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Pathophysiology and Treatment of Nephrolithiasis and Crystal-Induced Kidney Disease Including Oxalate Nephropathy and Nephrocalcinosis

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Learning Objectives

1. To explain the epidemiology, clinical presentation and pathophysiology of nephrolithiasis and crystal-induced kidney diseases
2. To identify diagnostic clues regarding the mechanisms of urinary lithogenesis and/or kidney crystal deposition on the basis of blood test, urinalysis, crystalluria, 24-hour urine collection, stone analysis, kidney biopsy, and imaging studies
3. To analyze the underlying cause of specific pathogenic factors, such as hypercalciuria or hyperoxaluria
4. To choose the best preventive and therapeutic strategies tailored to the underlying pathology

Introduction

Kidney stones consist of hard deposits made of salt and minerals that form within the urinary space of the kidney or, more rarely, in the bladder. Kidney stones, or nephrolithiasis, are highly prevalent in humans, variable in their composition and associated risk factors. Their formation is influenced by both genetic and environmental factors (1). Crystal-induced kidney diseases, or crystalline nephropathies, are characterized by the histologic finding of intrarenal crystal deposition in the tubulointerstitium (2). Both kidney stones and crystal-induced kidney disease have a significant effect on public health, altering quality of life and potentially leading to acute kidney injury (AKI) and chronic kidney disease (CKD). Additionally, nephrolithiasis predicts metabolic and cardiovascular complications (1,3).

The objectives of this review are to (*1*) understand the underlying mechanisms of stone formation and crystal deposition, (*2*) examine the classification of nephrolithiasis and crystal-induced nephropathies and their associated risk factors and underlying causes, and (*3*) review management strategies and preventive measures.

Epidemiology and Risk Factors

Nephrolithiasis affects approximately 10% of the population in the United States, with a male-to-female ratio of about 2:1. Nephrolithiasis is more common in White patients than in Asian and Hispanic patients, with Black patients being the least affected (1). Crystal-induced kidney disease is less common than nephrolithiasis, but its true prevalence is unknown. Crystalline nephropathies are probably under-reported, notably because kidney biopsy is required for diagnosis (4).

Several risk factors contribute to the formation of nephrolithiasis: metabolic, environmental, and genetic factors. Obesity, diabetes, a sedentary lifestyle, dietary factors (such as low fluid intake and increased salt and protein intake), high temperatures, age, male gender, certain medications, a family history of nephrolithiasis, urinary tract abnormalities promoting urinary stasis, and inherited metabolic disorders all predispose to stone formation (5,6). Nephrolithiasis is largely a recurrent disease, with a 5-year relapse rate of 50%. This underscores the importance of identifying predisposing factors and implementing preventive measures to reduce relapse risk. Dietary factors, inherited metabolic disorders, certain medications, and obesity also predispose individuals to crystalline nephropathies.

Pathophysiology

Nephrolithiasis formation involves several combined mechanisms: urine solute supersaturation, crystal nucleation, and the growth and aggregation of stone-forming salts on this nucleus (Figure 1). Supersaturation is the driving force for crystallization in urine and occurs when the concentration of certain solutes—such as calcium, oxalate, phosphate, and uric acid—exceed their solubility limits. Supersaturation results from an imbalance between the concentrations of stone-forming solutes (such as hypercalciuria, hyperoxaluria, and hyperuricosuria) and crystallization inhibitors. Urine volume and urine pH influence supersaturation. Reduced fluid intake leads to higher solute concentrations whereas urine pH affects the solubility of solutes. Alkaline urine increases the solubility of uric acid and cystine while decreasing the solubility of calcium phosphate. Crystallization inhibitors—such as citrate—bind to calcium, reducing supersaturation and thus inhibiting crystal formation. In addition, urinary anatomic abnormalities that lead to urinary stasis can further promote stone formation (1).

Nucleation (microscopic crystal formation) occurs in the context of supersaturation, either spontaneously or in the presence of a "nucleating agent" such as an organic material, cells, or debris in the urine, which serves as a scaffold for crystal growth (7). Crystals grow as more solutes deposit onto the crystal surface, and can aggregate together. The rate of crystalline growth depends on urine pH and the presence of inhibitors, such as citrate (1,8). Kidney stone nucleation can sometimes form on preexisting calcium phosphate deposits at the tip of the renal papilla. These structures, called Randall's plaques, are most likely caused by transient episodes of hypercalciuria.

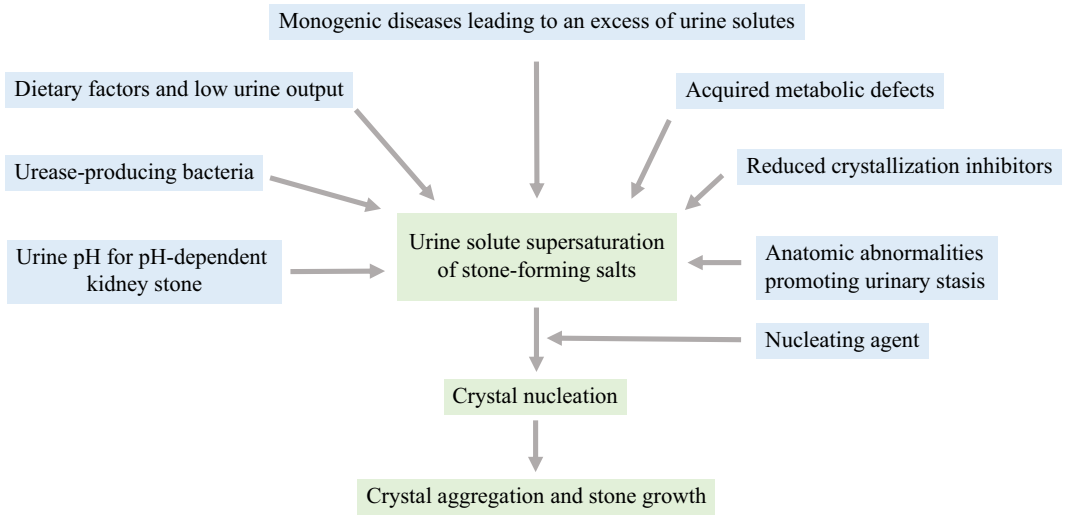

Figure 1. Overview of the pathogenesis of kidney stones.

An increased frequency of these plaques in children nowadays has been hypothesized to be related to the overprescription of vitamin D supplements during infancy in recent decades (9).

The pathogenesis of crystalline nephropathies involves several stages, also beginning with the supersaturation of urine with specific substrates and crystal nucleation. Crystal deposition causes tubular obstruction and both direct and indirect crystal-related kidney injury. When crystals are phagocytosed by tubular cells, they can destabilize lysosomes, inducing cellular stress and tubular cell death. This crystal-induced cellular necrosis leads to neighboring cell necrosis and a cascade of inflammatory responses. Key elements of the inflammatory injury include the release of danger-associated molecular patterns, activation of Toll-like receptors, complement activation, leukocyte infiltration, induction of the NLRP3 inflammasome, and secretion of interleukin-1β. It is likely that crystal-induced tubulointerstitial inflammation and tubular injury play significant roles in the development of kidney injury (2,4,10).

Clinical Presentation and Work-up

The hallmark of nephrolithiasis is renal colic, which is severe, sharp pain that typically starts in the back and radiates to the lower abdomen or groin. The pain often comes in waves as the stone progresses down the urinary tract. Macrohematuria or microhematuria is common, resulting from injury to the urinary tract. Dysuria and frequent urination may also occur, and nausea and vomiting can accompany severe pain. Nephrolithiasis may also be incidentally detected during routine imaging in asymptomatic patients. In such cases, asymptomatic nephrolithiasis is typically managed conservatively, with a focus on observation and preventive measures. However, intervention is considered if there is stone growth with a potential for obstruction, if there are complications, or in the setting of infection-related lithogenesis requiring complete stone removal.

Crystalline nephropathies are often asymptomatic and discovered as part of a work-up for increased serum creatinine levels (AKI or CKD).

The work-up for patients with nephrolithiasis includes history taking, physical examination, blood tests, urinalysis, crystalluria assessment, 24-hour urine collection, stone analysis, and imaging studies. The medical history review should include family history of nephrolithiasis, age at first kidney stone event and disease activity, dietary habits (fluid intake and sodium, calcium, oxalate, protein, and purines consumption), medication use, and other relevant comorbidities such as diabetes, autoimmune diseases like Sjögren's syndrome, recurrent urinary infections, pathologic bone fractures, chronic diarrhea, history of bariatric surgery, and gout. Blood tests should include dosage of creatinine, calcium, phosphate, bicarbonate, uric acid, 25-hydroxyvitamin D3 (25(OH)D3) and parathyroid hormone (PTH) levels, and a metabolic profile (fasting glycemia).

Crystalluria can be detected using a phase contrast microscope with a polarized light device on a fresh urine sample once it has been centrifuged (ideally within 2 hours of voiding). The type of crystals can often be identified on the basis of their shape, size, color, and polarized light birefringence. Crystalluria is very helpful in assessing metabolic disorders associated with nephrolithiasis, diagnosing rare inherited kidney stone diseases (such as cystinuria and adenine phosphoribosyltransferase [APRT] deficiency), and identifying drug-induced crystals (11). A 24-hour urine collection is useful to evaluate the excretion of substrates that may contribute to nephrolithiasis formation, such as calcium, uric acid, oxalate, and citrate (Table 1). Noncontrast low-dose computed tomography (CT) scan is the most sensitive and widely used imaging modality for diagnosing and assessing nephrolithiasis.

Given the importance of stone composition in targeting treatment and preventive measures, the work-up of all patients with nephrolithiasis should, when available, include stone analysis. The gold standard for stone evaluation is Fourier transform infrared spectroscopy combined with morphologic analysis (11–14). This morphoconstitutional analysis examines both the surface and cross section of the stone, providing information about its crystalline phase, the different components, and their distribution within the stone. The morphoconstitutional classification of Michel Daudon can be used to differentiate stones. Stones are classified into seven principal groups and 22 subgroups (14) (Table 2). This classification is of clinical importance, because certain predisposing factors are

Table 1. Interpreting of 24-hour urine collections to evaluate the risk of recurrent kidney stone formation

Pathologic Parameter	Definitions
Low urinary output	<2 L/d
Hypercalciuria	>0.1 mmol/kg per day (flow hypercalciuria) >3.8 mmol/L (concentration hypercalciuria)
High sodium intake	>6–9 g/d
High protein intake	>1 g/kg per day
Hyperoxaluria	>40 mg/d
Hypocitraturia	<1.5 mmol/d
Hyperuricuria	>750 mg/d

characteristic of specific stone groups. For example, carbapatite (subtype IVa2) is associated with genetic or acquired distal tubular acidosis. Most stones are made of calcium oxalate, calcium phosphate, uric acid, struvite, and cystine, representing together 98% of all urinary stones (15). Stone type Ia (calcium oxalate monohydrate) is the most frequently identified type, followed by stone type IIa (calcium oxalate dihydrate), stone type IIIb (uric acid dihydrate), and stone type IVa1 (carbapatite) (14).

Some patients may have anatomic abnormalities involving the ureters (such as ureteropelvic junction obstruction or duplicated collecting system) that contribute to stone formation and necessitate corrective surgery. Medullary sponge kidney is a congenital anomaly of the intrarenal collecting system, with dilated renal pelvis and calyceal abnormalities, that predisposes individuals to kidney stone formation. The diagnosis of medullary sponge kidney involves imaging studies such as contrast-enhanced CT and intravenous pyelogram.

The work-up for crystalline nephropathies is similar to that of nephrolithiasis, with the exception of stone analysis. Medications are an important cause of crystalline nephropathy, including antivirals, chemotherapy agents, and antibiotics. A kidney biopsy can confirm crystalline nephropathy and reveal evidence of interstitial nephritis and/or tubular damage caused by crystal deposition. The type of crystals can sometimes be identified using polarized light or special immunohistochemical staining techniques (4).

▸ The work-up of all patients with nephrolithiasis should, when available, include stone analysis, in addition to metabolic tests, urinalysis, crystalluria assessment, and 24-hour urine collection. A kidney biopsy will confirm crystalline nephropathy and help in identifying the type of crystal deposited.

General Management

The management of nephrolithiasis involves pain management and hydration in the acute setting, and surgical interventions in cases of obstructive stones with infection, AKI, large stones (generally >5–10 mm), failure of conservative measures, and recurrent infection related to stones. Surgical options include ureteroscopy, extracorporeal shock wave lithotripsy, and percutaneous nephrolithotomy. Effective management of nephrolithiasis outside the acute setting requires a multidisciplinary approach, including dietitians, urologists, and nephrologists, to address the complex interactions between diet, lifestyle, and individual susceptibility (15,16). To prevent recurrence of nephrolithiasis, adequate fluid intake to produce 2–2.5 L of urine per day is encouraged, as is a balanced healthy diet and weight management. Other therapeutic strategies will depend on stone composition (see below).

AKI associated with crystalline nephropathies should be managed with hydration and specific therapies according to the underlying metabolic, drug-related, or infectious cause (see below).

Specific Risk Factors and Management

Hypercalciuria, Hypocitraturia, and Nephrocalcinosis Mechanisms: Implications and Treatment. Stones whose main component contains calcium account for more than 80% of total stones (15). Low urine volume, hypercalciuria, hypocitraturia, hyperoxaluria, and hyperuricosuria predispose to calcium stone formation (1). The definition of hypercalciuria is controversial but has been historically determined as a urine calcium excretion >0.1 mmol/kg per day (4 mg/kg per day) measured in a complete 24-hour urine sample. Other definitions include a sex-specific upper normal limit of 6.25 mmol/24 h in women and 7.5 mmol/24 h in men (16). Actually, calciuria-dependent stone formation shows a graded response, largely depending on the concentration calciuria that is considered pathologic when exceeding >3.8 mmol/L (17). Hypercalciuria-dependent kidney stones include type II (calcium oxalate dihydrate) and type IV (calcium phosphate stones; carbapatite and brushite) stones. An alkaline urine pH reduces the solubility of phosphate and may promote crystallization of calcium phosphate (18). Thus, alkaline urine in association with hypercalciuria and hypocitraturia may induce calcium phosphate stone formation. Type IV stones encompass stones made of phosphate (calcium phosphate but also struvite, which is composed of magnesium ammonium phosphate). Brushite (IVd subtype) is a specific form of calcium phosphate stone associated with metabolic abnormalities such as hypercalciuria and phosphate leak notably found in primary hyperparathyroidism. Brushite stones have high density and are therefore resistant to extracorporeal shock wave lithotripsy.

Figure 2 illustrates the diagnostic approach to hypercalciuria, which requires the assessment of serum calcium, phosphate, PTH, and 25(OH)D3 levels. If the patient presents with hypercalcemia and a nonsuppressed or elevated PTH, the most likely diagnosis is primary hyperparathyroidism. A thorough review of the patient's treatment should exclude the use of any medication known to cause hypercalciuria through various mechanisms, such as acetazolamide, topiramate, and excessive vitamin D or vitamin A supplementation. In other cases, dietetic hypercalciuria must be ruled out by evaluating salt and protein intake on the basis of 24-hour urine collection, because diet is the most frequent cause of hypercalciuria in adults (19). If dietetic hypercalciuria is excluded or hypercalciuria persists after proper dietary adaptation, an oral calcium load test (or Pak test) can be performed to identify the mechanism causing hypercalciuria and, particularly, to exclude normocalcemic primary hyperparathyroidism (20–23). This dynamic test includes serial blood and urine sampling

Table 2. Classification of stones according to Michel Daudon (with permission from Michel Daudon)

Subtype	Main Component	Associated Conditions
Ia	Calcium oxalate monohydrate (whewellite)	Low urinary output Dietary hyperoxaluria Medullary sponge kidney
Ib	Calcium oxalate monohydrate (whewellite)	Low urinary output Dietary hyperoxaluria Medullary sponge kidney
Ic	Calcium oxalate monohydrate (whewellite)	Primary hyperoxaluria
Id	Calcium oxalate monohydrate (whewellite)	Low urinary output Dietary hyperoxaluria Urinary stasis
Ie	Calcium oxalate monohydrate (whewellite)	Enteric hyperoxaluria
IIa	Calcium oxalate dihydrate (weddellite)	Hypercalciuria
IIb	Calcium oxalate dihydrate and monohydrate (weddellite + whewellite)	Hypercalciuria and hyperoxaluria
IIc	Calcium oxalate dihydrate (weddellite)	Hypercalciuria Urinary stasis
IIIa	Uric acid anhydrous	Low urine pH Urinary stasis
IIIb	Uric acid dihydrate	Low urine pH Insulin resistance Hyperuricuria
IIIc	Urate salts including ammonium hydrogen urate	Hyperuricuria with alkaline pH Urease-producing bacteria
IIId	Ammonium hydrogen urate	Hyperuricemia, diarrhea and low phosphate intake
IVa1	Carbapatite	Hypercalciuria Primary hyperparathyroidism Alkaline pH
IVa2	Carbapatite	Distal renal tubular acidosis
IVb	Carbapatite and struvite	Urinary tract infection Urease-producing bacteria
IVc	Struvite	Urinary tract infection Urease-producing bacteria
IVd	Brushite	Hypercalciuria Primary hyperparathyroidism Phosphate leak
Va	Cystine	Cystinuria
Vb	Cystine	Cystinuria with alkaline therapy
VIa	Proteins	Chronic pyelonephritis
VIb	Proteins and drugs or metabolic compounds	Drug-induced kidney stone
VIc	Proteins and whewellite	Kidney failure Dialysis
VII	Miscellaneous	Uncommon purines Drugs, other components
Mixed types		
I+II	I (a or b) + II (a or b)	Dietary hyperoxaluria and hypercalciuria
I+III	I (a or b) + III (a or b)	Type 2 diabetes Metabolic syndrome
I+II+IV	I (a or b) + II (a or b) + IV (a or d)	Medullary sponge kidney
II+IV	II (a or b) + IVa1	Primary hyperparthyroidism Hypercalciuria

Stone analysis includes a morphologic analysis and infrared spectroscopy that gives the constitutional analysis. The classification is divided into seven groups and 22 subgroups. Specific types of stones are associated with particular conditions.

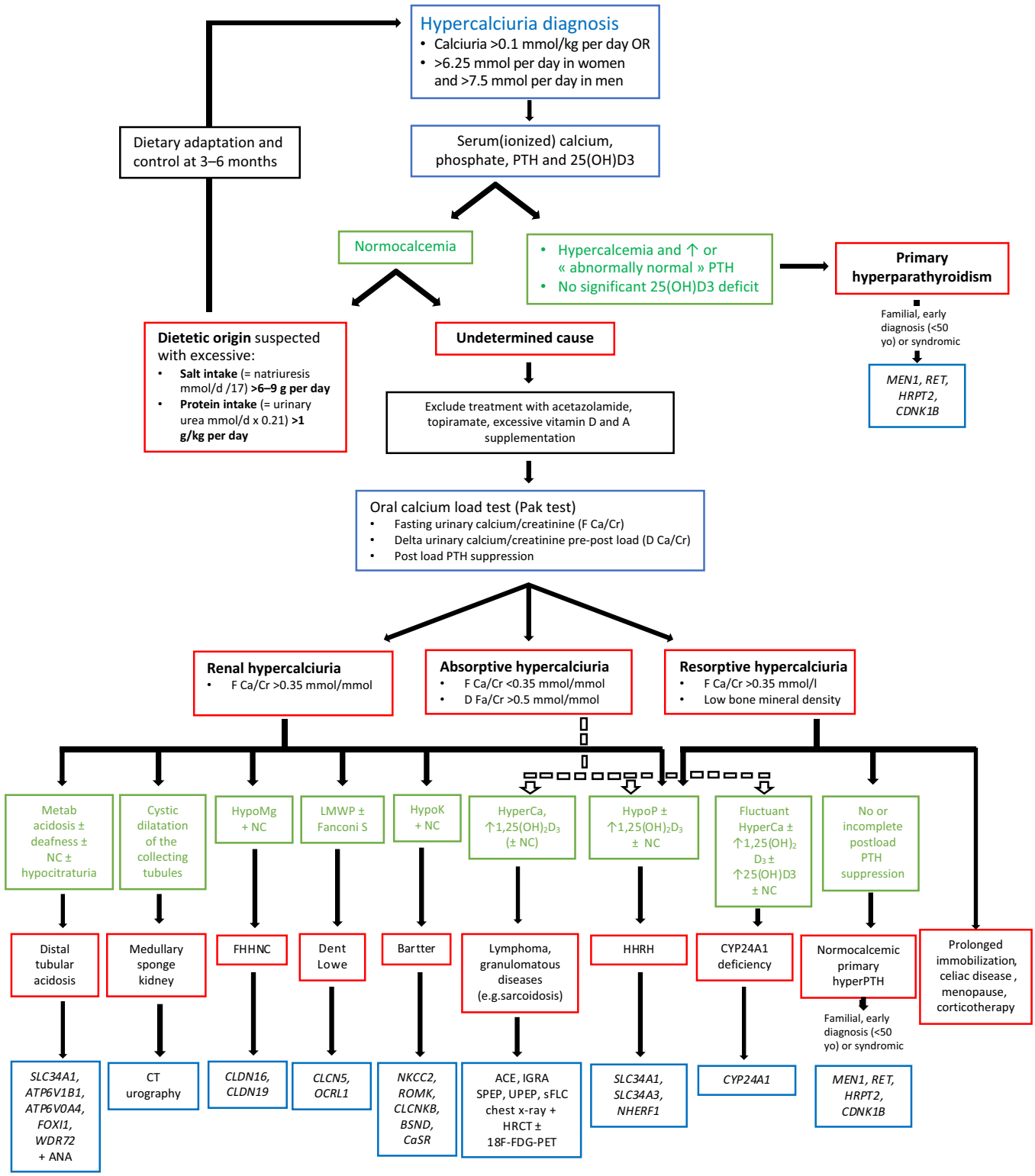

Figure 2. Hypercalciuria diagnosis algorithm. 1,25(OH)2D3, 1,25-dihydroxyvitamin D3; ^{18}F-FDG-PET, ^{18}fluoro-D-glucose positron emission tomography; ACE, angiotensin-converting enzyme; ANA, antinuclear antibodies; FHHNC, familial hypomagnesemia with hypercalciuria and nephrocalcinosis; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; HRCT, high-resolution computed tomography; HyperCa, hypercalcemia; HyperPTH, hyperparathyroidism; HypoK, hypokalemia; HypoMg, hypomagnesemia; HypoP, hypophosphatemia; IGRA, interferon-γ release assay; LMWP, low molecular weight proteinuria; NC, nephrocalcinosis; PTH, parathormone; sFLC, serum free light chains; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; yo, years old. Modified from ref. 23.

over 4 hours after an oral calcium load of 1 g following a low-calcium diet (3–7 days). Fasting urinary calcium-to-creatinine ratio and the difference between the same ratios after oral calcium load can help discern between resorptive, absorptive, or renal hypercalciuria. Depending on the type of hypercalciuria and associated biologic or radiologic signs, a genetic analysis or other imaging techniques can be performed to determine the precise diagnosis (Figure 2) (23,24).

Treatment of hypercalciuria-dependent kidney stones first relies on general dietary measures, especially increased hydration (sufficient to allow urine volume of at least 2.5 L/d), but also salt and protein restriction (6 g/d and 0.8–1 g/kg per day, respectively) (25–27). Appropriate calcium intake (0.8–1 g, and 1.2 g for menopausal women) is recommended because low calcium intake may lead to associated secondary hyperoxaluria and bone demineralization. Moreover, equal distribution of calcium intake between the three main meals of the day may prevent prandial calciuria peaks (experts' opinion) (26). In case of associated hypocitraturia after dietary adaptation, and in the absence of bacterial contamination, citrate supplementation can be introduced in order to inhibit calcium oxalate crystallization (27,28). Finally, in cases of persistent hypercalciuria after dietary adaptation and after exclusion of hypercalcemia and primary hyperparathyroidism, thiazides have been used as a way to decrease calciuria. Up until recently, only small randomized controlled trials (RCTs) had been performed with various agents and doses and did not demonstrate a significant effect of thiazides on the prevention of kidney stones, and had several methodologic limitations that limited interpretation. Recently, the Standard and Low Dose Hydrochlorothiazide (HCTZ) in the Recurrence Prevention of Calcium Nephrolithiasis (NOSTONE) trial, a large RCT evaluating the effect of 12.5 mg, 25 mg, or 50 mg hydrochlorothiazide once daily on a composite outcome of symptomatic or radiologic recurrence of kidney stones, showed no significant effect of HCTZ on stone recurrence (29). Nevertheless, this study bore multiple significant limitations. Patients were selected on the basis of stone composition rather than the presence of hypercalciuria, and the precise type of calcium oxalate stone was not determined. The absence of categorization of the type of calcium oxalate stone is problematic because calcium oxalate monohydrate is oxalate dependent and not calcium dependent. Moreover, the clinical stone passage outcome cannot account for previously formed stones, and follow-up may have been too short to detect a significant effect of HCTZ on stone recurrence. Finally, the definition of hypercalciuria was inaccurate, and patients seemed to have a high-salt diet, potentially limiting the effect of thiazides on calciuria (29–31).

Patients suffering from calciuria-dependent kidney stones are exposed to a higher risk of bone fractures, because of a negative calcium balance. Use of thiazides but also of alkali treatment in this population may limit demineralization, but this warrants further investigation. Of note, thiazide use has been associated with an increased risk of skin cancer, and sun protection measures and early screening should be encouraged (28). Overall, considering the potential beneficial effects of thiazides on both stone recurrence and bone density, and the significant limitations of the NOSTONE trial, use of thiazides can still be recommended in cases of persistent hypercalciuria with recurrent stone disease after dietary adaptation and exclusion of primary hyperparathyroidism.

Hypocitraturia also contributes to the formation of nephrolithiasis, particularly calcium-based stones. Citrate is the most abundant anion in the urine and normally acts as a natural crystallization inhibitor by binding calcium. Citrate also increases urine pH, increasing solubility of calcium phosphate and calcium oxalate. The causes of hypocitraturia are divided into metabolic and dietary factors. Metabolic causes that contribute to hypocitruria include renal tubular acidosis, chronic diarrhea, hyperparathyroidism, carbonic anhydrase inhibitors, and certain inherited diseases. Dietary causes contributing to hypocitraturia include low potassium intake and high animal protein consumption. Hypocitraturia is diagnosed using a 24-hour urine collection. Therapeutic management involves dietary changes (increasing intake of potassium- and citrate-rich foods such as fruits and vegetables). If hypocitraturia persists after these changes, potassium citrate supplements may be started.

Nephrocalcinosis refers to the generalized deposition of calcium salts in the kidney tissue and is detected on ultrasound or CT scans. Nephrocalcinosis occurs in the renal tubules or interstitium and is an indicator of abnormal calcium metabolism, such as hypercalcemia, vitamin D intoxication, hyperparathyroidism, or certain inherited disorders. Nephrocalcinosis may precede the formation of nephrolithiasis, but it does not necessarily result in stone formation. Genetic kidney diseases associated with nephrocalcinosis include variants leading to gain of function in the calcium sensing receptor (*CaSR* gene), homozygous or heterozygous pathogenic variants in *CYP24A1* gene, mono- or biallelic variants leading to disorders of the proximal tubular transport of phosphate (*SLC34A1* and *SLC34A3* genes or *SLC9A3R1* gene encoding for NHERF1—a regulatory factor for the expression of NPT2a), familial hypomagnesemia with hypercalciuria and nephrocalcinosis (*CLD16* and *CLD19* genes), distal renal tubular acidosis (*ATP6V0A4*, *ATP6V1B1*, *SLC4A1*, *FOXI1*, and *WDR72* genes), Dent and Lowe syndromes (*CLCN5* and *OCRL* genes), and Bartter syndrome (types 1, 2, and 3) (32–33).

Hyperoxaluria: Primary versus Secondary, Oxalate Stones and Nephropathy, Management. Hepatic oxalate production from glyoxylate accounts for approximately 60%–80% of plasma oxalate, whereas the remaining 20%–40% comes from the intestinal absorption of dietary oxalate (4) (Figure 3). Only 5%–15% of dietary oxalate is absorbed, largely due to the binding of oxalate to calcium in the gut and its degradation by *Oxalobacter formigenes* in the intestine. Hyperoxaluria is characterized by urinary oxalate excretion greater than 40–45 mg/24 h (500 μmol/L) or by using urinary oxalate-to-creatinine ratio. This condition can result from either an inherited disorder of glyoxylate metabolism, which leads to excessive oxalate production by the liver (primary hyperoxaluria), or increased absorption of oxalate in the intestine (secondary hyperoxaluria) (Figure 3) (4). Primary hyperoxaluria includes types 1, 2, and 3, which are rare autosomal recessive disorders caused by mutations in the *AGXT*, *GRHPR*, or *HOGA1* genes, respectively. These disorders of glyoxylate metabolism lead to accumulation of oxalate in various organs, including the kidneys, where it causes nephrolithiasis (typically of calcium oxalate monohydrate type I) and calcium oxalate deposition. Over time, this contributes to CKD, which further decreases urinary oxalate excretion. Systemic oxalosis results when oxalate deposits accumulate in tissues such as the bone, skin, retina, and central nervous system, particularly when the glomerular filtration rate (GFR) drops below 30–45 ml/min per 1.73 m^2. Primary hyperoxaluria should be considered in children with kidney stones or nephrocalcinosis, and in adults with recurrent calcium oxalate

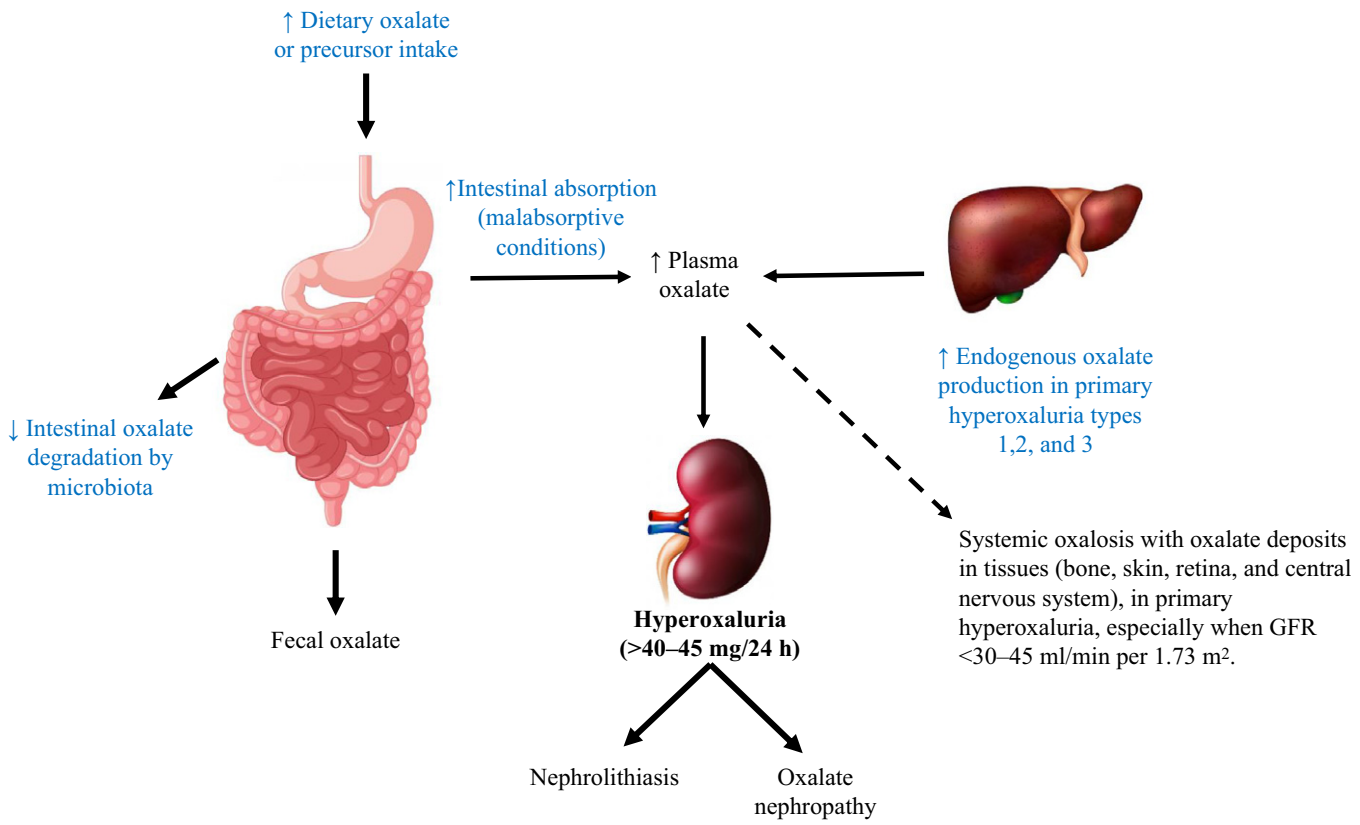

Figure 3. Primary and secondary hyperoxaluria. Causes of primary and secondary hyperoxaluria are highlighted in blue. Hyperoxaluria may lead to nephrolithiasis and oxalate nephropathy. Systemic oxalosis (deposition of calcium oxalate in different tissues such as bones) is associated with primary hyperoxaluria, especially when GFR drops under 30–45 ml/min per 1.73 m^2. Images used from https://www.freepik.com. Adapted from ref. 4.

nephrolithiasis, especially if stone analysis shows a subtype Ic (Table 2).

Secondary hyperoxaluria results from increased dietary oxalate or oxalate precursor intake (vitamin C, and gelatin-based sweets through hydroxyproline metabolism), fat malabsorption (chronic pancreatitis, gastric bypass, and short bowel syndrome) and decreased intestinal oxalate degradation due to alterations in gut microbiota (antibiotherapy) (4). The subtype of stone linked with enteric hyperoxaluria is typically Ie (Table 2).

Secondary hyperoxaluria is the main risk factor for calcium oxalate nephrolithiasis. Obesity and metabolic syndrome are also associated with calcium oxalate nephrolithiasis. In patients with malabsorption, fluid loss, and citrate level also contribute to the pathogenesis of urolithiasis. Hyperoxaluria may also lead to the deposition of calcium oxalate crystals in the tubulointerstitium, a condition referred to as oxalate nephropathy. Kidney biopsy in such cases typically shows oxalate crystals within tubular lumens and tubular epithelial cells and, less frequently, in the interstitium. These crystals are strongly birefringent under polarized light, a characteristic that distinguishes them from calcium phosphate crystals (4,34). We recently suggested incorporating an oxalate crystal-to-glomerulus ratio of ≥0.25 in the definition of oxalate nephropathy. This is because small amounts of calcium oxalate crystals may also be present in tubules in patients with other causes of kidney damage, especially in those with reduced GFR. The prevalence of oxalate nephropathy remains unclear. In a study of 2265 consecutive native kidney biopsies performed over 9 years, we identified 22 cases (1%) of oxalate nephropathy (34). Most of the patients presented with hypertension, diabetes, and/or a history of CKD. The most common causes of oxalate nephropathy in this cohort were chronic pancreatitis and gastric bypass surgery (34). Recent studies have identified a link between the use of certain hair-straightening products containing glyoxylic acid and the development of oxalate nephropathy, which was supported by animal model data (35–37). Calcium oxalate crystal formation and deposition in patients with secondary hyperoxaluria may be triggered by additional factors such as hypovolemia, use of diuretics and/or renin-angiotensin system blockers, use of antibiotics, and inflammation (4). The prognosis of oxalate nephropathy varies widely. Approximately half of patients progress rapidly to kidney failure. However, outcomes tend to be more favorable in individuals who develop oxalate nephropathy secondary to the acute ingestion of large amounts of dietary oxalate (35).

Management of oxalate nephropathy includes adequate hydration, appropriate dietary calcium intake and calcium supplementation during meals that binds oxalate in the gut and reduces its absorption, and use of potassium citrate to prevent formation of

calcium-oxalate crystals. The underlying cause of hyperoxaluria should be addressed, such as RNA interference therapies in primary hyperoxaluria, dietary modifications to reduce oxalate intake, and pancreatic enzyme therapy in certain malabsorptive states (4,38).

Uric Acid Stones

Low urinary pH is the primary driver for uric acid stone formation, because uric acid becomes less soluble when the pH falls below 5.5. Patients with insulin resistance and metabolic syndrome, commonly seen in patients with type 2 diabetes, often have impaired renal ammonium excretion, contributing to urinary acidification. Additionally, hyperuricosuria can exacerbate this process. Uric acid stones are typically radiolucent and have a CT scan density of less than 600 Hounsfield units. Deficiencies in URAT1 (*SLC22A12*) and GLUT9 (*SLC2A9*), which are responsible for urate reabsorption, can lead to hypouricemia and hyperuricuria, contributing to uric acid–related issues.

The cornerstone of uric acid stone management is urine alkalinization. The treatment of choice is the use of potassium citrate, which not only increases urine pH but also inhibits the calcium-oxalate crystallization often present in mixed stone cases. Xanthine oxidase inhibitors, such as allopurinol and febuxostat, can also help lower hyperuricosuria in patients with recurrent uric acid stones and hyperuricemia.

Dietary recommendations for patients with uric acid stone disease include adequate hydration and an alkalinizing diet with limited protein intake, but also a limited intake of purine-rich foods and a reduction in dietary fructose intake, which can lead to hyperuricemia (1).

Drug-Induced Stones and Nephropathy

Certain drugs can either directly or indirectly induce nephrolithiasis, accounting for approximately 1%–2% of kidney stones. To confirm drug-induced urolithiasis, stone analysis using physical methods such as infrared spectroscopy or x-ray diffraction is necessary to detect the drug or its metabolites within the stone (39). Drug-induced urolithiasis can be classified into two categories according to the drugs' direct or indirect effects. The first category encompasses poorly soluble drugs with high urinary excretion, especially when taken in high doses, which may crystallize in the urine. These include protease inhibitors (such as indinavir and atazanavir) and sulfadiazine, a first-generation sulfonamide (26). Notably, indinavir stones are completely radiolucent on plain abdominal x-ray, similarly to many other drug-induced stones. However, indinavir stones have the unique characteristic of being undetectable on noncontrast CT scans and can only be visualized using ultrasonography or contrast-enhanced CT. Additionally, indinavir's solubility is highly pH dependent, decreasing when urinary pH is higher. Conversely, sulphonamide-induced kidney stones have greater solubility at alkaline urine pH.

Other antibacterial agents can also contribute to kidney stone formation. For example, ampicillin, ciprofloxacin, and third-generation cephalosporins may lead to crystal formation. Amoxicillin, when administered in high intravenous (IV) doses, can precipitate as amoxicillin trihydrate crystals in the urine, causing AKI through amoxicillin crystalluria. This condition almost exclusively occurs with high doses of intravenous amoxicillin, because the oral absorption of amoxicillin in adults is nonlinear and saturable (40). Additionally, vancomycin has been linked to obstructive tubular casts with aggregates of vancomycin entangled with uromodulin in certain patients, providing a new insight into tubular cast formation (41). Diagnosis of this type of drug-induced kidney stone involves using a phase contrast microscope with polarized light to identify the characteristic crystals (stone analysis) associated with the specific drug.

The second category includes medications that affect urinary pH or influence the renal excretion of calcium, phosphate, oxalate, citrate, uric acid, or other purines, leading to stone formation. For example, carbonic anhydrase inhibitors such as acetazolamide and topiramate increase urinary pH, which can promote the formation of calcium phosphate stones. Similarly, calcium supplements, particularly when combined with vitamin D, can lead to hypercalciuria and nephrolithiasis. Some individuals, particularly those who are predisposed to enhanced conversion of 25(OH)D3 to calcitriol, may be more prone to developing kidney stones in response to vitamin D supplementation (9).

Ascorbic acid (vitamin C) overdose has been linked to an increased risk of oxalate-dependent nephrolithiasis, because it is a precursor of oxalate. However, a daily intake below 500 mg is not associated with kidney stone formation (42). Orlistat, a medication that inhibits dietary fat absorption, can also induce secondary hyperoxaluria (4). Sodium phosphate, used as a purgative for colonoscopy, can induce AKI due to calcium phosphate deposition in the kidneys (43).

Drug-induced crystalline nephropathies are associated with AKI and/or CKD, crystalluria, and detection of crystals within the kidney biopsy. Medications associated with nephrolithiasis may also cause crystalline nephropathies (sulfadiazine, sulfamethoxazole, indinavir, atazanavir, darunavir, amoxicillin, vancomycin, ascorbic acid, orlistat, and sodium phosphate laxatives). Additionally, high-dose IV methotrexate may induce AKI through direct cytotoxicity and precipitation of crystals within the tubular lumens, leading to urinary flow obstruction and generation of tubulointerstitial inflammation. Urine sediment may reveal free methotrexate crystals and crystal-containing casts. Kidney biopsy shows small needle-shaped crystals with weak periodic acid-Schiff staining and a yellow or brown stain on hematoxylin and eosin stain and are strongly birefringent with polarization (2). Patients receiving iv methotrexate should receive iv hydration and urine alkalinization to elevate pH above 7.

Protease inhibitor–induced crystalline nephropathy is more likely to occur in cases of volume depletion, high drug dosing, underlying liver disease, and alkaline urine. Atazanavir and darunavir are associated with crystalline nephropathy, and boosting with ritonavir increases the risk for darunavir-associated intratubular crystal formation (2). Rapid iv infusion and/or high doses of acyclovir can cause crystalluria and crystalline nephropathy. Kidney biopsy will show needle-shaped acyclovir crystals that are birefringent on polarization. Oral use of ciprofloxacin has also been associated with crystalline nephropathy.

Management of drug-induced crystalline nephropathies includes discontinuation of the causative drug, iv hydration to increase urine flow, and modification of urine pH according to stone type.

Infection-Related Stones

Chronic or recurrent urinary tract infections caused by urease-producing microorganisms can lead to the formation of magnesium

ammonium phosphate stones, also known as struvite stones. Urease-producing bacteria include *Proteus*, *Klebsiella*, *Staphylococcus*, *Pseudomonas*, *Providentia*, *Serratia*, and *Morganella*. The urease enzyme produced by these bacteria breaks down urinary urea into ammonia and carbon dioxide (CO_2). Subsequent hydrolysis of ammonia leads to the formation of ammonium and bicarbonate. This process significantly increases urinary pH, making it alkaline (pH >7). The elevated pH promotes the supersaturation of magnesium ammonium phosphate and calcium phosphate (apatite). The apatite crystals can become enriched with carbonate ions, leading to an increased carbonate-to-phosphate ratio (also known as the carbonatation rate). When the carbonatation rate exceeds 15%, the formation of struvite stones becomes more likely. This high carbonatation rate further facilitates the precipitation of struvite, contributing to stone formation in the urinary tract. Moreover, bacterial biofilm also plays a role in crystal precipitation.

In developed countries, the prevalence of struvite stones is relatively low, accounting for about 4% of urinary stones. However, in developing countries, this figure rises significantly, ranging from 10% to 20% (44). Struvite stones are much more common in women because of their higher susceptibility to urinary tract infections compared with men. Additionally, individuals with urinary catheters, neurogenic bladder, or urinary diversion are at an increased risk of developing infection stones. The elevated risk of struvite stones in certain individuals is primarily due to chronic bacterial colonization of the urinary tract.

Struvite stones are typically radiopaque because of their calcium content and are usually present with a CT scan density of up to 900 Hounsfield units. These stones can grow rapidly, and large struvite stones often develop into staghorn calculi, which can expand and block the renal pelvis and calyces. However, not all staghorn stones are struvite based. Any major active lithogenic mechanisms—such as increased calcium, phosphate, or other metabolic factors—can lead to the formation of staghorn calculi.

Urine culture or stone culture is essential for diagnosing infection-related kidney stones. The primary treatment goal is complete stone removal and urinary infection eradication. Failure to achieve complete stone clearance can lead to a high recurrence rate. There are limited data to guide the nonsurgical treatment of staghorn calculi apart from the use of culture-specific antibiotics, ideally those with good tissue penetration. The European Association of Urology (EAU) Guidelines (2024 edition) provide further insights on the management of these conditions (45). The EAU Guidelines confirm the importance of eradicating the infection after complete surgical stone removal. However, there are no conclusive data regarding the optimal duration for postoperative antibiotic therapy. These guidelines also propose, as a weak recommendation, the use of ammonium chloride or methionine to promote urinary acidification and limit calcium phosphate or struvite crystallization. Occasionally, urease inhibitors, such as acetohydroxamic acid, can be used, when available, to acidify urine. Acetohydroxamic acid has been shown to reduce struvite stone growth and lower recurrence rates by decreasing urinary alkalinity and ammonia levels. However, its use is often limited by significant side effects, including phlebitis, rash, and hemolytic anemia. Additionally, correcting underlying anatomic abnormalities or functional bladder disorders that predispose patients to urinary infections, along with addressing other prolithogenic factors, is essential in preventing infection-related stone recurrence (45).

Genetic Kidney Stones (Cystinuria and 2,8-Dihydroxyadenine Stones)

Kidney stone formation is strongly influenced by genetic factors, with a positive family history reported in 30%–60% of patients with stones (46). Mendelian causes of nephrolithiasis are observed in up to 30% of children and 1%–5% of adults who develop kidney stones. A recent review of 13 studies including 1675 patients (77% pediatric) found that 333 (20%) affected patients had a monogenic disorder. The rate of detection was higher in children (26%) in comparison with adults (8%) (47). Among the reviewed studies, seven (54%) used a Whole Exome Sequencing approach, whereas six used a targeted panel approach. Cystinuria was the most common diagnosis in both populations (23% in pediatric patients and 45% in adult patients).

Cystinuria (Online Inheritance in Mendelian Man [OMIM] #220100) is an autosomal recessive disorder characterized by defective reabsorption of dibasic amino acids (cystine, ornithine, lysine, and arginine, referred to as COLA) in the renal proximal tubule and epithelial cells of the gastrointestinal tract. This disease has a global prevalence of about one in 7000 births. Biallelic pathogenic variants in *SCL7A9* or *SLC3A1* genes, which code for a heterodimeric complex responsible for reabsorbing cystine in the proximal tubule, lead to abnormal renal excretion of COLA amino acids. Because of cystine's poor solubility at physiologic urine pH, it is the only dibasic amino acid that can form recurrent kidney stones. Stone analysis and the presence of crystalluria, with characteristic hexagonal crystals, can aid in diagnosis. This can be confirmed by quantifying 24-hour urinary cystine excretion (48,49).

Recent consensus statements on cystinuria management further highlight advances in understanding and treatment strategies (50,51). The cornerstone of stone prevention in cystinuria involves high fluid intake sufficient to keep urine cystine concentration below 1 mmol/L. Additionally, a low-salt and low–animal protein diet along with urinary alkalinization are essential strategies to increase cystine's urinary solubility. Although the exact mechanism is poorly understood, dietary sodium restriction has been shown to lower urinary cystine levels. Similarly, reducing the intake of animal protein decreases cystine excretion, likely by limiting both cystine and its precursor, methionine. In addition, reducing protein intake decreases the number of protons in the urine, leading to a higher urinary pH, which, in turn, increases cystine solubility. Urinary alkalinization is also recommended as a strategy to enhance cystine solubility. Potassium citrate, typically in dosages of 40–80 mEq per day, is the first-line agent recommended to achieve a urinary pH of 7.5 to 8.

If kidney stone formation persists despite these conservative measures, pharmacologic thiol-containing drugs may be considered as an adjunct to further reduce cystine crystallization. The thiol-containing drugs α-mercaptopropionylglycine (tiopronin) and D-penicillamine work by reducing the disulfide bonds in cystine, forming a more soluble drug-cystine complex, which ultimately lowers urinary cystine levels. However, their use is limited because of a range of adverse effects, including drug sensitivity reactions, secondary membranous nephropathy, and liver and hematologic toxicities. Currently, tiopronin is not widely available outside the United States.

Adenine phosphoribosyltransferase (APRT) deficiency (OMIM #614723) is a rare autosomal recessive disorder of purine metabolism. APRT normally converts adenine to adenine monophosphate,

but, when APRT is deficient, adenine is instead converted to 2,8-dihydroxyadenine (2,8-DHA) by xanthine oxidase (XO). This results in the overproduction and excretion of poorly soluble 2,8-DHA, leading to the formation of radiolucent kidney stones and crystalline nephropathy, which can cause progressive CKD. The global prevalence of APRT deficiency varies across populations: one in 50,000 to 100,000 in Caucasians, one in 27,000 in the Japanese population, and more than one in 15,000 in the Icelandic population (52,53).

Diagnosis can be made through the identification of 2,8-DHA crystals in kidney stones *via* spectrophotometry, the presence of typical crystalluria (with spherical crystals displaying a characteristic Maltese cross pattern under polarized light), absent APRT activity in red blood cell lysates, or the identification of biallelic pathogenic variants in the APRT gene. DHA crystals may be mistaken for calcium oxalate crystals on kidney biopsy because both are birefringent under polarized light (54). However, DHA crystals are typically brownish, and affected infants may present with dark urine stains in their diapers. Primary treatments for APRT deficiency include high fluid intake and XO inhibitors, such as allopurinol or febuxostat. These therapies reduce 2,8-DHA excretion, helping to prevent stone formation and the progression of CKD. These treatments should be initiated early to limit kidney damage, emphasizing the importance of early diagnosis to prevent kidney failure. Additionally, kidney transplant patients with unrecognized APRT deficiency are at risk of disease recurrence in the renal graft, which may lead to secondary graft loss (55).

Lesch-Nyhan syndrome (OMIM #300322) is an X-linked disorder of purine metabolism caused by a complete deficiency of hypoxanthine-guanine phosphoribosyltransferase. This deficiency leads to uric acid overproduction, which results in severe gout and uric acid kidney stones. The condition is also associated with significant neurologic and behavioral issues. Management typically involves XO inhibitors, urine alkalinization, and high fluid intake.

Xanthinuria (OMIM #278300 and #603592) is a rare, recessive disorder caused by the deficiency of xanthine oxidoreductase, which impairs the breakdown of hypoxanthine and xanthine into uric acid, leading to the accumulation of xanthine. Patients with xanthinuria have marked hypouricemia and high urinary xanthine, which has low solubility and may result in the formation of kidney stones, although the condition is not pH sensitive. There is no specific treatment for xanthinuria other than a low-purine diet and high fluid intake.

Innovative Therapies in Managing Nephrolithiasis

Recent studies have explored the potential role of sodium-glucose cotransporter 2 (SGLT2) inhibitors in preventing kidney stone formation. Large cohort studies of patients with type 2 diabetes reported risk reductions of 26%–49% for incident kidney stone events with SGLT2 inhibitors use (56). A meta-analysis including 739,197 patients treated with SGLT2 inhibitors revealed a lower risk of nephrolithiasis (odds ratio 0.66 [95% CI, 0.47 to 0.93, $P=0.02$]) compared with the placebo group (57). The reduction in risk may be attributed to the drug's effects on fluid balance, urinary calcium levels, and overall urine volume.

The SWEETSTONE (empagliflozin in nondiabetic individuals with calcium and uric acid kidney stones) trial was the first prospective trial evaluating the effect of therapy with an SGLT2 inhibitor (empagliflozin) in patients with calcium or uric acid kidney stones who did not have diabetes (58). In this study, empagliflozin significantly lowered urine relative supersaturation ratios for calcium phosphate (relative difference −36% [95% CI, −48% to −21%, $P<0.001$]), but not calcium oxalate or uric acid, in patients with calcium stones. In patients with uric acid stones, empagliflozin reduced relative supersaturation ratios for uric acid (relative difference −30% [95% CI, −44% to −12%, $P=0.002$]) but not for calcium oxalate or phosphate. Relative supersaturation ratios are key validated surrogate parameters for kidney stone formation risk.

Conclusions

Nephrolithiasis is a prevalent and multifactorial condition that significantly affects public health, potentially leading to acute kidney disease, CKD, and metabolic and cardiovascular complications. Understanding the mechanisms behind stone formation and crystal deposition, along with identifying the risk factors and underlying causes, is essential for effective management and prevention. The disease often recurs, highlighting the importance of tailored preventive measures.

Crystal-induced nephropathies, although less common, can also cause significant renal damage and are characterized by crystal deposition leading to tubular injury and inflammation.

Both conditions require comprehensive diagnostic evaluation, including imaging, urine analysis, and stone composition analysis, which guide appropriate treatment and management strategies.

Nephrolithiasis is largely a recurrent disease, with a 5-year relapse rate of 50%. This underscores the importance of identifying predisposing factors and implementing preventive measures to reduce relapse risk.

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