workplace accommodations do not feel comfortable reporting the condition to their employer. For example, that same study found that 42% either lacked information about or did not feel safe requesting accommodations.[27] Proactive and transparent discussions with employees about health, possible accommodations, request processes, and workplace expectations would be useful.[20]

While employers frequently reported workplace adaptions for acute COVID-19 (e.g., masks), there was less awareness and concern about Long COVID, consistent with previous findings.[27] In a roundtable discussion with US business leaders and employers in January 2022, many reported that they remained focused on the immediate issues of acute COVID-19 (e.g., testing and vaccination) and employee mental health, with limited time and resources to also focus on the impact of Long COVID.[28] Employers also expressed that the lack of clarity on clinical aspects of the condition, its impact on function, and possible accommodations limited their ability to anticipate employee needs within ADA requirements and other federal guidance.[29-31] The lack of clarity on Long COVID may also reflect greater availability of resources regarding how employers can support employees with COVID-19[32,33] versus Long COVID,[34] although the extent to which workplaces would actively seek out these types of resources is unclear. Nonetheless, clear and accessible resources on Long COVID with actionable steps that employers can take now to support their employees may be useful for improving awareness and concern about the condition among employers, particularly if disseminated through existing infrastructure routinely accessed by employers. Additional research with employers would be valuable to identify demand for this type of information, as well as preferred strategies and infrastructure for dissemination.

Despite limited concern about Long COVID among workplace leaders, almost all workplaces in the present study reported granting the types of accommodations that had been requested. Additionally, workplaces that did not have any known employees with Long COVID also anticipated providing a variety of accommodations, if requested in the future. These findings are consistent with a national survey that found that 99% of people with Long COVID received some or all of their requested accommodations, and that 84% were at least neutral or satisfied with their employer's response.[27] In the present study, employers reported that Long COVID accommodations were often helpful, as a majority of workplaces that granted accommodations found them to provide at least some improvement in employee productivity, mirroring prior evidence that disability accommodations increase productivity and allow employers to retain valued employees.[35] Given the benefits of workplace accommodations and receptivity of employers to grant accommodations, it is especially important for employers to foster a workplace environment that encourages employees to seek supports for health conditions.

This study was subject to important limitations. First, the survey does not provide insight on the underlying prevalence of Long COVID among employees because respondents (employers) were only able to report on cases of Long COVID that had been reported to them (i.e., likely only the most severe cases). However, this study complements prior work by its focus on the impacts of Long COVID on workplaces as a whole, as opposed to individual employee or patient experiences with Long COVID. Second, although the study included a statewide sample of workplaces in Rhode Island identified through the D&B Hoover platform, the extent to which the platform's data are up-to-date and representative of all workplaces in Rhode Island is uncertain. In a data quality review of a subset of 7% of contacts, most (87%) were identified as valid, providing some confidence in the data quality. Third, the response rate was low (8%) despite repeated contact attempts, though it was encouraging that participating workplaces were generally similar to those that did not participate. Nonetheless, most of the participating workplaces were small, private, and independent organizations, and the sample was too small to stratify analyses by workplace size and type. While the overall sample generally aligns with the types of workplaces most common in Rhode Island,[36,37] the findings are less generalizable to other types of workplaces and workplaces in other regions of the US. Finally, there are multiple definitions of Long COVID, and the symptoms associated with Long COVID are also associated with other conditions and factors.[38] We provided survey respondents with the World Health Organization consensus definition[4] to provide standard terminology for those unfamiliar with the definition; however, there are important limitations to this definition.[39] Additionally, the clinical characteristics of employees reporting having Long COVID to their employers are unknown (e.g., whether they had a diagnosis and, if so, by what criteria).

In conclusion, just under one third of surveyed workplaces reported having an employee with Long COVID, though this is likely an underestimate due to some employees not sharing the condition with their employer despite functional limitations and limited awareness of the condition

among employers. Very few employees with Long COVID discontinued employment. Others reduced their workload or requested workplace accommodations, which were generally beneficial for improving their productivity. These findings highlight the importance anticipating the long-term effects of infection on the workforce as a key component of pandemic preparedness planning. Resources with actionable steps that employers can take now to support their employees with post-viral syndromes may be useful for improving awareness of the conditions, facilitating more rapid support for impacted employees in future pandemics, and minimizing the economic impacts of viral pandemics.

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Epidemiological Patterns of HIV Diagnoses Among Women in Rhode Island: An Overview

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BACKGROUND

Women have been affected by HIV since the beginning of the epidemic and face unique challenges in accessing optimal prevention, care, and treatment resources.[1] In 2019, 258,000 women were living with HIV in the United States (US), which accounted for 23% of all people living with HIV (PLWH). Women of color, particularly Black/African American women, are disproportionately affected, bearing the majority of new HIV infections, the greatest prevalence, and the highest rates of HIV-related deaths among women living with HIV.[1]

Most women (84%) who were diagnosed in 2019 acquired HIV through heterosexual contact, while 16% were infected through injection drug use (IDU).[2] Women are most commonly infected through condomless penile-vaginal sex with a male partner who has HIV. Receptive vaginal or anal sex in women presents a greater risk for HIV infection than penile insertive sex.[3] In addition, pre-exposure prophylaxis (PrEP) uptake for HIV prevention is suboptimal for women who would benefit from PrEP, as only 10% of women have received a prescription.[1,2] Women are more likely to know their HIV status but less likely to achieve viral suppression compared to all people living with HIV.[2] Women living with HIV are disproportionately affected by socioeconomic and structural barriers such as poverty, cultural inequities, and intimate partner violence, which limit access to the services and care they need.[1]

In Rhode Island, women constitute a smaller but important subset of HIV diagnoses. In this paper, we review the demographics of women living with HIV in Rhode Island to understand better how to prevent transmission and address barriers to care.

METHODS

Data were reviewed from the HIV Surveillance database eHARS (Enhanced HIV/AIDS Reporting System) of women diagnosed with HIV in Rhode Island from 2003 to 2022. Individuals for whom sex at birth was "female" were included in this analysis and may include individuals whose current gender may be different from their sex at birth (i.e., transgender men). Descriptive characteristics including age, race and ethnicity, mode of transmission, and country of birth were examined. The 2021 American Community Survey (ACS) 5-year Estimates[4] were used to compare the rate of HIV diagnoses among women by race and ethnicity and age group. All analyses were performed using SAS (version 9.4).

HIV diagnoses were combined into two 10-year periods (2003–2012 and 2013–2022) and a t-test (α=0.05) was performed to determine whether case counts were statistically significant over time.

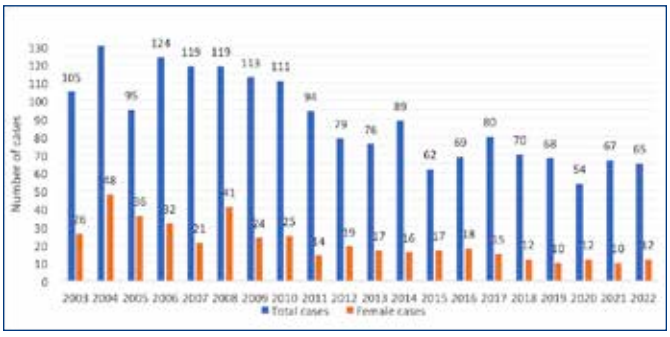
RESULTS

A total of 1,796 cases of HIV were diagnosed between 2003–2022 in RI, of which 425 cases (23%) were among women (**Figure 1**). From 2003 to 2022, there was a 38% reduction in the number of newly diagnosed cases of HIV in Rhode Island from 105 to 65 cases per year. In 2003–2012, the average number of cases diagnosed per year was 110, which reduced significantly to an average of 70 cases diagnosed per year in 2013–2022 ($p<0.05$). Likewise, the average number of newly diagnosed cases among women also decreased significantly in the two time periods, 29 in 2003–2012 vs. 14 in 2013–2022 ($p<0.05$). However, the proportion of cases diagnosed among women has remained fairly consistent over the last two decades with an average of 23% of all newly diagnosed cases being among women ($p=0.07$).

Of the 425 women diagnosed in the last 20 years, over 50% were in the age groups 30–39 and 40–49 when they were first diagnosed with HIV. The average age at diagnosis was 38 years. In the last five years, the rates of newly diagnosed cases of HIV among women has remained consistently high for women in their 40s (**Figure 2**).

While HIV diagnoses in general and among women have decreased in the last 20 years, disparities in HIV rates among racial and ethnic groups in Rhode Island persist. Even though

Figure 1. Number of cases among women by HIV diagnosis year in Rhode Island



the rates among Black/African American women seemed to have decreased in the last two years, they continue to have the highest diagnosis rates in the state. In 2022, the rates were four times higher for Black/African American women and Hispanic/Latino women than non-Hispanic White women (**Figure 3**).

HIV infection associated with sexual transmission was the most common mode of exposure among women newly diagnosed with HIV from 2003–2022, followed by Intravenous Drug Use (IDU) as the second most common mode of HIV transmission. Between 2003–2012, the mode of exposure for 17% of newly diagnosed women was IDU, which decreased substantially to 9% during 2013–2022 (**Figure 4**).

More than 50% of women newly diagnosed with HIV in RI in the last 20 years were born outside of the US (**Figure 5**). Among those born outside of the US, most of the women were born in Liberia (11%), Dominican Republic (7%), and Puerto Rico (7%). A total of 32% of all women diagnosed with HIV between 2003 and 2022 had concurrent AIDS at the time of diagnosis. An AIDS diagnosis suggests someone who was living with HIV for a long time before being diagnosed or suboptimal engagement in care. In the last five years, 46 babies were born to women living with HIV in Rhode Island, of which less than five were perinatal transmissions.

The HIV Care Continuum is a visual representation of the care status of individuals diagnosed with HIV who reside in Rhode Island. As the HIV Care Continuum indicates in 2021, 94% of women in Rhode Island knew their status, 75% were engaged in care, and 68% were virally suppressed (**Figure 6**). When we look at viral suppression among those engaged in care, 92% of women were virally suppressed.

Figure 2. Rates of newly diagnosed cases of HIV among women in Rhode Island, by age, 2018–2022

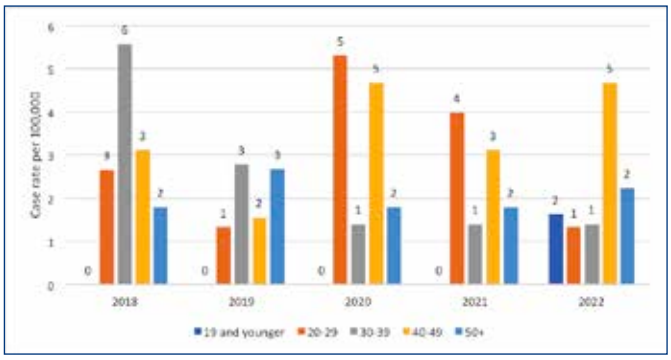


Figure 3. Rates of newly diagnosed cases of HIV among women by racial and ethnic groups in Rhode Island, 2018–2022

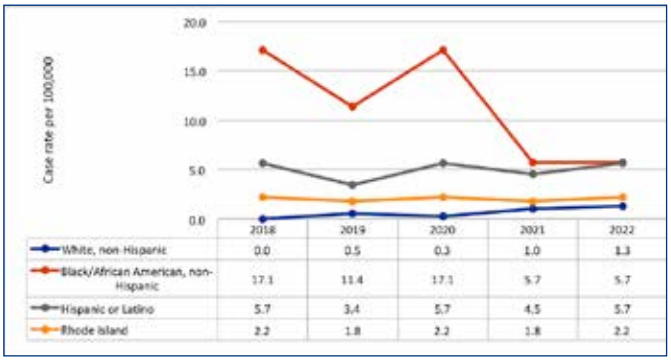
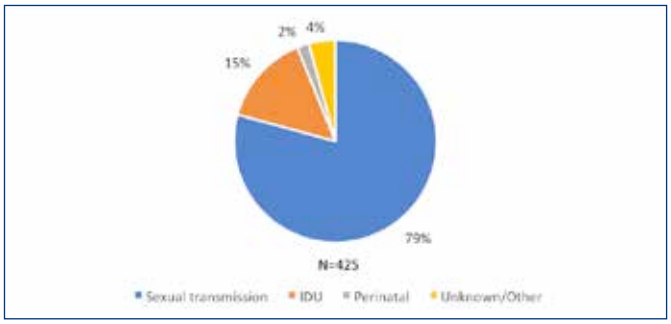


Figure 4. Mode of exposure among women newly diagnosed with HIV in Rhode Island, 2003–2022



*Note: Sexual transmission includes both high-risk and presumed heterosexual transmissions. "High Risk Heterosexual" refers to a female whose primary risk is that she has had sex with a male who is known to have HIV or engage in intravenous drug use. "Presumed heterosexual" refers to a female whose only known risk is sex with a male with unknown HIV status.

Figure 5. Country of birth of women newly diagnosed with HIV in Rhode Island, 2003–2022

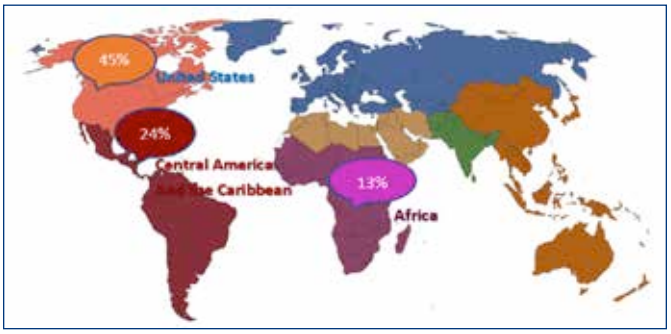
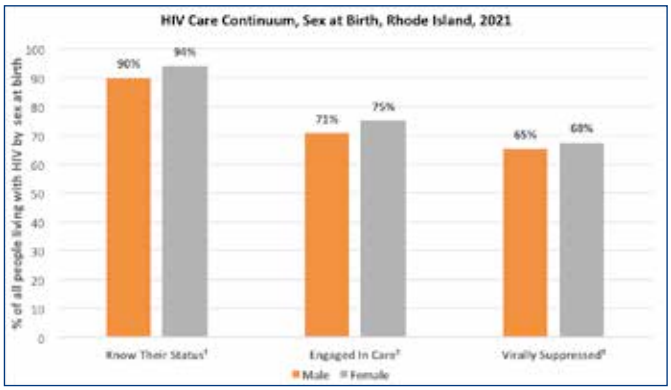


Figure 6. Linkage to care and viral suppression among women living with HIV in Rhode Island, 2021



¹ The number of people diagnosed («know their status») with HIV reflects persons diagnosed through 2020 and alive through the end of 2021 with most recent residence in Rhode Island.

² Receipt of care is defined as at least one care visit during the calendar year (2021).

³ A VL test result of < 200 copies/mL indicates HIV viral suppression. VL test results are from the most recent test during the specified year (2021).

DISCUSSION

Despite the trend in reduced number of new HIV diagnoses in Rhode Island, it is noteworthy that women continue to represent a significant proportion of new HIV diagnoses in the state. Specific population groups continue to be affected, including Black/African American and Hispanic women, who have four times higher incidence rates compared to non-Hispanic White women. The likelihood of a woman being diagnosed with HIV in her lifetime is significantly higher for Black/African American women (1 in 54) and Hispanic/Latino women (1 in 256) than for White non-Hispanic women (1 in 941).[5]

Studies at the national level have indicated higher rates of HIV diagnoses among non–US-born people than among US-born people, both overall and by sex at birth.[6] This is very much in alignment with findings from Rhode Island, where more than 50% of women newly diagnosed with HIV in the last 20 years were born outside of the US. However, as observed nationally, it is unclear to what degree non-US-born people are arriving in the country with HIV infection or acquiring HIV after arrival. Nevertheless, country of birth seems to have important implications for HIV testing. Foreign-born women should be screened at least once for HIV and more frequently if they have ongoing risk factors, which is consistent with the Centers for Disease Control and Prevention (CDC) and US Preventative Services Task Force (USPSTF) Guidelines.

Many social determinants of health present significant barriers to engaging in HIV care and treatment among women, which could include the cost of services, language barriers, stigma, and other barriers. In Rhode Island, however, a consistent effort has been made to employ approaches to improve access to HIV care. These include the Ryan White program, which covers the cost of medical care, including antiretrovirals (ARVs) for people with HIV who can't pay. Clinics who care for PLWH have language and interpreter services available. In addition, staff at RIDOH partner services interview every new patient with an HIV diagnosis to identify sexual and needle-sharing partners and refer patients to needed services. RIDOH also implements a return-to-care program to engage people who may have difficulty engaging in care.

The findings of this study also have important considerations for HIV prevention among women. As mentioned above, routine HIV testing in clinical settings, including pregnant women, is critical. One significant public health intervention in Rhode Island that has proven effective in reducing mother-to-child transmission of HIV is the enactment of HIV testing as part of prenatal care into Rhode Island General Laws in 2009.[7] There have been only two cases of mother-to-child transmission of HIV in the last 10 years in Rhode Island. Primary prevention efforts to reach high priority female populations (i.e., people who use drugs, commercial sex workers, homeless individuals) are traditionally done through harm reduction programs funded by RIDOH. These community-based programs distribute condoms, clean syringes, and early pregnancy test kits, as well as provide counseling/referral on PrEP, social services, and SUD care. Other important HIV-prevention approaches in Rhode Island include condoms and HIV test kits by mail and Testing 1-2-3 for HIV/HCV/STIs testing. For more information about these services, please refer to RIDOH's HIV, Hepatitis C, STD, and Tuberculosis Prevention Resource Guide for Community and Clinical Providers.

This analysis found that even though the number of new HIV infections among women in Rhode Island is falling, addressing the epidemic's impact on women remains of critical importance in ensuring these encouraging trends continue.

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UTPALA BANDY, MD, MPH
INTERIM DIRECTOR, RHODE ISLAND DEPARTMENT OF HEALTH
COMPILED BY ROSEANN GIORGIANNI, DEPUTY STATE REGISTRAR

Rhode Island Monthly Vital Statistics Report
Provisional Occurrence Data from the Division of Vital Records

VITAL EVENTS	REPORTING PERIOD		
	APRIL 2023	12 MONTHS ENDING WITH APRIL 2023	
	Number	Number	Rates
Live Births	864	11,003	10.4*
Deaths	941	10,957	10.3*
Infant Deaths	4	49	4.5#
Neonatal Deaths	3	35	3.2#
Marriages	399	6,985	6.6*
Divorces	178	2,709	2.6*

* Rates per 1,000 estimated population
# Rates per 1,000 live births

Underlying Cause of Death Category	REPORTING PERIOD			
	OCTOBER 2022	12 MONTHS ENDING WITH OCTOBER 2022		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	222	2,420	220.5	3,389.5
Malignant Neoplasms	173	2,173	198.0	4,107.0
Cerebrovascular Disease	56	502	45.7	629.5
Injuries (Accident/Suicide/Homicide)	93	1,072	97.7	14,353.0
COPD	35	442	40.3	400.0

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.
(b) Rates per 100,000 estimated population of 1,097,379 for 2020 (www.census.gov)
(c) Years of Potential Life Lost (YPLL).

NOTE: Totals represent vital events, which occurred in Rhode Island for the reporting periods listed above.
Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

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Thanks to RIMJ's Guest Editors of 2023

This issue marks the completion of 106 years of the *Rhode Island Medical Journal* (RIMJ), which transitioned to an online-only journal in 2013, available at http://rimedj.org.

Although the platform of the Journal has changed to a digital one, its mission remains the same as it has for more than a century – to be the medical journal of record for the state and now regionally, offering diversity of content with a wide variety of article types which have implications for current clinical practice.

Going digital and a LinkOut icon to free articles indexed on PubMed.gov has enhanced its scope exponentially; this year the Journal has reached approximately 58,000 unique viewers worldwide to date.

As RIMJ is about to enter its 107th year, RIMJ's editors thank the guest editors and contributors of this year and over the decades. Without them and the support of its publisher, the Rhode Island Medical Society (RIMS), and the RIMJ Editorial Board, the ongoing success of the Journal for more than a century would not be possible. ❖

APRIL 2023

THE YOUNG ADULT MENTAL HEALTH CRISIS

SAMANTHA R. ROSENTHAL, PhD, MPH
GUEST EDITOR

Rhode Island Young Adult Survey Reveals Mental Health Crisis
SAMANTHA R. ROSENTHAL, PhD, MPH

The Mental Health Consequences of Losing a Loved One to COVID-19
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Brain Injury and Substance Use in Young Adults: The Need for Integrating Care
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Pornography: A Concealed Behavior with Serious Consequences
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Smartphone Addiction and Mental Illness In Rhode Island Young Adults
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MAY 2023

GERIATRIC MEDICINE & CARE

JAMES L. RUDOLPH, MD, SM; MRIGANKA SINGH, MD
GUEST EDITORS

Geriatric Medicine: Treatises on Assessment of Function
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Class II/III Obesity Prevalence in Residents of US Nursing Homes: Cross-sectional Study and Forecasting 2030 with COVID-19 Perspective
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Cancer Genetics: From Then to Now
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A Genetic Revolution: Cancer Genetic Testing and Counseling
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Hereditary Cancer Genes and Related Risks
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Management of Cancer Genetic Testing: A Brief Overview
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Showcasing Innovations and Initiatives in Undergraduate, Graduate Medical Education
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A Challenging Future Ahead for Undergraduate Medical Education
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A Community-engaged Curriculum at Alpert Medical School: Centering Patient Communities in Medical Education
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A History of Child Abuse Pediatrics: Training, Research, and Clinical Diagnosis
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JIE TANG, MD, MPH; GYAN PAREEK, MD
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GYAN PAREEK, MD

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Hyperoxaluria – A Major Metabolic Risk for Kidney Stone Disease
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Dietary Magnesium Intake and Kidney Stone: The National Health and Nutrition Examination Survey 2011–2018
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Diet Interventions for Calcium Kidney Stone Disease
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Renal Imaging in Stone Disease: Which Modality to Choose?
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RIDOH issues Compliance Order to owners of Roger Williams, Fatima hospitals

PROVIDENCE – The Rhode Island Department of Health (RIDOH) issued an Immediate Compliance Order in November, requiring the owners of Roger Williams Medical Center and Our Lady of Fatima Hospital to ensure the continuity of health services and care at the facilities by acting immediately to stabilize the two facilities financially.

This Immediate Compliance Order was issued to the California-based Prospect Medical Holdings and related entities after a thorough, extensive review by RIDOH determined that Prospect's underfunding of the hospitals is impacting operations. For example, in October 2023, at least 19 elective surgeries at the facilities were canceled because the proper equipment and supplies were not available because of non-payment to vendors. These latest issues are part of a pattern of Prospect Medical Holdings engaging in non-compliance and creating delays in making required disclosures of financial information.

The Immediate Compliance Order requires the owners to hire an independent Fiscal Monitor and cover all operating costs of the hospitals, as determined by that Fiscal Monitor. Prospect also must create a "cash on hand" escrow account to ensure the stability of the facilities, and have an independent Operations Monitor on site who will report to RIDOH daily. The Compliance Order includes many additional, stringent requirements in the areas of finance, operations, and oversight.

"The healthcare providers at Roger Williams Medical Center and Our Lady of Fatima Hospital are amongst the best in the state. People receive very high-quality care at these hospitals," said Interim Director of Health **UTPALA BANDY, MD, MPH**. "However, these facilities need more consistent support from their corporate owners. The action we took today will ensure immediate accountability and get the hospitals on sounder footing. This is critical for the state as a whole, and for the communities these facilities serve as safety net hospitals."

While Rhode Island law requires hospitals to maintain local governing bodies, much of the financial decision-making for these two hospitals happens in California. Prospect Medical Holdings sweeps all patient care revenue from Roger Williams and Fatima every day and then returns an operating allowance back to the hospitals once a week. The amounts of these allowances vary and are determined by Prospect Medical Holdings. The amounts of these allowances are inadequate to pay vendors in a timely manner, leading to interruptions in services.

A RIDOH investigation revealed that, as of October 24, more than 250 of the hospitals' approximately 830 vendors were operating with the hospitals on a "cash on demand" basis. This means they only deliver supplies if they are paid at the time of delivery. This is generally reserved for payors with a history of non-payment. The average time it takes the hospitals to pay bills ("days payable outstanding," or DPO), was in excess of the 90-day limit set when the acquisition of the facilities was approved in 2021.

Unpaid vendors have included suppliers of hip joints, catheters, endoscopes, and eye lenses. The procedures that were canceled included endoscopies, eye surgeries, and a spinal surgery. There is no indication that issues with vendors ever prevented emergency procedures from being performed.

Among other requirements, the Immediate Compliance Order requires Prospect Medical Holdings to:

- Retain a third-party Fiscal Monitor for six months. This person will immediately determine the average monthly operational expenses for the hospitals and create a plan to ensure that the DPO for all vendors is less than 90 days. The Fiscal Monitor will report to RIDOH weekly on the progress of vendor accounts and the general fiscal standing of the hospitals.
- Retain a third-party Operations Monitor for six months. This person will be charged with doing an assessment of the extent to which vendor non-payment has previously impacted patient care and resulted in canceled surgeries. This person will report to RIDOH daily on census numbers at the hospitals, as well as on staffing and any procedure cancellations.
- Provide funding over and above the weekly allowances to the hospitals to cover all operational expenses.
- Create and fund a separate "cash on hand" escrow account equaling 30 days of average daily operational expenses for the sole use of operations at the hospitals. This account will be maintained by a RIDOH-approved escrow agent, located in Rhode Island.

In addition to these requirements, the Immediate Compliance Order states that RIDOH reserves the right to order a cease and desist on the daily sweeping of patient care revenue from the hospitals to the parent company in California. ❖

State House Dome shines a green light on injury prevention

PROVIDENCE – In support of National Injury Prevention Day on November 18, Rhode Island joined other states around the country in "shining a light" on efforts to stop injuries and violence — the number one cause of death and hospitalization nationally for people ages 1 to 44.

"All of us, at every stage of life, can act to prevent injuries and violence. For some, injury prevention means safe sleep practices, putting children in car seats, fastening seatbelts, and wearing bike helmets. For some other folks, it may mean fall prevention strategies or safe firearm storage," said **UTPALA BANDY, MD, MPH**, Interim Director of the Rhode Island Department of Health (RIDOH). "We can all take steps to make our homes and communities safer places to live."

RIDOH's Violence and Injury Prevention Program and partners are working to address all forms of injury and violence. Examples of projects include fall prevention initiatives; suicide prevention campaigns aimed at youth and Veterans; sexual violence prevention; and transportation safety. Earlier this year, Rhode Island was awarded $915,000 in federal funds from the Centers for Disease Control and Prevention (CDC) to develop a coordinated, data-driven suicide prevention program for higher-risk populations.

Falls remain the most common injury sending Rhode Islanders to the emergency department (ED). Falls are also common causes of inpatient hospital admissions.

"Older adults can reduce the risk of falls by staying physically active, removing tripping hazards at home, keeping living spaces well lit, and using grab bars and railings," said **TOSIN OJUGBELE, MD, MPH**, the Medical Director of RIDOH's Division of Community, Health, and Equity.

Data on injuries

- Data from 2016 to 2022 indicate that while annual ED visits for injuries have decreased from nearly 87,000 to nearly 63,000, disparities persist. Black non-Hispanic people and Hispanic people continue to have higher rates of injury-related ED visits compared to White people.
- Common injury-related causes of ED visits after falls, include being struck by an object, motor vehicle-related injuries, assaults, and traumatic brain injury. Rhode Island data from 2022 show that females have higher fall rates compared to males. However, males have higher rates of being struck by an object, motor vehicle/traffic-related injuries, and assault.
- While Rhode Island has one of the lowest rates of suicide deaths per 100,000 population in the country, suicide is the second leading cause of death for those ages 10-34 and the eleventh leading cause of death among all Rhode Island residents.

Organized by the Injury Free Coalition for Kids and its partners, the fourth annual National Injury Prevention Day aims to raise awareness about the effects of injury and violence on the public's health, as well as actions needed to build safer communities. Partners include Safe Kids Worldwide, Safe States Alliance, the American Trauma Society, the American Academy of Pediatrics, Be SMART— a program of Everytown for Gun Safety Support Fund, the Society for Advancement of Violence and Injury Research, the Trauma Center Association of America, and JPMA Cares.

For more information and resources on violence and injury prevention, visit health.ri.gov/violence. ❖

New report reveals RI leads nation in five-year survival, overall treatment rates for lung cancer

PROVIDENCE – The 2023 "State of Lung Cancer" report reveals that Rhode Island ranks #1 in the nation for five-year survival and treatment rates for lung cancer. The American Lung Association's 6th annual report, released in mid-November, highlights the toll of lung cancer in Rhode Island and around the country, and examines key indicators including new cases, survival, early diagnosis, surgical treatment, lack of treatment and screening rates.

In Rhode Island, data showed that the number of new lung cancer cases declined, while the rate of early detection and five-year survival rates increased. Nationally, the "State of Lung Cancer" report found that lung cancer survival rates are improving for everyone, including people of color. In fact, the five-year lung cancer survival rate for people of color has increased by 17% in the last two years, helping close the health disparity gap.

"Thankfully, in Rhode Island, the lung cancer survival rate has improved because of increased awareness, improved access to healthcare and cutting-edge research into new treatments for the disease," said **DANIEL FITZGERALD**, director of advocacy at the American Lung Association. "However, lung cancer is still the leading cause of cancer deaths here in the Ocean State and across the nation, and our recent report makes it clear that we have more work to do to reduce the burden of lung cancer and increase screening rates for those at risk."

The report found that Rhode Island ranked:

- 1 in the nation for survival at 33.3%. The national rate of people alive five years after a lung cancer diagnosis is 26.6%.
- 1 in the nation for lack of treatment at 13.2%. Nationally, 20.6% of cases receive no treatment.
- 3 in the nation for early diagnosis at 31.9%. Nationally, only 26.6% of cases are diagnosed at an early stage when the survival rate is much higher.
- 3 in the nation for surgery at 26.9%. Lung cancer can often be treated with surgery if it is diagnosed at an early stage and has not spread. Nationally, 20.8% of cases underwent surgery.
- 6 in the nation for lung cancer screening at 9.1%. Lung cancer screening with annual low-dose CT scans for those at high risk can reduce the lung cancer death rate by up to 20%. Nationally, only 4.5% of those at high risk were screened.
- 41 in the nation for rate of new lung cancer cases at 64.4 per 100,000 The national rate is 54.6 per 100,000. ❖

Appointments

Linda L. Brown, MD, named Chair of Emergency Medicine and Physician-in-Chief at Lifespan, Brown

PROVIDENCE – Lifespan and Brown University recently announced the appointment of **LINDA L. BROWN, MD, MSCE**, as the Chair of the Department of Emergency Medicine and physician-in-chief of emergency medicine for Rhode Island Hospital and its Hasbro Children's Hospital, The Miriam Hospital, and Newport Hospital, which became effective November 1. Dr. Brown will also assume the role of president of Brown Emergency Medicine, a faculty practice group that is a member of Brown Physicians, Inc. In addition, she will hold the Frances Weeden Gibson-Edward A. Iannuccilli, MD, Professorship in Emergency Medicine.

Dr. Brown, a professor of emergency medicine and pediatrics, previously served as the Vice Chair of pediatric emergency medicine for Brown Emergency Medicine and as the Director of the Lifespan Medical Simulation Center. Since December 2022, she has been serving as the interim chair of Emergency Medicine and physician-in-chief.

"I am thrilled to have one of our own former trainees take the helm of the Department of Emergency Medicine, which plays such an important role not only in our academic medical center but in the health care of Rhode Islanders," said Lifespan President and CEO **JOHN FERNANDEZ**. "Dr. Brown is widely recognized as a national leader in pediatric emergency medicine, and is a highly accomplished researcher on pediatric resuscitation and pediatric disaster triage. She is thoroughly qualified and has earned this well-deserved appointment."

"Among Dr. Brown's many qualities is a deep commitment to medical education and mentoring," said Brown University Senior Vice President for Health Affairs and Dean of Medicine and Biological Sciences **MUKESH K. JAIN, MD**. "She is an outstanding educator and leader for our medical students and residents."

Throughout her tenure at The Warren Alpert Medical School and Lifespan, Dr. Brown has received numerous accolades, including the Brian J. Zink, MD Outstanding Leadership in Emergency Medicine Award, the Brown EM Foundation Award, the Libby Nestor, MD Outstanding Mentor Award, the Jacek Franaszek Exemplary Educator Award, and the Barnet Fain Quality Award, among others. Nationally, she has been honored with the Dr. Marianne Gausche-Hill Award for Teaching Mentorship and the Society for Academic Emergency Medicine Simulation Academy Distinguished Educator Award.

"I am honored to lead a department dedicated to providing the highest quality, compassionate, and equitable emergency care to the patients in our communities," said Dr. Brown. "I am eager to support and expand the strong tripartite mission of the Department of Emergency Medicine, with a focus on innovation in education and research, diversity and inclusion, community engagement, and improving the well-being of all physicians and providers."

Dr. Brown earned her undergraduate degree in biology from Colby College in 1992 and her medical degree from Pennsylvania State College of Medicine in 1997. She completed her residency in pediatrics, including a year as chief resident, at Hasbro Children's Hospital/Brown University. Following this, she pursued a fellowship in pediatric emergency medicine at the Children's Hospital of Philadelphia in 2004, during which time she also obtained a Master of Science in Clinical Epidemiology from the University of Pennsylvania. Dr. Brown returned to Brown and Hasbro Children's Hospital in 2007 after working as an attending physician at Yale-New Haven Children's Hospital and an assistant professor of pediatrics and emergency medicine at Yale School of Medicine. ❖

Recognition

Sanjay Mishra, PhD, recognized by National Academies of Science, Engineering and Medicine

PROVIDENCE – **SANJAY MISHRA, MS, PhD**, Research Program Manager at the Lifespan Cancer Institute, has received the Eric and Wendy Schmidt Award for Excellence in Science Communications from the National Academies of Science, Engineering and Medicine in partnership with Schmidt Futures. This prestigious award recognizes science journalists, research scientists, and science communicators who have developed creative, original work to communicate issues and advances in science, engineering, and medicine to the public.

The National Academies gave 24 Eric and Wendy Schmidt Awards in 2023: nine for science communication by research scientists, nine for science journalists, and six for science communicators. Mishra was honored in the "Research Scientist: Early Career" category.

Mishra is the coordinator of the Brown University/Lifespan Center for Clinical Cancer Informatics and Data Science (CCIDS) where he promotes research, operation, and education of clinical cancer informatics. He also serves as a coordinator for the COVID-19 and Cancer Consortium (CCC19), where he collects data about patients with cancer who have been diagnosed with COVID-19.

In collaboration with hundreds of international researchers, Mishra's research has helped understand the effect of COVID-19 on people with cancer; and has highlighted the racial disparities in healthcare outcomes and access to treatments. Previously, Mishra worked on developing vaccine candidates against Zika and Dengue; and uncovered the evolutionarily conserved role of stress-responding proteins in aging and preventing diseases.

"This award assures me that my peers value my efforts to share the joy of scientific discoveries. This recognition is also very motivational because growing up, English was not my first language. This award reminds me that institutional support exists to popularize science, although academic research is often more celebrated,"said Dr. Mishra.

The winners will be honored during an invitation-only workshop and recognition event on Jan. 11 and 12, 2024, in Washington, D.C. ❖

Newsweek names RIH, Miriam, Newport hospitals among America's Best-In-State

PROVIDENCE – Newsweek has named Rhode Island Hospital, The Miriam Hospital, and Newport Hospital to their 2024 America's Best-In-State Hospitals list. Rhode Island Hospital was ranked first in the state with a score of 81.39%, The Miriam Hospital was ranked third with a score of 79.89%, and Newport Hospital was ranked fourth with a score of 78.18%.

The America's Best-In-State Hospitals 2024 ranking was created to identify the top hospitals at the state level. Hospitals from all US states were eligible for the ranking and included in the nationwide survey. The 25 states with the most hospitals according to the Center for Medicaid and Medicare Services (CMS) were surveyed individually.

Four data sources were used for the evaluation:

- Nationwide online survey:
  Over 10,000 medical professionals (doctors, hospital managers, and healthcare workers) were asked to recommend the best hospitals (in and out of state) based on their expertise.
- Quality Metrics Data:
  Data from Medicare and Medicare Services available for Mortality, Safety, Readmission, Experience, Timely & Effective Care was considered.
- Patient Experience:
  Cleanliness of the hospitals and quietness, communication of the nurses/doctors and staff responsiveness, care transition, medicine communication, and discharge information.
- PROMS Implementation survey:
  To account for the increasing importance of Patient Reported Outcome Measures (PROMs). ❖

Lifespan's nursing assistant training school graduates first class

PROVIDENCE – Lifespan's nursing assistant school graduated its first class on November 17th. The school was licensed in May 2023 by the Rhode Island Department of Health as an approved training program for nursing assistants. Sixteen students graduated, nearly half (seven) from Providence.

All 16 graduates will stay on and work as nursing assistants at Lifespan hospitals or facilities for at least a year. Training was provided at no cost to students, and all expenses were paid including tuition, textbooks, supplies, exam fees and any other associated costs such as childcare and transportation. ❖

Sara Kavanagh is one of 16 graduates of Lifespan's first nursing assistant program. [LIFESPAN]

Places

University Gastroenterology introduces Velacur to help combat fatty liver disease

PROVIDENCE – In an effort to combat fatty liver disease – a condition that affects one in every three adults in the United States – University Gastroenterology (UGI) has added a new liver assessment tool to its arsenal. Velacurä is an ultrasound-based imaging tool capable of helping quantify the amount of fat and fibrosis in the liver by measuring the liver's stiffness and attenuation.

By 2030, it is estimated 100 million Americans will be affected by this condition.

The Liver Center at UGI

The Liver Center at University Gastroenterology was the first in Rhode Island to introduce noninvasive liver imaging technology seven years ago when it implemented Fibroscan testing. The practice is now excited to be the first center in Rhode Island to offer the Velacur imaging system, reinforcing its commitment to providing cutting-edge care.

In contrast with existing diagnostic methods such as liver biopsy and MRI technologies, which are invasive and costly, Fibroscans and Velacur scans are a quick, painless, non-invasive alternative that can be conducted in the physician's office with immediate results.

DR. TOM SEPE at University Gastroenterology commented on the introduction of Velacur. "Fatty liver disease is a silent but rapidly growing concern, and early detection is the key to combating its devastating effects. With Velacur now available to patients in Portsmouth and East Greenwich and with Fibroscans still being performed in Providence, we now have tools throughout the state allowing us to reach more patients and provide both faster diagnosis and more effective management of this condition. Patients will benefit tremendously from the increased access to these non-invasive tests." ❖

From left to right: **Sarah DelSesto**, Project Sweet Peas; **Laurie Hoffman, MD**, NICU Associate Medical Director; **Meghan Murray**, March of Dimes NICU Family Support Program Coordinator, Women & Infants Hospital; **Janie Carlisle**, Cigna Healthcare; **Victoria Gomez**, NICU mom; **Jack Tanner, BSN, RN**, Nurse Director of the NICU and Respiratory Care; **Julie Traynor** Senior Manager, Cigna Healthcare, A Common Thread, National Co-Lead; **Sophie Pickering**, NICU mom; **Megan Feeley-Couns**, NICU mom; **Ailyn Bohan**, Assistant Nurse Manager NICU; **Robert Cormier**, US President and CEO, Sentec; **Michelle Gagne**, Assistant Nurse Manager NICU; **Brittany Wishart**, Director of Marketing, Sentec; **Chuck Smith**, Digital Marketing Manager, Sentec; **Sofia Billeri**, Assistant Nurse Manager NICU. [CARE NEW ENGLAND]

W&I NICU receives holiday donations from Sentec, Cigna

PROVIDENCE – Women & Infants Hospital is giving thanks this holiday to Sentec and Cigna Healthcare who are helping families in the Neonatal Intensive Care Unit (NICU) celebrate Thanksgiving with the generous donation of baby caps and meals.

"It is hard to have a baby in the NICU, especially during the holidays. Something as simple as the gift of a cozy hat and a special meal prepared just for them can make all the difference for our families," **JACK TANNER, BSN, RN**, Nurse Director of the NICU and Respiratory Care at Women & Infants Hospital.

A group of Cigna Healthcare employees started A Common Thread as a community service project to knit or crochet baby caps. [CARE NEW ENGLAND]

Sentec provided Thanksgiving meals, prepared by Russ Morin Fine Catering and Events, along with desserts for the NICU staff working on Thanksgiving. Sentec is headquartered in Lincoln and considers Women & Infants their "hometown hospital". They hope these delicious meals give the families a taste of home on this special day as well as on Christmas.

A group of Cigna Healthcare employees started A Common Thread as a community service project to knit or crochet baby caps to provide warmth for babies facing serious health challenges. Since the group started, more than 25,000 baby hats have been donated to NICUs throughout the country, including 700 caps being donated to the Women & Infants Hospital NICU. ❖