Literature Review

The Risk Factors and Mechanisms of Kidney Stone Formation

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ABSTRACT

Kidney stone disease (KSD), also known as urolithiasis or nephrolithiasis, is a prevalent urinary tract disorder with rising global incidence, affecting approximately 10–15 % of adults worldwide and imposing substantial healthcare burdens. The primary mechanism of stone formation is urine supersaturation and crystallization, which is influenced by urine pH and excess concentration of stone-forming substances such as calcium oxalate (70–80 % of cases), calcium phosphate, and uric acid. Dehydration is a common risk factor that causes these substances to concentrate and form crystals that then coalesce into kidney stones. This narrative review synthesizes recent evidence on modifiable risk factors and pathogenesis, emphasizing preventive strategies capable of reducing recurrence by up to 50%.

INTRODUCTION

Urolithiasis or kidney stone disease (KSD) is one of the most common urinary tract disorders in the world. The prevalence and incidence of KSD has increased globally in the last decade, with lifetime prevalence rates of 7–15 % in North America, 5–9 % in Europe, and 1–8 % in Asia.[1,2]

Nephrolithiasis is an indicator of increasing chronic kidney disease. Chronic kidney disease is likely caused by kidney damage due to obstructive nephropathy, which blocks the urinary tract, obstructing the flow of urine from the kidneys. The most common type of stone is calcium oxalate (70–80 %), followed by calcium phosphate (10–15 %), uric acid (8–10 %), struvite (3–5 %), and cystine (1–2 %).[3,4]

Before delving into the main discussion of the mechanism of kidney stone formation, knowledge of the location, morphology, and relationships between urinary tract components such as the kidneys, ureters, bladder, and urethra is essential for understanding how the normal excretion process occurs. Furthermore, understanding kidney physiology, such as the mechanisms of glomerular filtration, reabsorption, secretion, and urine formation, can more easily understand and identify disorders or pathological changes that can trigger kidney stone formation. This literature review aims to elucidate the risk factors and pathogenesis of kidney stone formation, with emphasis on modifiable factors and preventive strategies.

METHODS

This narrative literature review employed purposive sampling of peer-reviewed articles published between 2016 and 2025, sourced from PubMed, Scopus, and Web of Science. Inclusion criteria comprised English-language original research and reviews addressing pathogenesis, risk factors, or prevention of nephrolithiasis. Approximately 45 high-impact articles were selected and analyzed thematically.

RESULT

Anatomy and Physiology of the Urinary Tract Relevant to Nephrolithiasis

The human urinary system consists of the kidneys, ureters, urinary bladder, and urethra. In nephrolithiasis, the process of stone formation mainly occurs in the kidneys and the collecting system, so the discussion focuses on the structure and function of these parts.[5,6]

Each kidney contains 1–1.5 million nephrons as functional units. Glomerular filtrate undergoes reabsorption and secretion along the tubules, then is concentrated in the renal medulla through the counter-current multiplier mechanism in the loop of Henle and the collecting ducts. The final urine concentration is greatly influenced by urine pH and daily urine volume, which are regulated mainly in the distal segment of the nephron and the collecting duct; the concentration of lithogenic ions (calcium, oxalate, phosphate, uric acid) and crystallization inhibitors (citrate, magnesium, Tamm-Horsfall protein); the presence of heterogeneous nucleation in the renal papillae, particularly Randall's plaque, which is a suburothelial calcium phosphate deposit that serves as an attachment point for calcium oxalate crystals.[4,7,8]

Crystal retention and kidney stone growth most often occur in the renal papillae and calyces. These locations are vulnerable due to slow urine flow and prolonged exposure to crystals. The most common triggering conditions are urinary obstruction, idiopathic hypercalciuria, and other metabolic disorders such as hyperoxaluria, hypocitraturia, or hyperuricosuria. These factors increase urine supersaturation and crystal adhesion to the tubular epithelium and papillae.[7,9]

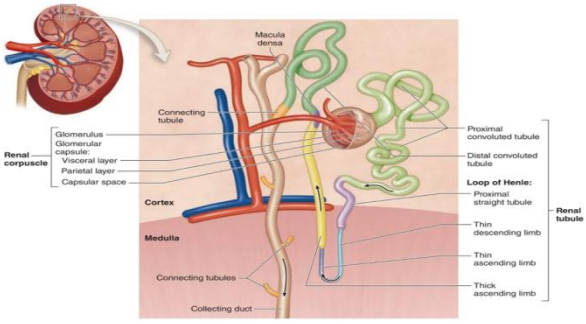

Figure 1. Structure of the nephron[10]

Pathogenesis of Nephrolithiasis

The formation of kidney stones (nephrolithiasis) is a complex process that begins with supersaturation of urine with lithogenic salts, particularly calcium oxalate (CaOx), calcium phosphate (CaP), uric acid, struvite, and cystine. Supersaturation occurs when the product of ion activity exceeds the solubility limit, influenced by low urine volume, extreme urine pH, and disturbances in the balance of promoters (osteopontin, coagulation proteins) and crystallization inhibitors (citrate, magnesium, Tamm-Horsfall protein/nephrocalcin, bikunin).[11,12]

Currently, two main mechanisms of stone formation are known. First, the fixed particle mechanism: CaOx crystals attach to Randall's plaque (suburothelial calcium phosphate deposition in the renal papillae) exposed to the surface of the Bellini duct due to epithelial erosion. This plaque becomes a heterogeneous nucleation site that facilitates progressive calcium stone growth, especially in idiopathic hypercalciuria.[13,14]

Second, the free particle mechanism: crystals form in the lumen of the tubules or collecting ducts, then undergo aggregation and intraluminal retention to form crystal plugs, especially in conditions of severe hyperoxaluria, urinary tract infection (struvite), or genetic deficiency (cystinuria). The combination of crystal retention,

slow urine flow, and local inflammation accelerates stone growth to clinically significant sizes.[15,16]

A. Risk Factors for Nephrolithiasis (Dehydration, Urine pH, and Diet)

Dehydration

Dehydration is a major risk factor for nephrolithiasis because it reduces daily urine volume (<2 L/day), leading to supersaturation of lithogenic ions such as calcium oxalate (CaOx) and uric acid. Prevention recommendations include increasing fluid intake to at least 2.5–3 L/day to achieve diuresis >2 L/day, supported by clinical trials showing a reduction in recurrence risk of up to 50%.[17,18] The use of diuretics such as thiazides may be considered in cases of refractory hypercalciuria, but fluid intake remains the most effective initial intervention.[6,18]

Urine pH

Chronically low urine pH (<5.5) is a major driver of uric acid stone formation, particularly in patients with type 2 diabetes and obesity, who often experience insulin resistance and decreased renal ammonium production. Hyperuricosuria combined with acidic pH increases the precipitation of uric acid dihydrate crystals, with a prevalence of up to 20–30% in this group. Urine alkalinization (target pH 6.5–7.0) via potassium citrate effectively prevents recurrence, especially in pure uric acid stones.[19,20]

Diet

Diet affects the risk of nephrolithiasis through the modulation of metabolic disorders such as hypercalciuria, hyperoxaluria, and hypocitraturia. The Mediterranean diet (rich in fruits, vegetables, unsaturated fats, low in red meat) is associated with a 40% reduction in risk because it increases urinary citrate and reduces oxalate. Conversely, a diet high in animal protein and sodium worsens hyperuricosuria and hypercalciuria.[4,21] Dietary modifications—such as limiting oxalate (<100 mg/day), sodium (<2.3 g/day), and animal protein (<0.8–1 g/kg BW/day)—as well as citrate supplementation can significantly reduce recurrence.[22,23]

B. Basic Clinical Correlation of Nephrolithiasis

The classic symptom of nephrolithiasis is acute renal colic: sudden flank pain, in the form of waves of cramps that radiate to the lower abdomen or genitals, accompanied by nausea, vomiting, and positional discomfort. This pain is caused by distension of the renal pelvis and ureter due to stone obstruction, with a duration of 20–60 minutes per episode.[18,24] Positive costovertebral angle palpation is often found.[25]

Hematuria is present in 85–90% of cases, both macroscopic (red/brown urine) and microscopic, due to ureteral mucosal erosion. However, the absence of hematuria does not rule out the diagnosis, as 10–15% of patients with stones are found to be without hematuria.[19] Other symptoms include dysuria, polyuria, and secondary urinary tract infections. Diagnosis is confirmed by non-contrast CT scan, which is >95% sensitive for detecting stones and complications such as hydronephrosis.[26]

CONCLUSION

Nephrolithiasis, with escalating global prevalence (10–15% lifetime risk), entails multifactorial stone genesis dominated by CaOx supersaturation (70–80%), succeeded by CaP, uric acid, struvite, and cystine. Core drivers—dehydration, pH extremes, diet-induced metabolic shifts—facilitate papillary/Bellini duct crystal nucleation/aggregation. Primary prophylaxis via hydration (>2.5 L/day),

Mediterranean diets, and pH alkalinization slashes recurrence 50–60% (GBDSG, 2024; Ferraro et al., 2021). Future inquiries must target molecular modulators (inhibitors/promoters) for precision therapies, mitigating KSD's economic/quality-of-life toll.

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