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AETIOLOGICAL INSIGHTS INTO RENAL CALCULI

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ABSTRACT

Renal calculi develop due to a complex interplay of metabolic, dietary, genetic, environmental, and lifestyle factors that disrupt the balance of stone-forming and inhibitory substances in urine. Key contributors include low fluid intake and dehydration, supersaturation of urine with calcium, oxalate, or uric acid, and deficiencies in natural inhibitors such as citrate and magnesium. Comorbid conditions like diabetes, metabolic syndrome, and hyperparathyroidism, along with infections, certain medications, dietary excesses, sedentary lifestyle, and climatic factors, further increase stone risk. Genetic predisposition and family history also play a significant role, highlighting the multifactorial nature of nephrolithiasis. Effective prevention and management require addressing hydration, diet, physical activity, and underlying metabolic or systemic conditions to reduce stone formation and recurrence.

KEYWORDS: Renal Calculi; Aetiology; Nephrolithiasis.

INTRODUCTION

Renal calculi, commonly known as kidney stones, are hard, crystalline mineral and salt deposits that form in the kidneys. Nephrolithiasis specifically refers to the presence of stones within the kidneys, whereas ureterolithiasis describes stones located in the ureters. Collectively, these conditions are encompassed under the broader term urolithiasis, which refers to calculi occurring anywhere in the urinary tract. These stones develop when urine becomes concentrated, allowing minerals such as calcium, oxalate, and uric acid to crystallize and stick together. Kidney stones vary in size, ranging from tiny grains to larger stones that can cause significant pain and obstruction in the urinary tract. They can be classified based on their composition, with the most common types being calcium oxalate, struvite, uric acid, and cystine stones. Symptoms of renal calculi include severe pain in the back or side (renal colic), hematuria (blood in urine), nausea, vomiting, and difficulty urinating. Diagnosis is typically done through imaging techniques such as ultrasound, CT scans, or X-rays. Treatment options depend on the size and type of the stone and may include increased fluid intake, pain management, medications, or medical procedures such as lithotripsy or surgical removal.[1]

AETIOLOGY

Renal calculi develop due to an imbalance in the concentration of stone-forming substances in the urine. Their formation is influenced by multiple factors, including metabolic, dietary, genetic, and environmental causes.

Low Fluid Intake & Dehydration: Low urine volume due to inadequate fluid intake or excessive fluid loss is a major risk factor for kidney stone formation. Dehydration from factors such as excessive sweating, physical exertion, stress, or chronic diarrhea increases urinary concentration and promotes stone development. Occupational factors also play a role; for example, steel workers, surgeons, professional drivers, pilots, and teachers often have limited access to fluids or bathroom breaks and show higher prevalence of nephrolithiasis. Clinical evidence strongly supports the role of adequate hydration in prevention: a randomized controlled trial demonstrated that maintaining a urine volume of at least 2 L/day significantly reduced recurrence of calcium oxalate stones compared to controls. Systematic reviews and meta-analyses further confirm that high fluid intake, sufficient to achieve urine volumes of 2–2.5 L/day, lowers recurrence risk across most stone types. Adequate hydration not only dilutes lithogenic substances but also facilitates the flushing of crystals through reduced

intratubular transit time. For patients with cystinuria, even higher urine output of at least 3 L/day is recommended to keep cystine concentrations below solubility thresholds and prevent recurrent stone formation.[2]

Supersaturation of Urine: Supersaturation of urine with stone-forming salts such as calcium and oxalate is the central driving force in renal calculi formation. When the concentration of these ions exceeds their solubility limit, the urine becomes metastable, favoring crystal nucleation and growth. In calcium oxalate stones, this process often begins with calcium oxalate dihydrate (COD) crystals, which nucleate more readily because of their lower interfacial energy despite being less stable than calcium oxalate monohydrate (COM). With persistent supersaturation, COD gradually transforms into the more stable COM, leading to the progressive growth of stones. Since the urinary environment remains highly supersaturated, neither COD nor COM crystals dissolve, allowing continuous crystal accumulation. Furthermore, supersaturation promotes protein–crystal interactions; urinary proteins aggregate with calcium oxalate crystals, stabilizing them and facilitating the development of a stone matrix. The persistent exposure of forming crystals to supersaturated urine therefore sustains crystal growth, aggregation, and retention in the kidneys, ultimately resulting in clinically significant calculi. Low urine volume due to dehydration increases the concentration of these substances, making stone formation more likely.[3]

Deficiency of Inhibitory Substances: Certain substances in urine prevent stone formation, including citrate, magnesium, and pyrophosphate. Low urinary citrate excretion, known as hypocitraturia, is a major risk factor for kidney stone formation because citrate normally acts as a natural inhibitor of crystallization. Under physiological conditions, citrate binds with calcium in the urine to form soluble calcium–citrate complexes, thereby lowering the concentration of free calcium available to combine with oxalate or phosphate. This reduces urinary supersaturation and prevents nucleation of calcium salts. Citrate also attaches to the surface of crystals, inhibiting their growth, aggregation, and adhesion to renal epithelial cells, all of which are critical steps in stone development. When urinary citrate levels fall below the protective threshold, these inhibitory mechanisms are lost. As a result, more free calcium remains in the urine, promoting supersaturation, crystal growth, and deposition, ultimately leading to the formation of calcium oxalate or calcium phosphate stones. Since urinary citrate levels are strongly influenced by acid–base balance, metabolic acidosis or conditions that increase renal citrate reabsorption can worsen hypocitraturia. Magnesium plays an important protective role in kidney stone disease by inhibiting the formation of calcium oxalate crystals. Clinical studies have demonstrated that supplementation with magnesium, even in patients without deficiency, can significantly reduce stone recurrence. Magnesium binds to oxalate in the urine to form soluble magnesium–oxalate complexes, thereby lowering the availability of oxalate to bind with calcium and reducing calcium oxalate supersaturation. In addition, magnesium therapy increases urinary magnesium and improves the urinary magnesium/calcium ratio to levels similar to those of healthy individuals, while also enhancing urinary citrate excretion, another important inhibitor of stone formation.[4,5]

Diabetes: The bidirectional relationship between nephrolithiasis and diabetes can be largely explained by insulin resistance, which often precedes the onset of clinical diabetes and contributes to urinary abnormalities. Insulin resistance impairs renal ammoniagenesis, leading to persistently low urinary pH. In diabetic stone formers, studies have shown significantly lower urine pH and increased urinary oxalate excretion compared to non-diabetic stone formers, both of which raise the risk of calcium oxalate stone formation. Additionally, the acidic urinary environment markedly increases the risk of uric acid stones, which are the most common type encountered in diabetic patients. Thus, metabolic disturbances in diabetes not only predispose to calcium oxalate stones but also strongly favor uric acid nephrolithiasis.[6]

Cardiovascular Diseases: Kidney stones and cardiovascular disease share common risk factors and overlapping pathophysiological pathways, making nephrolithiasis a systemic disorder rather than an isolated renal condition. Epidemiological studies consistently show that stone formers have a higher risk of hypertension, myocardial infarction, stroke, and subclinical atherosclerosis, particularly in women. While calculi may predispose to hypertension, the reverse association is less consistent. At the mechanistic level, calcium metabolism disturbances play a key role. Arterial calcification and inappropriate osteogenic transformation of renal epithelial cells parallel vascular calcification, leading to calcium phosphate crystal deposition and Randall's plaque formation. Imaging studies confirm that stone formers exhibit greater abdominal aortic calcification compared to controls. Furthermore, dysfunction of the calcium-sensing receptor, expressed in both kidneys and vascular tissues, may link abnormal calcium handling to vascular and renal pathology. Oxidative stress and chronic inflammation further contribute, promoting endothelial dysfunction, atherosclerosis, and stone formation, thereby connecting renal calculi and cardiovascular disorders.[7]

Metabolic Syndrome: Nephrolithiasis is increasingly recognized as a systemic disorder strongly associated with obesity and metabolic syndrome rather than a purely renal condition. Epidemiological evidence, including NHANES data, demonstrates that the prevalence of kidney stones rises with the number of metabolic syndrome traits such as hypertension,

dyslipidemia, abdominal obesity, and hyperglycemia. Obesity contributes to stone formation through multiple mechanisms, including impaired carbohydrate metabolism, increased urinary excretion of calcium, sodium, oxalate, and uric acid, reduced urinary citrate, and defective renal ammoniagenesis leading to persistently acidic urine. These changes create a lithogenic urinary environment that favors calcium oxalate and uric acid stone formation. Large cohort studies confirm that higher BMI, waist circumference, and long-term weight gain significantly increase stone risk in both men and women, with obese individuals showing the highest prevalence. Interestingly, while weight gain consistently increases risk, weight loss does not always reduce it, as bariatric surgery patients demonstrate higher stone incidence due to enteric hyperoxaluria despite reduced BMI.[8]

Hyperparathyroidism: In primary hyperparathyroidism, persistently elevated parathyroid hormone increases serum calcium levels through enhanced bone resorption, increased intestinal absorption via $1,25(OH)_2D$ stimulation, and increased renal tubular calcium reabsorption. The higher filtered calcium load at the glomerulus leads to hypercalciuria, which is one of the main drivers of renal stone formation. Excess calcium in urine predisposes to supersaturation and crystallization, most often resulting in calcium oxalate stones, though the slightly alkaline urine in PHPT can also favour calcium phosphate stone formation.[9]

Climate: Climate has a significant impact on the development and prevalence of renal calculi, particularly through the effects of heat and hydration status. Kidney stones are observed more frequently in hot climates and during summer months, largely due to increased insensible water loss through perspiration and reduced fluid intake, which together cause urinary concentration and supersaturation of lithogenic salts such as calcium, oxalate, phosphate, and uric acid.

This mechanism explains the clustering of nephrolithiasis cases in the so-called “stone belt” of the southeastern United States, where warmer temperatures correlate with higher stone risk. Epidemiological studies further support that episodes of symptomatic kidney stones rise sharply with higher daily temperatures, with men demonstrating a stronger susceptibility than women, possibly due to behavioral or physiological differences. Climate change and global warming are predicted to exacerbate this burden, with modeling studies estimating millions of additional cases worldwide by 2050. Humidity adds complexity, as high wet-bulb temperatures appear to predict kidney stone presentations more accurately than dry-bulb measurements, suggesting that the combined effects of heat and humidity amplify the risk.[10]

Lithogenic drugs: Diagnostic and therapeutic drugs can promote urolithiasis through different mechanisms. They may alter the urinary pH, creating conditions that favor crystallization of lithogenic substances. Some drugs interfere with renal function by modifying glomerular filtration, tubular reabsorption, or secretion, which can increase stone-promoting factors or reduce natural inhibitors of crystallization. In addition, certain drugs or their metabolites may precipitate directly within the urinary tract, forming part or even the whole of a stone. Thus, drug-induced urolithiasis can result from either metabolic alteration in urine chemistry or direct crystallization of drug compounds. Drug-induced calculi account for 1–2% of all renal stones and arise through two main mechanisms. The first group includes poorly soluble drugs that are excreted in large amounts in urine, leading to crystallization and stone formation. Triamterene, for example, was the leading cause of drug-related calculi and continues to be implicated. In recent decades, medications used in HIV therapy, particularly indinavir and sulfadiazine, have become the most frequent culprits. The second group includes drugs that promote calculi indirectly through metabolic alterations, such as calcium or vitamin D supplementation. These stones are harder to differentiate from common metabolic calculi and are likely underdiagnosed.[11,12]

Genetic and Family History: A family history of kidney stones increases the likelihood of stone formation due to inherited metabolic disorders. Cystinuria and primary hyperoxaluria are hereditary conditions leading to recurrent stone formation. Genetic factors. Nephrolithiasis is known to have a familial nature and significant heritability, and genes that may be involved in renal stone formation have been identified. Genome-wide association studies and candidate gene studies have implicated genes involved in renal tubular handling of lithogenic substrates, such as calcium, oxalate, and phosphate, and of inhibitors of crystallization, such as citrate and magnesium. Using whole-exome sequencing, Daga et al detected monogenic causative mutations in 15 of 51 families with members who presented before age 25 years with at least one renal stone or with a renal ultrasound finding of nephrocalcinosis. Identified mutations were in seven recessive genes (AGXT, ATP6V1B1, CLDN16, CLDN19, GRHPR, SLC3A1, SLC12A1), one dominant gene (SLC9A3R1), and one gene (SLC34A1) with both recessive and dominant inheritance. In patients with idiopathic hypercalciuria and calcium-containing kidney stones, genetic screens of nephrolithiasis determinants have identified candidates involved in renal calcium handling, such as the transient rec eptor potential vanilloid 5 (TRPV5), which is an important player in Ca2+ homeostasis. TheTRPV5 channel also plays a role in renal calcium transport, and may be the future target of therapies for individuals at risk for nephrolithiasis.[13]

Infections: Infections contribute significantly to the pathogenesis of renal calculi, particularly struvite (infection) stones, which arise almost exclusively in the setting of urinary tract infections with urease-producing

microorganisms. These bacteria secrete urease, an enzyme that hydrolyzes urea into ammonia and carbon dioxide. The released ammonia raises urinary pH above 7.2, creating an alkaline environment that reduces the solubility of phosphate salts. Consequently, magnesium, ammonium, and phosphate ions precipitate to form struvite (magnesium ammonium phosphate) and carbonate apatite crystals, which can grow rapidly into large staghorn calculi that occupy the renal pelvis and calyces. Among the most common urease-positive pathogens are *Proteus mirabilis* (the leading cause), *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Providencia stuartii*, *Morganella morganii*, *Staphylococcus saprophyticus*, and *Ureaplasma urealyticum*. In addition to these classic organisms, increasing evidence highlights the role of non–urease-producing bacteria, particularly *Escherichia coli*, in the genesis of calcium oxalate stones. Although they do not alter urinary pH significantly, these organisms can adhere to calcium oxalate crystals, promote aggregation, and form biofilms that serve as a nidus for crystal retention within renal tubules. Bacterial polysaccharides, outer membrane vesicles, and other metabolites may bind calcium ions, accelerating nucleation and growth of stones. Furthermore, chronic infection can sustain low-grade inflammation, which releases cellular debris and proteins into urine, providing additional matrix material for crystal adherence. Thus, infection-related nephrolithiasis is not confined to struvite stones but may also facilitate calcium oxalate stone formation. The clinical consequence is a vicious cycle: infection promotes stone growth, and stones, in turn, harbor bacteria within their porous matrix, protecting pathogens from antibiotic penetration and leading to persistent or recurrent urinary tract infections.[14]

Dietary Factors: Diet plays a central role in the development and prevention of renal calculi, as specific nutrients directly influence urinary composition and the risk of stone formation. High sodium intake enhances urinary calcium excretion and increases urinary osmolarity, thereby promoting hypercalciuria and calcium stone formation. Diets rich in animal protein (>2 g/kg/day) increase uric acid production, reduce urinary pH, and enhance citrate reabsorption in the renal tubules, leading to hypocitraturia, hypercalciuria, and an elevated risk for both calcium oxalate and uric acid stones. Excessive oxalate intake, or large doses of vitamin C supplementation (>1,000 mg/day), elevates urinary oxalate, contributing to hyperoxaluria and calcium oxalate stone formation. Conversely, very low dietary calcium increases intestinal oxalate absorption, while excessive calcium intake predisposes to milk-alkali syndrome and hypercalciuria; thus, moderate calcium intake is recommended. Inadequate hydration is another major risk factor, as low urine volume favors supersaturation of lithogenic salts, making sufficient fluid intake to maintain >2 L/day urine output essential. Additionally, sugar-sweetened beverages are linked to higher stone risk, while coffee consumption appears protective, likely due to increased urine output. Fruit and vegetable-rich diets provide citrate and alkalinize urine, lowering stone risk, with lemon juice offering specific benefit from its high citrate content.[15]

Sedentary Lifestyle: In individuals without vigorous recreational activity, kidney stone prevalence tended to increase with longer daily sitting times, although this trend was not statistically significant. In contrast, participants who engaged in vigorous recreational activity had a lower risk of kidney stones even if they sat 6–8 hours per day, suggesting that vigorous activity may counteract the negative effects of prolonged sitting. Low physical activity and prolonged sedentary behavior, such as bed rest or hospitalization, are linked to an increased risk of kidney stones, partly due to reduced calcium deposition and concentrated urine. Moderate physical activity helps prevent stones by promoting hydration, urine dilution, and proper calcium metabolism, but excessive or strenuous activity can increase risk through dehydration and excessive sweating.[16]

CONCLUSION

Renal calculi arise from multifactorial causes, including metabolic, dietary, genetic, environmental, and lifestyle factors. Dehydration, urinary supersaturation, low inhibitors, comorbidities, infections, drugs, dietary excesses, sedentary habits, climate, and genetic predisposition collectively disrupt urinary balance, promoting stone formation.

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