IJKD KIDNEY DISEASES

Review

Kidney Calculi
Pathophysiology and as a Systemic Disorder

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Keywords. nephrolithiasis, obstructive uropathy, pathphysiology

The pathophysiology of urinary stone formation is complex, involving a combination of metabolic, genetic, and environmental factors. Over the past decades, remarkable advances have been emerged in the understanding of the pathogenesis, diagnosis, and treatment of calcium kidney calculi. For this review, both original and review articles were found via PubMed search on pathophysiology, diagnosis, and management of urinary calculi. These resources were integrated with the authors' knowledge of the field. Nephrolithiasis is suggested to be associated with systemic disorders, including chronic kidney insufficiency, hematologic malignancies, endocrine disorders, autoimmune diseases, inflammatory bowel diseases, bone loss and fractures, hypertension, type 2 diabetes mellitus, metabolic syndrome, and vascular diseases like coronary heart diseases and most recently ischemic strokes. This is changing the perspective of nephrolithiasis from an isolated disorder to a systemic disease that justifies further research in understanding the underlying mechanisms and elaborating diagnostic-therapeutic options.

IJKD 2017;11:180-91
www.ijkd.org

INTRODUCTION

Kidney calculus has become pandemic.[1] The prevalence of kidney calculi has doubled during the past 3 decades in the United States.[1] According to the National Health and Nutrition Examination Survey (NHANES) cross-sectional data analysis from 2007 to 2010, kidney calculi affected 8.8% of the United States population. This is while in 1994, the NHANES reported that the prevalence of calculus disease was 5.2%. In the last 25 years the male-female ratio has also been subjected to a dramatic change from 3:1 to less than 2:1.[2] The recent NHANES data also showed that the prevalence of calculus disease was highest among "non-Hispanic white" individuals (10.3%), while non-Hispanic black individuals were least affected (4.3%). The rise in the prevalence of kidney calculi was not limited to one specific demographic cohort. This surge in prevalence was noted in both sexes all ages and ethnic groups. Diet and lifestyle factors likely play an important role in changing the epidemiology of nephrolithiasis.[3]

In recent years, the association of kidney calculi with systemic disorders such as chronic kidney disease, osteopenia or osteoporosis, hypertension, type 2 diabetes mellitus (DM), metabolic syndrome, coronary artery disease, and most recently, ischemic stroke has changed the view and approach towards it.[4-7]

Nephrolithiasis is a chronic illness. Without any medical treatment, the recurrence rate is more than 50% over 10 years.[8] The annual expenditure for nephrolithiasis exceeds $5 billion in the United States, attesting that the economic and social burden of nephrolithiasis cannot be ignored.[9]

COMPOSITION OF CALCULI

Approximately, 75% of urinary calculi are calcium based, 80% of which are calcium oxalate, with the remaining being calcium phosphate.[3,10] Pure uric acid calculi comprise 5% to 10%; struvite-infection-related calculi, 10% to 15%; cystine calculi, < 1%;

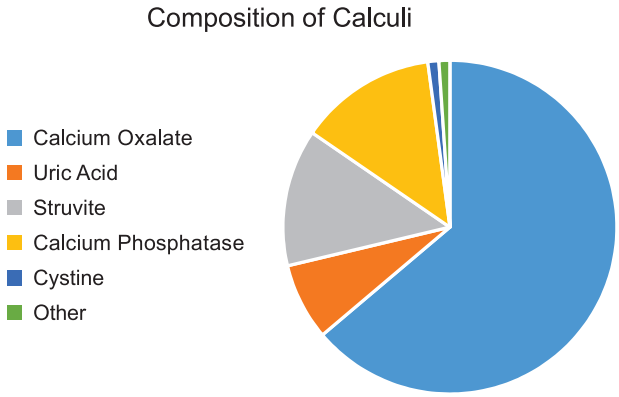

Figure 1. Prevalence of urinary calculi composition.

and other types of calculi including indinavir, xantine, and triamterene contribute to < 1% of all calculi (Figure 1).[11]

PATHOPHYSIOLOGY OF CALCIUM CALCULI

The pathophysiology of calcium calculi is complex and includes low urine volume, hypercalciuria, hyperuricosuria, hyperoxaluria, hypocitraturia, and abnormalities in urine pH,[12] which lead to supersaturation of urine, formation of crystals, and their subsequent aggregation into urinary calculi.[13] In this review, we focus on the recent advances in the pathophysiology of calcium stone formers, and the systemic diseases that are more commonly associated with nephrolithiasis.

HYPERCALCIURIA

Definition and Epidemiology

Hypercalciuria is defined as a 24-hour urine calcium excretion greater than 250 mg/d (> 6.24 mmol/d) in women and greater than 300 mg/d (> 7.49 mmol/d) in men. Between 30% and 60% of adults with nephrolithiasis have hypercalciuria.[14] Calcium homeostasis involves an interaction between mineral handling by intestine, kidney and bone, under the influence of parathyroid hormone (PTH) and 1,25-dihydroxyvatamine D (Figure 2).[10]

Secondary causes of hypercalciuria include primary hyperparathyroidism, chronic acidemia, granulomatous diseases, malignancy-associated hypercalcemia (bone metastasis and multiple myeloma), Paget disease, prolonged immobility, and medications side effect (loop diuretics, acetazolamide, vitamin D, topiramate, and orlistat),

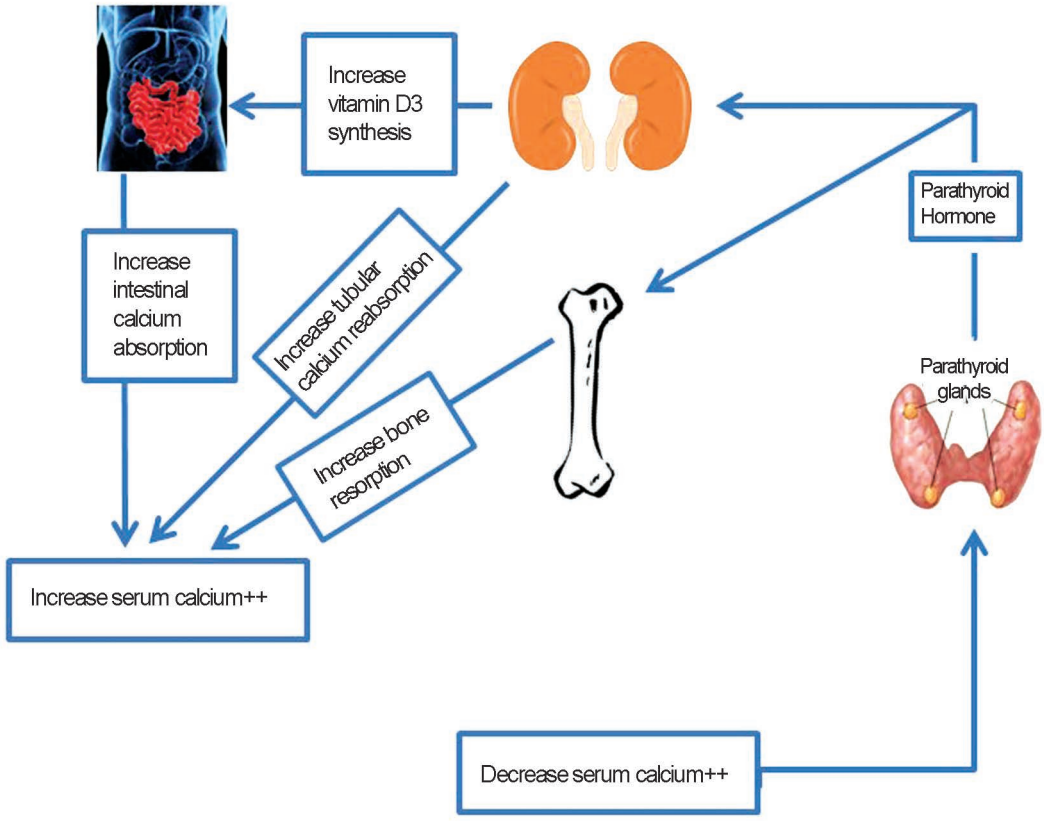

Figure 2. Calcium homeostasis.

and calcium alkali syndrome. However, in the majority (> 90%) of hypercalciuric stone formers, we do not find any of these disorders, and thus the term *idiopathic hypercalciuria* has been adopted for them.[14-16]

Etiologies of Idiopathic Hypercalciuria

Patients with idiopathic hypercalciuria have been categorized according to their primary site of dysfunction namely intestine (absorptive hypercalciuria), kidney (renal hyperphosphaturia or renal leak hypercalciuria), and bone (PTH-independent resorptive hypercalciuria).[10] More than 1 defect may be present in an individual, and they all predispose to bone loss and bone fractures.[7,17,18] In patients with idiopathic hypercalciuria, significant correlations were found between monocyte interleukin-1 (IL-1), hydroxyproline (a marker of bone resorption), quantitative vertebral bone mineral density, and urinary calcium excretion,[19] attesting to a close relationship between these entities. The different pathophysiologies involved in idiopathic hypercalciuria are shown in Table 1.

Absorptive Hypercalciuria

Increased intestinal absorption is present in almost all patients with idiopathic hypercalciuria.[20,21] The hallmark of patients with absorptive hypercalciuria (AH) is low fasting urinary calcium. Three variants of AH have been recognized. In AH type I (AH-I) that is the more severe variant; fasting urinary calcium-creatinine ratio is high (> 0.11 mg/mg) and urinary calcium excretion remains elevated (> 200 mg/d) despite severe dietary restriction (< 400 mg calcium and < 100 mEq sodium per day over 1-week period) with a low to normal serum PTH level. In patients with AH-II, urinary calcium normalizes on a calcium-restricted diet.[12,22] In AH-III, the primary defect is in the proximal tubule reabsorption of filtered phosphate, and thus, it will be discussed under renal hypercalciuria.

The possible mechanism behind AH-I and AH-II is an overexpression of vitamin D-responsive genes in response to small levels of the active form of vitamin D (1,25-dihydroxyvitamin D3),[23] with a consequent enhancement in transcription of proteins involved in intestinal calcium absorption, such as epithelial calcium channels (transient receptor potential cation channel 6 [TRPV6] in gut), calbindins, and calcium-sensing receptor. Increased levels of calcium-sensing receptor protein and mRNA have also been found in the kidneys of genetic hypercalciuric stone-forming rats compared to control rats being fed with the same diet.[24]

An important clinical point is that there is no evidence supporting a role for dietary calcium restriction in reducing urinary stone formation, and this practice should be avoided unless the calcium intake exceeds 2 g/d. This was shown in a randomized controlled trial assigned men with hypercalciuria to follow either a diet low in calcium (400 mg/d) and oxalate or a diet higher in calcium (1200 mg) with restricted intake of oxalate, protein, and salt.[25] After 5 years of follow-up, the latter group had a 51% lower rate of calculus recurrence than those following a low-calcium diet. Moreover, a calcium-restricted diet has been shown to predispose such patients to bone loss and fractures.[18]

1,25-Dihydroxyvitamin D and Hypercalciuria

Despite earlier reports of high-circulating 1,25-dihydroxyvitamin D in hypercalciuric stone formers,[26,27] several studies have shown that urine calcium concentration or chance of stone formation is independent of serum

Table 1. Different Categories of Idiopathic Hypercalciuria

Characteristic	Type of Idiopathic Hypercalciuria		
	Absorptive	Resorptive	Renal leak
Mechanism	Intestinal gene and protein overexpression in response to 1,25-dihyroxyvitamin D	Monocyte interleukin-1 hyperactivity resulting in bone resorption	Renal tubule calcium or phosphate leak (transporter defect: NPT2a, NPT2c, ? NHERF1, ?TRVP5)
Fasting urine calcium	Low	Elevated	Elevated
Parathyroid hormone	Normal/Low	Normal	Elevated
1,25-dihyroxyvitamin D	Normal	Normal	Elevated
Serum calcium	Normal	Normal	Normal
Other	Normal interleukin-1 activity	High urinary hydroxyproline	Calcium phosphate calculus in renal phosphate leak

concentration of vitamin D.[28-30] As mentioned above, enterocyte gene hypersensitivity to small levels of 1,25-dihydroxyvitamin D seems to be the underlying mechanism of absorptive hypercalciuria.[23,24]

25-hydroxyvitamin D and Hypercalciuria

A challenging caveat here is that many physicians are hesitant to supplement vitamin D in patients with vitamin D deficiency and hypercalciuric urinary calculus. In 2012, 29 patients with a history of nephrolithiasis and 25-hydroxyvitamin D deficiency, and urinary calcium excretion between 150 mg/d and 400 mg/d were recruited by Leaf and colleagues.[31] The 24-hour urinary calcium excretion was measured after 8 weeks of ergocalciferol therapy (50000 IU/wk).[31] Although remarkable increase in vitamin D level was observed in all patients, the mean 24-hour urinary calcium excretion did not change (257 ± 54 mg/d and 255 ± 88 mg/d at baseline and at follow-up, respectively, P= .90).[31] However, 11 participants showed 20 mg/d and greater increase in urinary calcium excretion. These participants also had an increase in urine sodium excretion, which likely reflected dietary variability.[31]

In 2013, a cross-sectional analysis of 25-hydroxyvitamin D serum level in 16286 NHANES III participants showed no difference between stone formers and non-stone formers (P = 0.6). Also, higher serum 25-hydroxyvitamin D concentrations were not associated with increased odds ratio for previous kidney calculi (odds ratio = 0.99) after adjustment for age, sex, race, history of hypertension, DM, body mass index, diuretic use, and serum calcium level.[32]

Furthermore, after dividing serum 25-hydroxyvitamin D concentrations into quartiles, or into groups using higher cutoffs (eg, 40 ng/mL and 50 ng/mL), there was still no significant difference in stone formation rate among different groups. The results of this study suggested that stone formers do not have an increased vitamin D store in the form of serum 25-hydroxyvitamin D concentration, and that higher serum concentration of 25-hydroxyvitamin D dose not appear to increase the risk of kidney stone disease.[32]

Considering the abovementioned findings, and the hypothesis of vitamin D gene overexpression in response to small amount of 1,25-dihydroxyvitamin D (active from of vitamin D), we recommend replacing vitamin D in calcium stone formers who have low levels of serum 25-hydroxyvitamin D in order to prevent the complications of vitamin D deficiency and bone loss.

Renal Hypercalciuria

It is suggested that kidneys are primarily responsible for hypercalciuria in two different ways of renal calcium leak and renal phosphate leak. It is estimated that 2% to 3% of idiopathic hypercalciuria is primarily due to renal calcium loss (also known as renal calcium leak).[33,34] Defective calcium reabsorption in proximal tubule, with compensatory elevation in serum PTH and calcitriol,[14,33] leads to an increase in calcium absorption from gut or mobilization from bone.[10] The underlying culprit for this subgroup of renal hypercalciuria is not well understood, but according to 2 studies, conducted by Sakhaee and colleagues and Sutton and colleagues, using a single dose of hydrochlorothiazide in calcium stone formers have linked the defect in proximal renal tubule.[35,36]

Renal phosphate leak (also known as AH III) is another underlying mechanism behind renal hypercalcuria. A defect in the proximal tubule leads to renal phosphate leakage with compensatory increase in PTH and calcitriol, which subsequently increases the absorption of calcium from the gut.[20] Renal phosphate leak is different from distal renal tubular acidosis, where hypocitraturia is responsible for calcium phosphate stone formation.[37] The mutations responsible for renal phosphate leak hypercalciuria are not well established. Mutations in sodium phosphate cotransporters, NPT-2a and NPT-2c, that are located on the apical membrane of the proximal convoluted tubules and are responsible for reabsorption of 80% of the filtered phosphate have been found in patients with hyperphosphaturia.[38,39] In such patients, low serum phosphate stimulates synthesis of 1,25-dihydroxyvitamin D, which increases the intestinal calcium and phosphate absorption that results in hypercalciuria.[40-42] The combination of hyperphosphaturia and hypercalciuria favors the formation of calcium phosphate calculi in this group.[43]

Another possible defect could be located in TRPV5, which regulates calcium transport in the distal tubule of nephron. It is closely related to the TRPV6, found in the gut,[44] which was mentioned in absorptive hypercalciuria. Like NPT-2a, TRPV5

is also controlled by the PTH-vitamin D axis, but further research is needed in order to establish a possible relationship between renal phosphate leak and this channel.[10]

Another possible mutation that needs more research in human subjects is sodium-hydrogen exchanger regulatory factor 1 (NHERF1), which induces alteration on NPT-2a function.[45,46] Targeted deletion of this gene in animal models has increased the excretion of phosphate, calcium, and uric acid in renal papilla, making them prone to calcium and uric acid calculi formation.[47]

Parathyroid Hormone-independent Resorptive Hypercalciuria

Patients with resorptive hypercalciuria have high fasting urine calcium and marked osteoporosis.[19] Monocyte-mediated IL-1 has been demonstrated to be involved in the pathophysiology of bone resorption in postmenopausal women.[48] Moreover, in patients with resorptive idiopathic hypercalciuria, it was shown that their monocytes express more IL-1 ($\alpha + \beta$) activity compared to patients with AH or nonhypercalciuric stone former controls.[19] These patients also demonstrated a higher excretion of hydroxyproline (a marker of bone turnover) in their urine, as compared to patients with AH or non-hypercalciuric stone former controls. Blood levels of osteocalcin and PTH were similar in the three groups.[19] Significant correlations were found between monocytes IL-1 activity and urinary hydroxyproline excretion, vertebral bone mineral density, and urinary calcium excretion.[18]

URINARY CALCULI AS A SYSTEMIC DISORDERS

A change in Perspective

In 2008, Sakhaee suggested the theory of systemic nature of nephrolithiasis. Before that, nephrolithiasis was often seen as an isolated benign disorder.[5]

In recent years the association of nephrolithiasis with systemic disorders such as chronic kidney insufficiency, malignancies, endocrine disorders, inflammatory bowel diseases, bone loss and fractures, hypertension, type 2 DM, metabolic syndrome, and vascular diseases like coronary heart disease and most recently ischemic strokes, have emerged. This would change the perspective toward this disorder and justifies a more comprehensive, multi-systemic investigation.[4-7]

Urinary Calculi and Metabolic Syndrome

Metabolic syndrome is characterized by a combination of insulin resistance, DM, obesity, hypertension, and hypertriglyceridemia.[49] A large prospective study on 250 000 patients demonstrated a relative risk (RR) of 1.44 in the incidence of urinary calculus over a course of 46 years' follow-up in men who weighted over 100 kg compared to those with a mean weight of 68.2 kg ($P = .002$). The increase was even more significant in female subjects (RR, 1.89 and 1.92 for older and younger women, respectively).[50,51]

The association of obesity, metabolic syndrome and insulin resistance with hyperuricemia, hyperuricosuria, and uric acid calculi is well established. Uric acid calculi constituted 34% of the calculi in patients with DM compared to 6% in stone-formers without DM.[52] A higher prevalence of uric acid calculi has also been observed among obese people.[51,53,54] A low urine pH -independent of dietary intake, and defective renal buffering (ammoniagenesis) seems to be involved in the pathophysiology of uric acid calculi in patients with MS.[55]

In 2012, Sakhaee and colleagues conducted a retrospective analysis on the relationship of metabolic syndrome features (from zero to 4) and the risk of calcium stone formation, by measuring urine calcium and supersaturation index of calcium oxalate.[56] The results demonstrated that in subjects without a history of urinary calculus, urine calcium, and supersaturation of calcium oxalate were significantly increased as the numbers of metabolic syndrome features added up (from zero to 4). However, in subjects who had a history of calcium calculi, the risk of calcium oxalate precipitation was much higher overall but was not independently associated with the number of metabolic syndrome features.[56]

Obesity and excess salt intake in patients with metabolic syndrome is associated with overproduction of reactive oxygen species (ROS) and oxidative stress. Oxidative stress has been proposed in the development of salt-sensitive hypertension, insulin-resistant DM, atherosclerosis, and myocardial infarction.[57]

There is increasing evidence that ROS are also produced during idiopathic calcium oxalate renal stone formation. The production of ROS during interaction between calcium oxalate and calcium

phosphate crystals with renal epithelial cells was observed in both tissue culture and animal models. Evidence of oxidative stress in the kidneys of stone formers was also observed in clinical studies.[58]

Aside from ROS, hypocitraturia associated with defective renal acid excretion and insulin resistance, and increased urinary uric acid and oxalate excretion have been suggested as the underlying cause of calcium stone formation in patients with metabolic syndrome.[50]

Urinary Calculi and Coronary Heart Disease

In 2004, Stoller and colleagues challenged the traditional hypothesis of urine supersaturation as a cause of stone formation in favor of a vascular etiology. The authors hypothesized that the site of the initial lesion may be the vascular bed at the tip of the renal papilla, where vascular injury may give rise to calcification, which in turn may grow and erode through the papillary epithelium and become a nidus for stone formation.[28] However, the lack of heart disease association with urinary calculi in men does not support this hypothesis.[29,59]

In 2012 Khan and coworkers found that composition of atherosclerotic plaques is identical to the subepithelial calcification of the renal papilla (Randall plaque) that serve as the nidus of the stone formation. In addition, the deficiency of pyrophosphates (calcification inhibitor) both in blood and urine could explain the link between coronary heart disease and kidney stone formation and envision a possible therapy that benefits both conditions.[58,60,61]

After multivariable analysis for coronary heart disease risk factors, a history of kidney calculus disease was independently associated with coronary heart disease.[62-65] These findings suggest that calcium deposition in papillary subepithelial interstitium probably has a vascular pathogenesis similar to calcium precipitation in the coronary arteries.

The result of a meta-analysis by Cheungpasitporn and coworkers in 2014 demonstrated a significant increased risk of coronary heart disease in women with prior urinary calculi (RR, 1.43), whereas the association was not significant in men (RR, 1.14). This finding suggests that a history of kidney calculus should be considered as a risk factor for coronary heart disease in women, and be considered in clinical decision making.[66]

Interestingly, the prevalence of urinary calculi is higher in men than in women (10.6% versus 7.1%, respectively),[3] and coronary heart disease is also more common in men (7.8% versus 4.6%).[59,67] Therefore, it is surprising that Cheungpasitporn and coworkers found that women with kidney calculus were significantly more likely to develop coronary heart disease.[66] Proposed theories for this discrepancy are dietary differences, estrogen and progesterone, pregnancy, muscle-to-fat composition, and genetic factors. Regardless, it would be reasonable to add a history of urinary calculus in women as a possible cardiac risk factor.[66]

Urinary Calculi and Ischemic Stroke

A nationwide cohort study in Taiwan reported the association of urinary calculi with ischemic stroke. Lin and colleagues followed 53 659 patients with urinary calculi and 214 107 age-, sex-, and comorbidity-matched controls for 13 years. The results demonstrated an increased chance of stroke in subjects with urinary calculi (1.06 fold higher risk) than those without urinary calculi.[4] The highest risk was in patients 20 to 34 years old (1.47 fold increase), followed by stone formers who were 35 to 50 years old (1.12 fold increase) as compared to non-stone formers.[4]

Despite the male predominance in the urinary calculus group, women (even after adjustment for age and other cardiovascular risk factors) with nephrolithiasis had a significantly increased risk for ischemic stroke (RR, 1.12). The chance of having a stroke was higher not only in women in general, but also in younger women (< 50 years old). The high risk of stroke in the relatively low cardiovascular risk young patients with nephrolithiasis suggests a causal role for nephrolithiasis in the development of stroke.[4]

It was also found that patients who had undergone more than 4 calculus-related surgeries had up to 42.5-fold increased risk of stroke compared with those treated by conservative therapy.[4] It is not clear if this observation was secondary to an advanced calculus disease, which shared the same pathophysiology with cerebrovascular disease or additive perioperative complications. Findings of this study further suggest an independent association between urinary calculus and the occurrence of ischemic stroke.

Urinary Calculi and Chronic Kidney Disease

While chronic kidney disease (CKD) could be associated with hereditary disorders such as primary hyperoxaluria or cystinuria, the association of nonhereditary kidney calculi and CKD was first observed in a cohort study by Rule and associates.[68] The prevalence of CKD in stone formers was 6.9% versus 3.1% in non-stone formers (odds ratio, 2.3). After excluding patients with preexisting CKD, stone formers were more likely to receive a new diagnosis of CKD (defined as estimated glomerular filtration less than 60 or serum creatinine greater than 97.5th percentile over a 90-day period) compared to control subjects (hazard ratio, 1.67). The higher incidence was independent of comorbidities associated with CKD such as DM, heart failure, and hypertension.[68] The limitation of this study was that the sample mainly consisted of Caucasians, and risk factors such as medications, type of the calculus, and history of lithotripsy were not included.[62]

Although more research is required to elicit a causal relationship between urinary calculi and CKD, it is reasonable for clinicians to perform frequent CKD screening (including urine albumin-creatinine ratio, serum creatinine, and estimated glomerular filtration) and implementing timely medical treatment for urinary calculi and kidney impairment.

Urinary Calculi and Malignancies

Cancers can cause urinary calculi through "malignant hypercalcemia" with subsequent hypercalciuria and calcium stone formation. Most common causes of malignant hypercalcemia and its mechanism are summarized in Table 2.[67] On the other hand, local inflammatory-proliferative changes, induced by urinary tract calculi can contribute to the development of cancer in genitourinary tracts.

Urinary Calculi and Genitourinary Cancers

Chronic irritation and infection with resultant proliferative changes has been linked to the development of urinary tract cancers. A cohort study in Sweden, followed up hospitalized patients with kidney, ureter, or bladder calculi for 25 years and examined the risks of developing renal, renal pelvis, ureter, or bladder cancers (excluding those diagnosed at year 1). The data showed a remarkable increase in the incidence of urinary tract malignancies, with a standardized incidence ratio of 2.5 for renal pelvis and ureter malignancies, and a standardized incidence ratio of 1.4 for bladder cancer. For women with urinary calculi the standardized incidence ratio for urinary tract malignancy was more than twice higher. No association was found between renal cell (parenchymal) carcinoma and nephrolithiasis.[69]

Table 2. Causes of Malignant Hypercalcemia

Cause	Malignancy
Parathyroid hormone-related protein	Squamous cell cancer Renal cell cancer Ovarian cancer Breast cancer Bladder cancer Hematologic malignancies
Osteolytic lesions	Breast cancer Multiple myeloma Lymphoma Leukemia
1,25-hydroxyvitamin D	Lymphoma Ovarian cancer-dysgerminoma
Ectopic parathyroid hormone secretions	Ovarian cancer Lung cancer Thyroid papillary cancer Rhabdomyosarcoma Pancreatic cancer

Transitional cell carcinoma was the dominant cancer type (71.7% to 90.3%), followed by squamous cell carcinoma that was observed in 5.3% to 17.4% of the cases. In patients with urinary tract calculus and urinary tract infection, the chance of urinary tract cancers rose to more than twice.[69] The assumption behind the development of squamous cell carcinoma is that urothelial metaplasia resulting from reaction to chronic irritation, may lead to dedifferentiation and dysplasia, evolving to squamous cell carcinoma.[70] In a case series of calculi-associated renal pelvic malignancies, Raghavendran and colleagues suggested that patients with long-standing calculus disease and associated poor kidney function or hematuria undergo a contrast enhanced computed tomography scan with computed tomography urography for screening and preoperative staging (if a suspicious lesion is observed).[71]

Urinary Calculi and Inflammatory Bowel Disease

Four percent to 23% of patients with inflammatory bowel disease experience renal complications. Kidney calculus, enterovesical fistula and

ureteral obstruction are the most common kidney complications associated with inflammatory bowel disease. Most prevalent calculus compositions in patients with inflammatory bowel disease are uric acid and calcium oxalate calculi.[72] The types and the risk factors for urinary calculi in patients with inflammatory bowel disease are summarized in Table 3.

Hydronephrosis has a propensity to occur on the right side due to the proximity of terminal ileum (the most common site of Crohn disease involvement) with the right ureter.[73]

A recent cohort study using ultrasonography on patients with inflammatory bowel disease who were "asymptomatic for renal stone" (defined as not being hospitalized for symptomatic nephrolithiasis) demonstrated a higher prevalence of kidney calculi than the previous reports. The study showed that 38% of patients with ulcerative colitis and 38% of patients with Crohn disease had nephrolithiasis.[74]

In patients with Crohn disease involvement of both colon and ileum (ileocolonic disease), and in patients with ulcerative colitis the "active status" of disease (regardless of severity) were associated with a significant increase in the incidence of nephrolithiasis (odds ratio, 2.3 and 4.2, respectively). The significant increase in the incidence of urinary calculi in active ulcerative colitis could be explained by frequent diarrhea, leading to metabolic acidosis and hypokalemia, both of which cause hypocitraturia that promotes crystallization.[74]

The underlying cause for uric acid stone formation is intestinal fluid and bicarbonate loss leading to formation of concentrated acidic urine, which predisposes to urate crystallization even though serum uric acid might not be elevated.[75]

Enteric hyperoxaluria (intestinal oxalate absorption greater than 48 mg/d), decreased urine volume, low levels of urinary crystallization inhibitors, ureteral obstruction, high urine levels of uric acid, acidic urine, corticosteroid use, and bed rest-related hypercalcuria are factors that can promote calcium stone formation in patients with inflammatory bowel disease. A well-described mechanism involves ileal dysfunction (either through the natural course of the disease or through surgical resection) that impairs bile acid reabsorption that results in fat malabsorption. The extra fatty acids bind and excrete the dietary calcium in the stool, leaving the free oxalate in the gut which gets absorbed in much higher amount and subsequently is excreted in urine, adopting the term enteric hyperoxaluria.[76,77]

A rare complication in patients with short gut syndrome and severe calcium oxalate nephrolithiasis is acute kidney injury due to exaggerated enteric hyperoxaluria. Early detection and hemodialysis is important in reversing this condition.[78]

In 1984, a fatal case of renocelebral oxalosis (diffuse calcium oxalate crystals deposition in central nervous system, presenting with coma and seizure) was reported following administration of high-dose xylitol for postoperative parenteral feeding following ileocecal resection.[79]

In order to prevent progression to CKD in patients with inflammatory bowel disease a thorough and timely investigation is warranted. [80] The effectiveness of ultrasonography in detecting large calculi (> 5 mm) coupled with its safety relative to computed tomorgaphy scan, makes it the screening modality of choice in this population. [80,81] However, non-contrast helical computed tomography scan has high sensitivity (> 95%) and specificity (> 96%) in the diagnosis of nephrolithiasis and remains as the initial imaging of choice in general population.[82]

We recommend routine screening, on at least a yearly basis, of serum creatinine level, estimated glomerular filtration measurement, random urine albumin-creatinine ratio, and renal ultrasonography in the following high-risk patients: (1) active ulcerative colitis, (2) ileocolic Crohn disease, (3) patients with resected or diseased ileum of more than 30 cm, and (4) patients who experience

Table 3. Types and Risk Factors of Urinary Calculi in Inflammatory Bowel Diseases

Calculus Type	Risk Factor
Uric acid	Diarrhea, ileostomy, hyperuricemia, and metabolic acidosis
Calcium oxalate	Ileal resection or disease and intestinal hyperoxaluria secondary to fat malabsorption
Calcium phosphate	Bed rest or immobility, steroids, increased urine calcium (mobilization from bone and decreased renal calcium reabsorption)
Sulfa crystals	Sulfasalazine or sulfapyridine medications

urologic symptoms (flank pain, hematuria, history of calculi, and recurrent urinary tract infection).

Urinary Calculi and Hypertension

Two large prospective studies have demonstrated that men with a history of nephrolithiasis have an increased risk (29%) of developing hypertension. However, an increased incidence of nephrolithiasis was not observed in hypertensive patients.[83] Another prospective study on middle-aged women with history of nephrolithiasis exhibited the same pattern of increased risk of hypertension (24%) after 12 years, but no increase in the incidence of nephrolithiasis in women with hypertension.[84] Hence, it would be safe to conclude that although nephrolithiasis is associated with an increased risk of hypertension, the reverse is not true.

Numerous studies have failed to find an independent link between hypertension and nephrolithiasis.[85] It seems that nephrolithiasis and hypertension are disorders that follow a common spectrum of pathogenesis like oxidative stress, obesity, metabolic syndrome, CKD, coronary heart disease, and ischemic stroke.

Urinary Calculi and Endocrine and Autoimmune Diseases

Kidney calculus could be the presenting feature in patients with sarcoidosis. A retrospective study demonstrated that 2.2% of patients with sarcoidosis first presented with urinary calculi (14 out of 618). In the same group, 9 more patients who presented with pulmonary manifestations, the presence of persistent hematuria and pyuria led to the diagnosis of urinary calculus (a total of 3.7%).[86] A 2-year prospective study showed that in 4% of patients with sarcoidosis, the first presentation was urinary calculus, which was the 2nd most common extrapulmonary manifestation after skin manifestations (eg, erythema nodosum).[87] The composition of calculi was usually calcium oxalate and less commonly calcium phosphate. Hypercalciuria blunts the effect of antidiuretic hormone, making polyuria as a heralding feature of nephrocalcinosis and stone formation.[88]

Aside from the increased incidence of urinary calculi in patients with hyperparathyroidism, a cross-sectional study showed that 50% of patients with active and 27% with treated Cushing syndrome had nephrolithiasis (compared to 6.5% in controlled group). Hyperuricosuria and hypertension followed by obesity, DM, hypercalciuria, hypocitraturia, hyperoxaluria, and cystinuria were found as frequent accompanying features in lithogenic group with Cushing syndrome.[89]

The data on Sjögren-associated nephrolithiasis is limited. However, it is suggested that distal renal tubular acidosis that is present in about 25% of such patients predisposes them to calcium phosphate nephrolithiasis.[90-92]

FUTURE DIRECTION

Physicians should be encouraged to change their view toward nephrolithiasis from an isolated benign disease to a disease that is associated with numerous systemic disorders, either as a cause or as an effect. This justifies a deeper probing for the mechanisms involved in stone formation and a more comprehensive, timely implementation of diagnostic and therapeutic measures.

ACKNOWLEDGMENTS

The authors acknowledge Dr Athena Hamidzadeh for her role in editing of this manuscript.

CONFLICT OF INTEREST

None declared.

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Received October 2016
Revised January 2017
Accepted January 2017