Urolithiasis Pathogenesis Risk Factors and Modern Treatment Approaches

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ABSTRACT

Urolithiasis, a prevalent urological disorder, is characterized by the formation of stones within the urinary tract due to supersaturation, crystallization, and aggregation of minerals. This review explores the epidemiology, pathogenesis, classification, risk factors, and management strategies for urinary stone disease. Genetic predisposition, metabolic disorders, dietary influences, urinary tract infections, and gut microbiota alterations contribute to stone formation. Calcium-based stones, particularly calcium oxalate, are the most common, followed by uric acid, struvite, cystine, and drug-induced stones. Diagnosis relies on clinical symptoms, urinalysis, biochemical evaluations, and imaging techniques such as computed tomography. Management approaches vary depending on stone size, composition, and location. Conservative strategies include pain control and medical expulsive therapy with alpha-blockers. Pharmacological interventions such as citrate supplements, urate-lowering agents, and thiazide diuretics help prevent recurrence. Minimally invasive procedures, including extracorporeal shock wave lithotripsy and ureteroscopy with laser lithotripsy, are effective for small to medium stones, while percutaneous nephrolithotomy is preferred for larger or complex calculi. Surgical interventions are reserved for refractory cases. Advances in precision medicine, microbiome research, and metabolic risk assessment may improve prevention and treatment. Future studies should focus on personalized therapeutic strategies to reduce recurrence rates and improve patient outcomes.

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Introduction

Definition and Significance of Urolithiasis

Urolithiasis, commonly referred to as urinary stone disease, is a pathological condition characterized by the formation of calculi within the urinary tract, including the kidneys, ureters, bladder, or urethra. These stones develop due to the supersaturation and crystallization of minerals in urine, often resulting in significant morbidity due to pain, obstruction, and complications such as infection and renal impairment [1,3]. The condition is a major urological disorder with a high recurrence rate, necessitating continuous medical surveillance and management [2].

The clinical presentation of urolithiasis varies widely depending on stone size, location, and degree of obstruction. While some patients remain asymptomatic, others experience acute colicky pain, hematuria, urinary urgency, and recurrent infections [4,5]. In severe cases, obstructive uropathy can lead to hydronephrosis, renal dysfunction, and end-stage kidney disease if left untreated [8]. Given its clinical and socioeconomic impact, urolithiasis remains a major public health concern, requiring multidisciplinary approaches for prevention, diagnosis, and treatment.

Epidemiology and Global Burden

Urolithiasis is a prevalent disease worldwide, with significant geographical and demographic variations. The estimated lifetime risk of developing urinary stones ranges between 5% and 12%, with higher incidence rates observed in developed countries [6]. The prevalence of urolithiasis has been increasing globally, attributed to changing dietary habits, climate change, and an aging population [5]. The disease affects both sexes but exhibits a male predominance, with a male-to-female ratio of approximately 2:1, although this gap has been narrowing due to lifestyle factors and dietary shifts [3,6].

Regional disparities in urolithiasis prevalence are largely influenced by environmental and genetic factors. Warmer climates and regions with high water hardness are associated with a higher incidence of kidney stone formation due to increased urinary concentration and mineral deposition [6,7]. Additionally, metabolic risk factors such as obesity, diabetes mellitus, and metabolic syndrome have been linked to an increased risk of stone formation, further contributing to the rising global burden of the disease [9]. The economic implications of urolithiasis are substantial, given the high healthcare costs associated with emergency visits, hospitalizations, surgical interventions, and long-term medical management [7,10].

Pathophysiological Mechanisms of Stone Formation

The formation of urinary calculi is a multifactorial process involving physicochemical, metabolic, and genetic factors. The pathogenesis primarily revolves around urine supersaturation, nucleation, crystal growth, and aggregation [8]. Under normal physiological conditions, urine contains various solutes and inhibitors that maintain mineral solubility and prevent crystallization. However, an imbalance in promoters (e.g., calcium, oxalate, uric acid, phosphate) and inhibitors (e.g., citrate, magnesium) of stone formation leads to nucleation and aggregation of crystals within the renal tubules [6,9].

The most common type of urinary stone, calcium oxalate, forms due to hypercalciuria, hyperoxaluria, and hypocitraturia, conditions influenced by dietary intake, metabolic disorders, and genetic predisposition [8]. Uric acid stones are associated with acidic urinary pH and hyperuricosuria, commonly seen in patients with metabolic syndrome and gout [5,8]. Struvite stones, also known as infection stones, arise due to urease-producing bacteria that alkalinize urine and facilitate precipitation of magnesium ammonium phosphate [10]. Less commonly, cystine stones develop in individuals with cystinuria, a hereditary disorder affecting renal tubular transport of amino acids [4,12].

Apart from biochemical abnormalities, urinary stasis, dehydration, and anatomical abnormalities (e.g., medullary sponge kidney, horseshoe kidney) contribute to stone formation by reducing urine flow and promoting crystal retention [9]. Recent studies have also highlighted the role of the gut microbiota, particularly Oxalobacter formigenes, in modulating oxalate metabolism and reducing the risk of calcium oxalate stone formation [16]. These insights have opened new avenues for potential therapeutic interventions targeting microbiome-mediated stone prevention.

Objectives and Scope of the Review

Despite advancements in understanding the pathophysiology of urolithiasis, its increasing incidence and high recurrence rates underscore the need for comprehensive prevention and management strategies. This review aims to provide an updated synthesis of current knowledge on urolithiasis, including its classification, risk factors, clinical presentation, and diagnostic approaches. Furthermore, the review will discuss recent advancements in preventive strategies, dietary modifications, pharmacological therapies, and surgical interventions. Special emphasis will be placed on emerging research areas, including the role of microbiota, genetic susceptibility, and novel treatment modalities.

By integrating findings from epidemiological, clinical, and translational research, this review seeks to enhance the understanding of urolithiasis and provide clinicians and researchers with evidence-based insights into optimizing patient care and reducing disease burden.

Classification of Urinary Stones

Urinary stones, or uroliths, are classified based on their chemical composition and anatomical location within the urinary tract. Understanding these classifications is essential for guiding diagnostic, preventive, and therapeutic approaches.

Classification Based on Composition

Calcium-Based Stones

Calcium-containing stones represent the most prevalent type of urolithiasis, accounting for approximately 70–80% of all urinary calculi [15]. These stones primarily consist of calcium oxalate and, to a lesser extent, calcium phosphate.

Calcium Oxalate Stones: Calcium oxalate stones occur in two forms—calcium oxalate monohydrate and calcium oxalate dihydrate. Hypercalciuria, hyperoxaluria, and hypocitraturia are major metabolic contributors to their formation [14]. Dietary factors, including excessive oxalate intake (e.g., spinach, nuts, and tea), reduced calcium intake, and dehydration, play significant roles in their pathogenesis [11].

Calcium Phosphate Stones: Calcium phosphate stones are commonly associated with alkaline urinary pH and conditions such as renal tubular acidosis and hyperparathyroidism [28]. They often co-exist with calcium oxalate stones and are known for their tendency to form larger calculi, leading to increased obstruction risks [6].

Uric Acid Stones

Uric acid stones account for approximately 5–10% of all urinary stones and are primarily linked to acidic urinary pH and hyperuricosuria [12]. Risk factors include purine-rich diets (e.g., red meat, seafood), metabolic syndrome, obesity, and gout [6]. Unlike calcium-based stones, uric acid stones are radiolucent on conventional radiographs but can be detected using ultrasound or computed tomography (CT) imaging [9]. Alkalization of urine with potassium citrate or sodium bicarbonate is a key therapeutic strategy to dissolve uric acid calculi [12].

Struvite (Infection) Stones

Struvite stones, also known as infection-related or triple phosphate stones, consist of magnesium ammonium phosphate and are strongly associated with urinary tract infections caused by urease-producing bacteria such as *Proteus mirabilis, Klebsiella pneumoniae*, and *Ureaplasma urealyticum* [12-14]. These bacteria hydrolyze urea into ammonia, increasing urinary pH and facilitating struvite precipitation [13]. Struvite stones often form large, branching staghorn calculi that occupy the renal pelvis and calyces, leading to recurrent infections and renal damage if untreated [7].

Cystine Stones

Cystine stones are rare, constituting less than 2% of all urinary calculi, and arise due to a genetic disorder known as

cystinuria, which impairs the renal tubular reabsorption of cystine and other dibasic amino acids [14]. Cystine is poorly soluble in urine, particularly in acidic pH, leading to precipitation and stone formation [3,8]. These stones are often recurrent and require lifelong management with increased fluid intake, urinary alkalization, and thiol-based medications to reduce cystine crystallization [14].

Drug-Induced Stones

Drug-induced calculi account for a small proportion of urolithiasis cases and result from the precipitation of poorly soluble medications or their metabolites in the urinary tract [17]. Commonly implicated drugs include:

Protease inhibitors (e.g., indinavir) – associated with stones in HIV patients [12].

Sulfonamides (e.g., sulfadiazine) – form crystals in acidic urine [13].

Triamterene – causes radiolucent stones in alkaline urine [14,17].

Ceftriaxone – may lead to calcium-ceftriaxone complex precipitation, particularly in children [18].

Prevention of drug-induced stones involves dose adjustment, hydration, and monitoring of at-risk individuals.

Classification Based on Location

The location of urinary stones determines the clinical presentation, complications, and choice of treatment.

Renal Calculi (Nephrolithiasis)

Renal calculi form within the kidney and may remain asymptomatic or cause intermittent flank pain and hematuria. Small stones (<5 mm) often pass spontaneously, whereas larger stones can cause obstruction, leading to hydronephrosis and renal damage [2,13]. Renal stones may also serve as a nidus for recurrent infections, increasing the risk of struvite stone formation [14].

Ureteric Calculi (Ureterolithiasis)

Ureteric calculi originate from the kidneys but become lodged within the ureters, often leading to acute renal colic due to ureteral obstruction and spasms [6,9]. Ureteric stones smaller than 5 mm may pass spontaneously with adequate hydration and pharmacological support, such as alpha-blockers (e.g., tamsulosin), whereas larger stones may require extracorporeal shock wave lithotripsy (ESWL), ureteroscopy, or laser lithotripsy for removal [10].

Bladder Stones (Cystolithiasis)

Bladder stones typically develop in patients with urinary stasis, neurogenic bladder, chronic infections, or indwelling catheters [16]. In contrast to upper urinary tract calculi, bladder stones often present with lower urinary tract symptoms, including dysuria, urinary urgency, and hematuria [12,17]. Large bladder stones may necessitate surgical intervention, such as cystolitholapaxy or open cystolithotomy [13].

Pathogenesis and Risk Factors

Urolithiasis is a complex condition influenced by genetic, metabolic, dietary, and environmental factors. The formation of urinary stones occurs when urine becomes supersaturated with stone-forming substances, leading to nucleation, crystal growth, and aggregation [13]. Several conditions contribute to this process, including genetic predisposition, metabolic disorders, dietary habits, urinary tract infections, anatomical abnormalities, and alterations in gut microbiota [12].

Genetic Predisposition and Hereditary Factors

There is strong evidence supporting the hereditary nature of urolithiasis, with familial clustering observed in patients with recurrent stones [13]. Twin studies and genome-wide association studies have identified genetic variations affecting calcium, oxalate, and uric acid metabolism as significant contributors to stone formation [14,17]. Certain monogenic disorders, such as cystinuria and primary hyperoxaluria, result from mutations in genes responsible for amino acid and oxalate metabolism. Cystinuria, an autosomal recessive disorder caused by mutations in the SLC3A1 and SLC7A9 genes, leads to defective renal tubular transport of cystine, promoting the formation of recurrent cystine stones [3,7]. Similarly, primary hyperoxaluria, resulting from mutations in AGXT, GRHPR, or HOGA1, causes excessive endogenous oxalate production, predisposing affected individuals to calcium oxalate nephrolithiasis [5,8]. Beyond these rare conditions, idiopathic calcium stone formation has been linked to genetic variations in CLDN14, a gene involved in renal calcium handling. These findings highlight the need for individualized preventive strategies, particularly for individuals with a strong family history of urolithiasis [4].

Dietary and Lifestyle Influences

Dietary habits and lifestyle choices play a crucial role in the development of urolithiasis by altering urinary composition [2]. Insufficient fluid intake results in concentrated urine, increasing the supersaturation of lithogenic solutes such as calcium, oxalate, and uric acid [14]. High dietary oxalate intake, commonly found in foods such as spinach, nuts, tea, and chocolate, exacerbates the risk of calcium oxalate crystallization, particularly in individuals with hyperoxaluria [16]. Excessive sodium consumption reduces renal calcium reabsorption, leading to hypercalciuria and increasing the likelihood of calcium-based stone formation [13,18]. Diets rich in animal protein contribute to stone formation by increasing urinary uric acid levels while simultaneously reducing urinary citrate, an important inhibitor of calcium crystal aggregation [16,18]. Additionally, obesity and metabolic syndrome have been associated with an increased risk of urolithiasis due to insulin resistance, altered acid-base metabolism, and reduced urinary citrate excretion [18]. Lifestyle modifications, including adequate hydration, dietary calcium regulation, and reduced sodium

and oxalate intake, are fundamental for both primary prevention and recurrence reduction [20].

Metabolic Disorders

Several metabolic abnormalities predispose individuals to urinary stone formation by altering urine chemistry [13,15]. Hypercalciuria, a condition characterized by excessive urinary calcium excretion, is one of the most significant risk factors for calcium-containing stones. It may result from primary hyperparathyroidism, excessive dietary sodium intake, or idiopathic familial hypercalciuria. Hyperoxaluria, another important contributor to stone formation, can arise from excessive dietary oxalate intake, fat malabsorption associated with inflammatory bowel disease or bariatric surgery, or primary hyperoxaluria. The presence of low urinary citrate levels, a condition known as hypocitraturia, further promotes stone formation by reducing calcium solubility [11,17]. This abnormality is frequently observed in patients with metabolic acidosis, chronic diarrhea, and high-protein diets. Hyperuricosuria, characterized by elevated urinary uric acid levels, increases the risk of both uric acid and calcium oxalate stone formation and is commonly seen in individuals with gout, diabetes, or high-purine diets. The identification of these metabolic disturbances through 24-hour urine analysis is essential for the implementation of targeted preventive and therapeutic strategies.

Urinary Tract Infections and Anatomical Abnormalities

Urinary tract infections play a direct role in the formation of struvite stones, which develop due to the activity of urease-producing bacteria such as Proteus mirabilis, Klebsiella pneumoniae, and Ureaplasma urealyticum [21]. These bacteria hydrolyze urea into ammonia, increasing urinary pH and promoting the precipitation of magnesium ammonium phosphate. Struvite stones often form large staghorn calculi that can obstruct renal function and lead to recurrent infections if not properly managed. In addition to infections, congenital and acquired anatomical abnormalities contribute to stone formation by impairing urinary drainage and promoting urinary stasis. Medullary sponge kidney, a congenital disorder characterized by cystic dilation of renal tubules, predisposes affected individuals to recurrent calcium-based stones due to urinary stasis and increased calcium deposition [13,17]. Similarly, horseshoe kidney, a condition in which the kidneys are fused at the lower poles, alters urine flow dynamics and increases the likelihood of nephrolithiasis. Ureteropelvic junction obstruction, a structural defect impairing urinary drainage from the renal pelvis to the ureter, further predisposes individuals to stone formation [12,17]. The management of such cases requires a combination of medical and surgical interventions to prevent recurrent stone formation and associated complications [19].

Role of Gut Microbiota in Stone Formation

Emerging research has highlighted the role of gut microbiota in the pathogenesis of urolithiasis, particularly in the regulation of oxalate metabolism [22]. The gut bacterium Oxalobacter formigenes plays a crucial role in degrading dietary oxalate and reducing its intestinal absorption [20]. Studies have demonstrated that individuals lacking O. formigenes in their gut microbiome exhibit higher urinary oxalate levels and an increased risk of calcium oxalate stone formation [21]. Dysbiosis, or microbial imbalance, due to antibiotic use, dietary changes, or gastrointestinal diseases, has been linked to increased intestinal oxalate absorption and heightened urinary oxalate excretion [19]. The modulation of gut microbiota through probiotics and dietary interventions is an area of growing interest, with potential implications for novel preventive strategies in urolithiasis management [8,19].

Treatment Approaches

The management of urolithiasis is determined by the stone's size, composition, location, and the presence of symptoms or complications. Treatment approaches range from conservative management and pharmacological therapy to minimally invasive and surgical interventions. The primary goals of treatment include symptom relief, stone expulsion, prevention of recurrence, and preservation of renal function.

Conservative Management

Small urinary stones, typically less than 5 mm in diameter, often pass spontaneously with adequate hydration and supportive care. Conservative management focuses on pain relief, facilitating stone passage, and preventing complications. Pain control is a crucial aspect of initial management, as renal colic can be excruciating. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or diclofenac, are the first-line analgesics due to their anti-inflammatory properties and ability to reduce ureteral spasms [16,18]. In cases of severe pain unresponsive to NSAIDs, opioids may be used, although their use is generally limited due to the risk of dependence and side effects [22].

For ureteral stones, particularly those between 5–10 mm, alpha-blockers such as tamsulosin are recommended to promote spontaneous stone passage. These agents work by relaxing the smooth muscle of the ureter, reducing ureteral spasms, and facilitating stone migration toward the bladder [18]. Medical expulsive therapy with alpha-blockers has been shown to increase the rate of spontaneous stone passage and reduce the need for surgical intervention [26].

Pharmacological Therapy

Certain pharmacological agents can prevent stone formation or dissolve specific types of urinary calculi. Uric acid stones, which form in acidic urine, may be dissolved by urinary alkalization with potassium citrate or sodium bicarbonate. These agents increase urine pH, enhancing the

solubility of uric acid and promoting its excretion in dissolved form. Urate-lowering agents such as allopurinol may be prescribed in patients with hyperuricosuria to prevent recurrent uric acid stone formation [4,8,16].

For calcium-based stones, citrate supplementation plays a key role in preventing recurrence. Citrate binds to calcium in urine, preventing its crystallization and promoting the dissolution of small stones [21]. Thiazide diuretics, such as hydrochlorothiazide, reduce urinary calcium excretion and are particularly beneficial in patients with recurrent calcium nephrolithiasis associated with idiopathic hypercalciuria [17]. Patients with cystine stones may require cystine-binding agents such as tiopronin or penicillamine to reduce cystine crystallization in urine.

Minimally Invasive Procedures

Minimally invasive techniques have revolutionized the management of urolithiasis by reducing morbidity and hospital stays while achieving high stone clearance rates. Extracorporeal shock wave lithotripsy (ESWL) is a non-invasive procedure that uses high-energy shock waves to fragment stones into smaller pieces, facilitating their natural passage through the urinary tract [12,17]. ESWL is most effective for stones less than 2 cm in the renal pelvis or upper ureter and has an overall success rate of 70–90% depending on stone composition and patient factors. However, ESWL may be less effective for dense stones, such as calcium oxalate monohydrate, and multiple treatment sessions may be required [4,7,8].

For larger or impacted stones, ureteroscopy (URS) with laser lithotripsy is an effective alternative. This endoscopic procedure involves the insertion of a flexible or semi-rigid ureteroscope through the urethra and bladder into the ureter or kidney. A laser fiber is then used to fragment the stone into smaller pieces, which are either extracted or allowed to pass spontaneously [4,6,13]. URS is particularly advantageous for ureteral stones, as it allows for direct visualization and precise stone fragmentation with minimal trauma to surrounding tissues.

Surgical Interventions

For large, complex, or staghorn calculi, percutaneous nephrolithotomy (PCNL) is the preferred treatment modality. PCNL involves the creation of a percutaneous tract from the skin into the renal collecting system, allowing for direct stone removal using specialized instruments [14,18]. This procedure is highly effective for stones larger than 2 cm and those that are resistant to ESWL or URS. PCNL has a high success rate but is associated with a greater risk of complications such as bleeding and infection, necessitating careful patient selection [5,8].

In rare cases where minimally invasive approaches are not feasible, open or laparoscopic surgery may be required. Open stone removal is now largely reserved for patients with anatomical abnormalities, large stone burdens, or failed prior interventions [3,7,18]. Laparoscopic procedures offer a minimally invasive alternative with shorter recovery times and reduced postoperative pain [5,8,22]. However, surgical intervention is typically considered a last resort when other treatment modalities are ineffective or contraindicated.

Conclusions

Urolithiasis remains a significant health burden due to its high prevalence, recurrence rate, and potential complications. The management of urinary stones has evolved considerably, with a range of conservative, pharmacological, and interventional strategies available to optimize patient outcomes. Small stones may be managed conservatively with pain control and medical expulsive therapy, while pharmacological interventions play a key role in both treatment and prevention. Advances in minimally invasive techniques, such as ESWL and URS with laser lithotripsy, have improved stone clearance rates while reducing the need for surgical interventions. However, for complex cases, PCNL and, in rare instances, open or laparoscopic surgery remain necessary options.

Clinically, the choice of treatment should be tailored to the individual patient based on stone size, composition, location, and underlying metabolic risk factors. Long-term prevention strategies, including dietary modifications, hydration, and targeted pharmacological therapy, are essential for reducing recurrence rates. Further research is needed to enhance our understanding of stone pathogenesis, improve risk stratification models, and develop novel therapeutic strategies, including microbiome-based interventions and genetic profiling. By integrating advancements in clinical practice and translational research, the burden of urolithiasis can be effectively mitigated, leading to improved patient outcomes and quality of life.

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