Kidney Stones 2012: Pathogenesis, Diagnosis, and Management

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Context: The pathogenetic mechanisms of kidney stone formation are complex and involve both metabolic and environmental risk factors. Over the past decade, major advances have been made in the understanding of the pathogenesis, diagnosis, and treatment of kidney stone disease.

Evidence Acquisition and Synthesis: Both original and review articles were found via PubMed search reporting on pathophysiology, diagnosis, and management of kidney stones. These resources were integrated with the authors’ knowledge of the field.

Conclusion: Nephrolithiasis remains a major economic and health burden worldwide. Nephrolithiasis is considered a systemic disorder associated with chronic kidney disease, bone loss and fractures, increased risk of coronary artery disease, hypertension, type 2 diabetes mellitus, and the metabolic syndrome. Further understanding of the pathophysiological link between nephrolithiasis and these systemic disorders is necessary for the development of new therapeutic options.

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The increased prevalence of kidney stone disease is pandemic (1). The lifetime risk of kidney stones is currently at 6–12% in the general U.S. population (2). Nephrolithiasis has become increasingly recognized as a systemic disorder (3) that is associated with chronic kidney disease, nephrolithiasis-induced bone disease (4), increased risk of coronary artery disease, hypertension, type 2 diabetes mellitus, and the metabolic syndrome (MS) (5). Without medical treatment, nephrolithiasis is a chronic illness with a recurrence rate greater than 50% over 10 yr (6). Given that the annual expenditure in the United States exceeds $5 billion, the economic and social burden of nephrolithiasis is immense (7).

Epidemiology

The prevalence of nephrolithiasis in the United States has doubled over the past three decades. This increase has also been noted in most European countries and Southeast Asia (1). Racial and ethnic differences are seen in kidney stone disease, primarily occurring in Caucasian males and least prevalent in young African-American females. The prevalence in Asian and Hispanic ethnicities is intermediate (1).

The incidence of nephrolithiasis is highest in Caucasian males (2), where the incidence of kidney stones rises after age 20, peaks between 40 and 60 yr of age (at approximately 3 per 1000 per year), and then declines (8). In females, the incidence rate is higher in the late 20s, decreases by age 50, and remains relatively constant thereafter (2, 8).

Pathophysiological Mechanism(s) of Calcium Stones

Approximately 80% of calcium kidney stones are calcium oxalate (CaOx) (9), with a small percentage (15%) of calcium phosphate (CaP) (10). The pathophysiological mechanisms for calcium kidney stone formation are complex and diverse and include low urine volume, hypercal-

Abbreviations: Ca:Cr, Calcium:creatinine (ratio); CaOx, calcium oxalate; CaP, calcium phosphate; dRTA, distal renal tubular acidosis; MS, metabolic syndrome; 1,25(OH)2D, 1,25-dihydroxyvitamin D; PBMC, peripheral blood mononuclear cells; RS, relative supersaturation; UA, uric acid; VDR, vitamin D receptor.
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Hypercalciuria is the most prevalent abnormality in calcium kidney stone formers. It is detected in 30–60% of adults with nephrolithiasis (12). In 1939, Flocks (13) initially described the link between hypercalciuria and nephrolithiasis. In 1958, Albright and Henneman (14, 15) applied the term “idiopathic hypercalciuria.” The pathophysiological mechanisms for hypercalciuria are numerous and may involve increased intestinal calcium absorption, decreased renal calcium reabsorption, and enhanced calcium mobilization from bone (4, 16–18). However, intestinal calcium hyperabsorption is the most common abnormality in this population (19). Hence, some have adopted the term “abnormal hypercalciuria” (19). Nevertheless, all the aforementioned physiological defects may coexist in individual patients, leading to decreased bone mineral density and bone fracture (4).

Hypercalciuria is a heterogeneous disorder in which intestinal calcium hyperabsorption may be dependent (20, 21) or independent (19, 22–25) of 1,25-dihydroxyvitamin D [1,25(OH)2D]. Classically, hypercalciuria is classified into two different groups. The most severe variant is characterized by normocalcemia, hypercalciuria, intestinal hyperabsorption of calcium, and normal or suppressed serum PTH and/or urinary cAMP. However, a less severe form shares many of the same biochemical characteristics, but hypercalciuria normalizes after a restricted calcium diet (<400 mg/d) (26).

1,25(OH)2D-dependent hypercalciuria

In two studies, increased serum 1,25(OH)2D concentration was reported in the majority of kidney stone formers with hypercalciuria (20, 21). Insgna et al. (21) demonstrated increased 1,25(OH)2D production rather than disturbed clearance in well-characterized patients with hypercalciuria. The underlying mechanism(s) of enhanced 1,25(OH)2D production have yet to be elucidated. However, in the majority of well-defined hypercalciuric stone formers, the main regulators of 1,25(OH)2D production, namely serum PTH, phosphorus, and tubular maximum renal phosphorus reabsorption, were all at comparable levels to those of normal non-stone-forming subjects (24). Few studies have suggested a link between renal tubular phosphorus abnormalities and serum 1,25(OH)2D levels (20, 27). Further supporting the role of 1,25(OH)2D-mediated hypercalciuria, several studies have shown excessive urinary calcium excretion in normal subjects challenged with a large dose of 1,25(OH)2D (20, 28). However, a disagreement has arisen between the origin of hypercalciuria in which one study supports the intestinal origin (20) and the other suggests calcium mobilization from bone (28).

1,25(OH)2D-independent hypercalciuria

Despite reports of high circulating 1,25(OH)2D in hypercalciuric stone formers (20, 21), several studies have shown that hyperabsorption of calcium is independent of vitamin D, with over two thirds of idiopathic hypercalciuric patients exhibiting increased intestinal calcium absorption with normal prevailing serum 1,25(OH)2D concentration (19, 22–25). To probe this possibility, short-term administration of ketoconazole, an antifungal agent known to reduce serum 1,25(OH)2D, was shown to significantly lower serum 1,25(OH)2D concentration without a significant alteration in intestinal calcium absorption in hypercalciuric subjects (29). Similarly, treatment with thiazide, glucocorticoids, and phosphate was shown to influence intestinal calcium absorption in this population, suggesting that calcitriol has a limited pathophysiological role in hypercalciuria (25, 30, 31).

Several studies have exhibited similar phenotypic characteristics in a model of hypercalciuric stone-forming rat (GHS rat). These studies demonstrated normal serum calcium and calcitriol concentrations, increased intestinal calcium absorption with the presence of CaP and CaOx stones (32, 33), enhanced bone resorption, and diminished renal tubular calcium reabsorption (32, 34, 35). In this rat model, an increased abundance of vitamin D receptor (VDR) was shown with normal circulating calcitriol levels and increased VDR protein in the intestine, kidney, and bone that was attributed to increased VDR half-life (34, 36). These results support the notion that prolonged VDR half-life increases VDR tissue expression, resulting in hypercalciuria mediated via VDR-regulated genes controlling vitamin D-regulated calcium transport mechanisms (36). The biological action of the VDR-1,25(OH)2D complex was supported by increased expression of both 9- and 28-kDa calbindin levels in the duodenum and renal cortical tissue of the GHS rat (36).

In human subjects with hypercalciuria, peripheral blood mononuclear cells (PBMC) were used as an organ model to further explore the functionality of the VDR-1,25(OH)2D complex (37). When the PBMC were activated with phytohemagglutinin, these patients showed a significantly greater concentration of VDR in the presence of normal serum calcitriol levels, suggesting 1,25(OH)2D-independent VDR up-regulation (37). In addition, higher VDR levels were detected in hypercalciuric subjects in PBMC without stimulation (38).

Renal leak hypercalciuria

Renal leak hypercalciuria is a second, less common variety of hypercalciuria in which defective renal tubular
Calcium reabsorption is accompanied by enhanced PTH, calcitriol, and net intestinal calcium absorption (39). Studies using a single dose of hydrochlorothiazide in both unselected and selected groups of calcium stone formers have linked defective renal calcium reabsorption to a proximal renal tubular defect (16, 17).

**Resorptive hypercalciuria**

The most common prototype of resorptive hypercalciuria is primary hyperparathyroidism. However, due to the more frequent early diagnosis of primary hyperparathyroidism, the prevalence of nephrolithiasis in this condition is nowadays approximately 2–8% (11). Hypercalciuria is perceived as a cause of kidney stones in this population. Nevertheless, the exact relationship between hypercalciuria and the risk of nephrolithiasis with primary hyperparathyroidism is not fully agreed upon (40, 41). It has been disputed whether hypercalciuria originates from increased calcium mobilization from bone or reflects increased intestinal calcium absorption (40, 42, 43). It is suggested that kidney stones are more prevalent in younger populations with primary hyperparathyroidism due to enhanced synthesis of 1,25(OH)2D with intact kidney function, and consequently increased intestinal calcium absorption (42). Bone disease may occur in older subjects due to their lower serum 1,25(OH)2D levels and consequently diminished intestinal calcium absorption.

**Hyperuricosuria**

Hyperuricosuria as an isolated abnormality is detected in 10% of calcium stone formers. However, in combination with other metabolic abnormalities it may be present in 40% of this population (44). The pathophysiological mechanism underlying hyperuricosuria is attributed to a high purine diet (45). However, in approximately one third of patients, endogenous uric acid (UA) overproduction prevails, and dietary restriction does not significantly alter urinary UA excretion (46). The physicochemical basis involved in this process has not been well established. Although one study has attributed the physicochemical process to urinary supersaturation with colloidal monosodium urate-induced CaOx crystallization (47), another study has shown a lack of effect of monosodium urate and attributes CaOx stone formation to decreased solubility of CaOx in solution, a process described as “salting out” (48). Additionally, a retrospective population-based study in a large number of patients has not shown a relationship between urinary UA and CaOx stone formation (49).

**Hypocitraturia**

Citrate is an endogenous inhibitor of calcium stone formation, and low urine citrate excretion (hypoctituria) is encountered in 20–60% of calcium nephrolithiasis (50). The major determinant of urinary citrate excretion is acid-base balance (51). Hypocitraturia commonly occurs with metabolic acidosis or acid loading mediated through up-regulation of proximal renal tubular reabsorption of citrate (52). The main conditions include distal renal tubular acidosis (dRTA) (53), carbonic anhydrase inhibitors (54, 55), and normal bicarbonatemic states (56), including incomplete dRTA (57), thiazide treatment with hypokalemia (58), primary aldosteronism (59), high protein consumption (60), excessive salt intake (61), and converting enzyme inhibitors (62). The physicochemical basis for the inhibitory role of citrate involves the formation of soluble complexes and reduction of urinary saturation with respect to calcium salts in addition to direct inhibition of CaOx crystallization processes (63).

**Hyperoxaluria**

Urinary oxalate and calcium are equally important in raising urinary CaOx supersaturation (5). Hyperoxaluria is detected in 10–50% of calcium stone formers (5). The underlying mechanisms of hyperoxaluria can be divided into: 1) oxalate overproduction as a result of an inborn error in metabolism; 2) increased dietary intake and bioavailability (64); and 3) increased intestinal oxalate absorption. Inborn errors in metabolism include type I hyperoxaluria resulting from a deficiency or mistargeting of hepatic alanine glyoxylate transferase, type II primary hyperoxaluria due to a deficiency in glyoxylate reductase/hydroxypyruvate reductase, and the rare type III hyperoxaluria as a result of the gain of function of hepatic or renal mitochondrial 4-hydroxy-2-oxoglutarate aldolase (65–67). Subsequent investigation substantiated such a mutation; however, it remains unknown how changes in enzyme activity result in hyperoxaluria (68). Recently, *Oxalobacter formigenes* in humans have been proposed to participate in intestinal oxalate metabolism (69). Although a putative anion exchange transporter SLC26A6 has been shown to play a key role in intestinal oxalate absorption in mice, phenotypic and functional analysis has excluded a significant effect of identified variants in the corresponding human gene on oxalate excretion in humans (70, 71).

The most important circumstances in clinical practice are intestinal malabsorptive disorders including chronic diarrhea, inflammatory bowel diseases, and intestinal resection as occurs post-gastric bypass surgery (72) leading to “enteric hyperoxaluria.” Normally, oxalate absorption takes place throughout the small intestine and, to a certain extent, in the colon (73). In enteric hyperoxaluria, the underlying mechanisms are purported to be increased permeability to oxalate with unabsorbed bile acid and fatty
acids interacting with divalent cations in the lumen of the intestine, thereby raising intestinal luminal oxalate content and resulting in excessive urinary oxalate excretion (74). In addition to hyperoxaluria, these disorders are associated with multiple other kidney stone risk factors including low urine volume, hypocitraturia, hypomagnesuria, and highly acidic urine.

**Disturbances in urinary pH**

Both highly acidic urine (pH ≤ 5.5) and highly alkaline urine (pH ≥ 6.7) predispose patients to calcium kidney stone formation. With unduly acidic pH, urine becomes supersaturated with undissociated UA that participates in CaOx crystallization (47). Significantly alkaline urine increases the abundance of monohydrogen phosphate [dissociation constant (pKa) ~ 6.7], which, in combination with calcium, transforms to thermodynamically unstable brushite (CaHPO4.2H2O) and finally to hydroxyapatite \([\text{Ca}_10(\text{PO}_4)_{6}(\text{OH})_2]\). In clinical practice, conditions associated with CaP stone formation include dRTA, primary hyperparathyroidism, and use of carbonic anhydrase inhibitors (75, 76).

**Histopathological mechanisms of calcium kidney stone formation**

One suggested mechanism for the formation of calcium stones is increased urinary supersaturation of stone-forming salts, which leads to homogeneous nucleation in the lumen of the nephron, followed by crystal growth and consequent obstruction in the distal nephron (5). However, over the past decade it has become apparent that CaOx stone formation differs histologically from that of CaP (77). CaOx stones have been shown to anchor on and grow from an interstitial apatite plaque (Randall’s plaque) that covers the renal papillary surface (77). The extent of plaque in the renal papilla has been positively correlated with urinary calcium excretion and negatively correlated with urinary volume (77). The decreased proximal tubular reabsorption of calcium and enhanced renal tubular calcium reabsorption at the thick ascending limb have been purported as the potential pathophysiological mechanism resulting in interstitial plaque formation. Unlike CaOx, in CaP stone formers there is apatite crystal deposition in the inner medullary collecting duct, producing plugs associated with interstitial scarring (77).

**Genetic basis of calcium stone formation**

A higher percentage of kidney stones has been reported in first-degree relatives and family members with kidney stones (78). This genetic link was further documented in a study showing a greater concordance with renal stone incidence in monozygotic than dizygotic twins (79). However, due to the complex nature of idiopathic hypercalciuria, many putative candidate genes have been identified that participate in this polygenic illness. Genome-wide linkage approach in three families with absorptive hypercalciuria discovered polymorphisms in the putative soluble adenylyl cyclase (ADCY10) gene on chromosome 1q23.4–1q24 (80). Another genome-wide screening in a large population from Iceland and The Netherlands with documented radio-opaque kidney stones found polymorphisms in sequence variants in the Claudin 14 (CLDN14) gene, which encodes for the tight junction protein in the kidney, liver, and inner ear (81). Another study has suggested an association between the calcium sensor receptor (CASR) gene polymorphism and recurrent nephrolithiasis (82). However, none of these instances established the functional significance of these polymorphisms. Future phenotype-genotype studies are needed to identify the associated gene defect.

**Pathophysiological Mechanism(s) of Non-Calcium Stones**

**UA stone formation and its link to the MS**

The etiological causes of UA stone formation are genetic, acquired, or a combination of both (60, 83). Over the past decade, the MS has been characterized as the most prevalent cause of UA stone formation (Fig. 1A) (84, 85). The underlying pathophysiological mechanisms responsible for UA nephrolithiasis are: 1) low urine volume; 2) hyperuricosuria; and 3) unduly acidic urine.

Unduly acidic urine (urinary pH ≤ 5.5) is an invariable feature in UA nephrolithiasis (5). In such an acidic milieu, the urinary environment becomes supersaturated with sparingly soluble undissociated UA (84). The two principal causes for acidic urine are: 1) impaired ammonium (NH4+) excretion; and 2) increased endogenous acid production (84, 85). Impaired NH4+ excretion in this population is shared with patients with the MS and type II diabetes mellitus without kidney stones (85). Recent experimental evidence using an established rodent model of obesity (Zucker diabetic fatty rat) and a renal proximal tubular cell line have demonstrated a causal role of renal steatosis in the pathogenesis of disturbed urinary acidification (86, 87). Increased endogenous acid production has been shown in both UA stone formers and diabetic non-stone formers (84, 85). However, the nature and source of this putative organic anion has not been fully elucidated. Hyperuricosuria may be encountered in certain clinical circumstances and/or rare genetic disorders linked to the UA synthetic pathway and as a result of a genetic mutation in renal UA transporters (83, 88).
Genetic basis of UA stone formation

Many monogenic mutations are associated with hyperuricosuria, hyperuricemia, gout, renal failure, and kidney stone formation (83, 88). However, most UA stone formers have a low fractional excretion of urate and low urinary pH (84). In one study conducted in a Sardinian cohort, most subjects exhibited low urinary pH with high urinary titratable acidity, with only one third showing elevated urinary UA excretion (89). In this study, genetic analysis identified a locus on chromosome 10q21-22 associated with increased propensity to UA nephrolithiasis. A subsequent study identified the putative gene as zinc finger protein 365 (ZNF365) (90). However, the functional importance of this finding and the role of the protein encoded by this gene have not been fully established.

Cystinuria

Cystine nephrolithiasis comprises only a small fraction of kidney stones in adults but is more prevalent among children and adolescents with stones (91). Cystinuria is either autosomal recessive (obligate heterozygotes with normal urinary cystine excretion) or autosomal dominant with incomplete penetrance (obligate heterozygotes with increased urinary cystine excretion but typically not enough to cause cystine stones). It is characterized by an inherited defect in renal cystine reabsorption expressed as $b^0_{ \text{out}}$ (SLC3A1 and SLC7A9). Although the defective renal tubular reabsorption affects other dibasic amino acids including arginine, lysine, and ornithine, cystine stones are the main complication of this genetic defect due to the low solubility of cystine in the urinary environment (Fig. 1B) (92). In a recent genetic classification, cystinuria is defined as type A if mutations are found in both SLC3A1 alleles, type B if mutations are found in both SLC7A9 alleles, and type AB if one mutation is found in each gene (93). With digenic inheritance, one would expect 50% of AB individuals to be affected by nephrolithiasis. However, cystine stones are rarely encountered in this genotype (94).

Infection and rare stones

The most important factors for the formation of infectious stones are highly alkaline urine pH (>7.2) in the presence of urease-producing organisms and supersaturated urinary environment with respect to magnesium, ammonium, and phosphate ions (Fig. 1C) (95). Rare forms of kidney stones such as dihydroxyadandine, ammonium urate, and stones resulting from protease inhibitor drugs may also occur.

Diagnosis

Medical history

In the diagnosis of these patients, systemic and environmental influences must be carefully identified. Systemic abnormalities include intestinal disease, disorders of calcium homeostasis such as primary hyperparathyroidism, conditions accompanied by extra renal 1,25(OH)$_2$D production such as granulomatous diseases, obesity, type II diabetes, recurrent urinary tract infection, bariatric surgery, medullary sponge kidney, and various drug treatments.

Diet plays a crucial role in the formation of kidney stones. High dietary salt and protein consumption are the two most common dietary aberrations that increase the risk of nephrolithiasis (61, 96). Epidemiological studies have shown an association between a higher risk of kidney stone formation and lower dietary calcium intake (97, 98). Although the exact pathophysiological mechanism has not been established, it has been suggested to be due to lowered urinary oxalate excretion or possibly a rise in urinary antilithogenic factors with a high-calcium diet. In contrast, increased calcium and vitamin D supplementation is reportedly accompanied by a higher risk of nephrolithiasis (99). Aside from dietary risk factors, it has been suggested that kidney stone risk increases in hot climates as well as with frequent and/or intense exercise, largely due to extra renal fluid loss as a result of perspiration, resulting in a significant fall in urine volume (83). It has also been suggested that certain professions associated with de-
creased fluid intake and/or increased perspiration are at high risk for kidney stones.

Although hypercalciuric nephrolithiasis is typically a polygenetic complex trait, in rare instances it may be a monogenetic disorder. The occurrence of hypercalciuric nephrolithiasis among male subjects accompanied by renal impairment and low-molecular-weight proteinuria is suggestive of x-linked recessive disorder detected in patients with Dent’s disease (100). The occurrence of kidney stones and nephrocalcinosis in male subjects with early cataracts, glaucoma, and neurological deficit is suggestive of Lowe syndrome (101). Aggressive nephrolithiasis, nephrocalcinosis, retarded growth, and deafness can be seen in patients with dRTA presenting with both autosomal dominant and autosomal recessive inheritance (102).

Laboratory diagnosis

Laboratory diagnosis includes stone analysis, imaging studies, blood profiles, and a urine metabolic evaluation (Table 2). Stone analysis plays a valuable role in the diagnosis of kidney stone patients, specifically in infrequently encountered kidney stones such as UA, cystine, infection-induced, drug-induced, and NH4+ urate stones. Imaging studies are valuable in the diagnosis of kidney stone disease. Despite numerous imaging methodologies, computed tomography is the most sensitive and specific mode of diagnosis (103). High fasting blood calcium, low phosphorus, and elevated PTH are suggestive of primary hyperparathyroidism. In that case, the patient must be considered for a noninvasive localization study followed by parathyroidectomy. Normal serum calcium, low serum phosphorus, elevated 1,25(OH)2D, and normal PTH are suggestive of renal phosphorus leak. The finding of low serum potassium and low CO2 is suggestive of dRTA. Hyperuricemia and high serum triglycerides are encountered in patients with UA stones.

Metabolic evaluation

A simplified metabolic evaluation starts with a random 24-h urinary profile (Table 2). However, there is disagreement whether a single collection or duplicate random 24-h urine collections are necessary to document kidney stone risk (104, 105). In some optional instances, 2-h fasting urinary calcium:creatinine ratio (Ca:Cr) and fasting urinary phosphorus are obtained to establish the diagnosis of renal leak calcium, excessive calcium mobilization from bone, and renal phosphorus leak. A 4-h urinary Ca:Cr after 1 g oral calcium load may follow the 2-h fasting Ca:Cr for indirect assessment of intestinal calcium absorption (19). An extensive metabolic evaluation may also include bone density analysis because the prevalence of bone fracture has been shown to be higher in kidney stone formers than in the general population (4). Although it is opinion-based, extensive metabolic evaluation may be performed in recurrent kidney stone formers, those with a family history of kidney stones, a history of bone fractures, dRTA, and chronic diarrheal state.

Urinary supersaturation

The utility of urinary supersaturation measurement as a surrogate of kidney stone incidence has not been fully studied. To date, only a single study has provided evidence that a reduction in CaOx supersaturation is associated with a fall in stone incidence (106). However, urinary supersaturation is reported in stone risk profiles by most commercial laboratories. Two methods applied for urinary supersaturation measurements are relative supersaturation (RS) ratio and urinary RS (106, 107). With RS ratio, values greater than 1 indicate supersaturation for all stone types. With RS, the upper limit of normal for oxalate, brushite, monosodium urate, and UA is defined as 2.

Treatment

Acute treatment for symptomatic stone passage is beyond the scope of this review and has previously been extensively described (108).

Conservative management

High oral fluid intake must be considered in all stone formers. A prospective controlled study has shown that increasing water intake to ensure a urinary volume of approximately 2.5 liters/d was associated with reduced urinary supersaturation with CaOx and a significant reduction in stone recurrence (109). Another study suggests that fluid intake as fruit juice, specifically orange juice, is also effective in reducing urinary CaOx saturation and increasing urinary citrate excretion (110). This effectiveness is not shared with apple juice, grapefruit juice, cola, and some sport drinks due to their elevated oxalate and fructose content (110–112). Based on one study in Italian men with hypercalciuria, great emphasis has been placed on low dietary sodium (<100 mEq/d) and animal protein consumption (50–60 g/d) as well as normal calcium intake (1200 mg/d) in the reduction of calcium stone recurrence (113). However, another study using only a low-fiber, low-protein diet in a cohort in the United States did not show decreased stone recurrence (114). Dietary oxalate restriction (<100 mg/d) is also useful in lowering urinary oxalate excretion. Foods that are known to raise urinary oxalate excretion include fruits such as raspberries, figs, and plums; vegetables such as spinach, rhubarb, and beets; and most nuts, tea, wheat bran, chocolate, and high
**TABLE 2.** Diagnostic evaluation and interpretation of laboratory profiles

<table>
<thead>
<tr>
<th>Simplified ambulatory metabolic evaluation</th>
<th>Extensive ambulatory metabolic evaluation</th>
<th>Expected daily values</th>
<th>Results interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random 24-h urinary profile</td>
<td>Random 24-h urinary profile and 24-h urine profile after 1 wk of dietary restrictions</td>
<td>≥2.5 liter</td>
<td>Indicative of daily fluid intake. This value diminishes with low fluid intake, sweating, and diarrhea.</td>
</tr>
<tr>
<td>Total volume</td>
<td>Total volume</td>
<td>5.9–6.2</td>
<td>Values &lt; 5.5 increase UA precipitation. Commonly found in UA stone patients, subjects with intestinal disease and diarrhea, and in those with intestinal bypass surgery. Values &gt; 6.7 increase CaP precipitation. Commonly found in patients with dRTA, primary hyperparathyroidism, alkali overtreatment, and carbonic anhydrase treatment. Values &gt; 7.0–7.5 indicate a urinary tract infection as a result of urease-producing bacteria.</td>
</tr>
<tr>
<td>pH</td>
<td>pH</td>
<td>100 mEq</td>
<td>Reflective of dietary sodium intake, given a lack of excessive sweating and/or diarrhea.</td>
</tr>
<tr>
<td>Sodium</td>
<td>Sodium</td>
<td>≤250–300 mg</td>
<td>There may be differences in male and female subjects. A higher value is expected in males.</td>
</tr>
<tr>
<td>Potassium</td>
<td>Potassium</td>
<td>≤25–30 mmol</td>
<td>Sulfate is a marker of an acid-rich diet that occurs as a result of increased oxidation of sulfur-rich amino acids (methionine) found in meat and meat products.</td>
</tr>
<tr>
<td>Calcium</td>
<td>Calcium</td>
<td>15–25 mg/kg body weight</td>
<td>An inhibitor of calcium stone formation. Hypocitraturia is commonly encountered in metabolic acidosis, dRTA, chronic diarrhea, excessive protein ingestion, strenuous physical exercise, hypokalemia, intracellular acidosis, with carbonic anhydrase inhibitor drugs (acetazolamide, topiramate, and zonisamide), and rarely with ACE-inhibitors.</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Magnesium</td>
<td>≤1100 mg</td>
<td>Indicative of dietary phosphorus intake and absorption. A higher excretion may increase the risk of CaP stone formation.</td>
</tr>
<tr>
<td>Oxalate</td>
<td>Oxalate</td>
<td>≤0.20 mg/mg Cr</td>
<td>Elevated Ca:Cr after a 1-g oral calcium load is suggestive of absorptive hypercalciuria.</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Phosphorus</td>
<td>≤0.11 mg/100 ml glomerular filtrate</td>
<td>Elevated fasting Ca:Cr, high serum calcium, and elevated PTH are suggestive of primary hyperparathyroidism. Elevated fasting Ca:Cr, normal serum calcium, and normal or suppressed PTH are suggestive of resorptive hypercalciiuria. Elevated fasting Ca: Cr, normal serum calcium, and elevated PTH are suggestive of renal hypercalciiuria.</td>
</tr>
<tr>
<td>Citrate</td>
<td>Citrate</td>
<td>≤0.20 mg/mg Cr</td>
<td>Elevated Ca:Cr after a 1-g oral calcium load is suggestive of absorptive hypercalciiuria.</td>
</tr>
<tr>
<td>Ammonium</td>
<td>Ammonium</td>
<td>≤30–40 mEq</td>
<td>Ammonium is a major buffer that neutralizes hydrogen protons secreted by the kidney. Its excretion corresponds with urinary sulfate (acid load). A higher ammonium:sulfate ratio indicates gastrointestinal alkalosis.</td>
</tr>
<tr>
<td>Chloride</td>
<td>Chloride</td>
<td>≤0.20 mg/mg Cr</td>
<td>Elevated fasting Ca:Cr, high serum calcium, and elevated PTH are suggestive of primary hyperparathyroidism. Elevated fasting Ca:Cr, normal serum calcium, and normal or suppressed PTH are suggestive of resorptive hypercalciiuria. Elevated fasting Ca: Cr, normal serum calcium, and elevated PTH are suggestive of renal hypercalciiuria.</td>
</tr>
<tr>
<td>Cystine</td>
<td>Cystine</td>
<td>≤0.20 mg/mg Cr</td>
<td>Elevated Ca:Cr after a 1-g oral calcium load is suggestive of absorptive hypercalciiuria.</td>
</tr>
<tr>
<td>2-h fasting Ca:Cr ratio</td>
<td>2-h fasting Ca:Cr ratio</td>
<td>≤0.20 mg/mg Cr</td>
<td>Elevated Ca:Cr after a 1-g oral calcium load is suggestive of absorptive hypercalciiuria.</td>
</tr>
<tr>
<td>4-h Ca:Cr ratio after a 1-g oral calcium load</td>
<td>4-h Ca:Cr ratio after a 1-g oral calcium load</td>
<td>≤0.20 mg/mg Cr</td>
<td>Elevated Ca:Cr after a 1-g oral calcium load is suggestive of absorptive hypercalciiuria.</td>
</tr>
<tr>
<td>Complete metabolic panel</td>
<td>Complete metabolic panel</td>
<td>Variable*</td>
<td>Low serum potassium, high serum chloride, and low serum total CO₂ content are suggestive of a diarrheal state of dRTA.</td>
</tr>
<tr>
<td>PTH</td>
<td>PTH</td>
<td>10–65 pg/ml*</td>
<td>High serum calcium, low serum phosphorus, and high PTH are suggestive of primary hyperparathyroidism.</td>
</tr>
<tr>
<td>1,25(OH)₂D</td>
<td>1,25(OH)₂D</td>
<td>Variable*</td>
<td>Normal serum calcium, normal PTH, and elevated 1,25(OH)₂D are suggestive of absorptive hypercalciiuria. Normal serum calcium, normal PTH, low serum phosphorus, and elevated 1,25(OH)₂D are suggestive of renal phosphorus leak.</td>
</tr>
<tr>
<td>Other evaluations</td>
<td>Bone mineral density measurements (DXA)</td>
<td>Z-score &gt; −2; T-score &gt; −2.5</td>
<td>Z-score &lt; −2 or T-score &lt; −2.5 indicates bone loss. This finding may be more prevalent in hypercalciiuric kidney stone formers.</td>
</tr>
</tbody>
</table>

Note: Z-scores are calculated from normal values. ACE, Angiotensin-converting enzyme; DXA, dual-energy x-ray absorptiometry.

*Expected values should be cross-checked with reference laboratory recommendations because these values may differ.
Thiazide diuretics and their analogs are commonly used medical treatments for lowering calcium excretion in recurrent calcium stone formers (108). In several randomized controlled trials, thiazide diuretics were effective in significantly reducing kidney stone recurrence (117–120).

The results were consistent with a number of open studies showing reduced kidney stone formation with thiazides (121–127). Thiazides are effective in treating hypercalciuria and reducing stone recurrence regardless of the underlying pathophysiological mechanism (127). The optimal effect of thiazides is achieved with a low-salt diet that attenuates urinary calcium excretion and the provision of sufficient potassium supplementation to avoid hypocitraturia (58). Potassium citrate holds an advantage over potassium chloride (128).

### Alkali treatment

Potassium citrate is used either alone or in combination with thiazide treatment in recurrent calcium or UA stone formers. In four randomized controlled trials, three nonrandomized nonplacebo controlled studies, and one nonrandomized controlled trial, this treatment was shown to significantly reduce stone recurrence (117–120).

### Pharmacological treatment

Pharmacological treatment is needed in most recurrent calcium kidney stone formers as well as in specific stone-forming populations such as UA, cystine, and infection-induced stones due to the lack of availability and/or consensus regarding the effectiveness of dietary restrictions (Tables 1 and 3) (113, 114).

#### Thiazide diuretic treatment

Thiazide diuretics and their analogs are commonly used medical treatments for lowering calcium excretion in recurrent calcium stone formers (108). In several randomized controlled trials, thiazide diuretics were effective in significantly reducing kidney stone recurrence (117–120).

#### Alkali treatment

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### TABLE 3. Major clinical trials in pharmacotherapy of calcium and non-calcium nephrolithiasis

<table>
<thead>
<tr>
<th>First author (Ref.)</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laerum (117)</td>
<td>Hydrochlorothiazide vs. placebo</td>
<td>50</td>
<td>RCT</td>
<td>Decreased new stone formation and prolonged stone-free interval</td>
</tr>
<tr>
<td>Ettinger (118)</td>
<td>Chlorothiazide vs. Mg hydroxide vs. placebo</td>
<td>124</td>
<td>RCT</td>
<td>Chlorothiazide more effective than Mg hydroxide or placebo in reducing stone events</td>
</tr>
<tr>
<td>Ohkawa (119)</td>
<td>Trichlormethiazide vs. no treatment</td>
<td>175</td>
<td>RCT</td>
<td>Decreased calcium and stone formation rate</td>
</tr>
<tr>
<td>Borgi (120)</td>
<td>Diet vs. diet + indapamide vs. diet + indapamide + allopurinol</td>
<td>75</td>
<td>RCT</td>
<td>Diet + pharmacotherapy better than diet alone</td>
</tr>
<tr>
<td>Yendt (121)</td>
<td>Hydrodiuril</td>
<td>33</td>
<td>NNT</td>
<td>Decreased number of stone events or invasive and noninvasive procedures</td>
</tr>
<tr>
<td>Coe (122)</td>
<td>Trichlormethiazide</td>
<td>37</td>
<td>NNT</td>
<td>Decreased new stone formation</td>
</tr>
<tr>
<td>Coe (123)</td>
<td>Trichlormethiazide vs. allopurinol vs. both</td>
<td>222</td>
<td>NNT</td>
<td>Decreased new stone formation</td>
</tr>
<tr>
<td>Yendt (124)</td>
<td>Hydrochlorothiazide</td>
<td>139</td>
<td>NNT</td>
<td>Decreased new stone formation or stone growth</td>
</tr>
<tr>
<td>Backman (125)</td>
<td>Bendrofumethiazide</td>
<td>44</td>
<td>NNT</td>
<td>Decreased new stone formation</td>
</tr>
<tr>
<td>Maschio (126)</td>
<td>Hydrochlorothiazide + amiloride vs. both + allopurinol</td>
<td>519</td>
<td>NNT</td>
<td>Decreased new stone formation</td>
</tr>
<tr>
<td>Pak (127)</td>
<td>Hydrochlorothiazide</td>
<td>37</td>
<td>NNT</td>
<td>Decreased new stone formation</td>
</tr>
<tr>
<td>Pak (129)</td>
<td>Potassium citrate vs. pretreatment in calcium and UA stone formers</td>
<td>89</td>
<td>NNT</td>
<td>Decreased stone events</td>
</tr>
<tr>
<td>Preminger (57)</td>
<td>Potassium citrate</td>
<td>9</td>
<td>NNT</td>
<td>Decreased new stone formation</td>
</tr>
<tr>
<td>Pak (130)</td>
<td>Potassium citrate</td>
<td>18</td>
<td>NNT</td>
<td>Decreased stone events</td>
</tr>
<tr>
<td>Barcelo (131)</td>
<td>Potassium citrate vs. placebo</td>
<td>57</td>
<td>RCT</td>
<td>Decreased new stone formation and increased urinary citrate</td>
</tr>
<tr>
<td>Hofbauer (132)</td>
<td>Diet + sodium potassium citrate vs. diet</td>
<td>50</td>
<td>RCT</td>
<td>No difference in stone formation</td>
</tr>
<tr>
<td>Ettinger (133)</td>
<td>Potassium magnesium citrate vs. placebo</td>
<td>64</td>
<td>RCT</td>
<td>Decreased new stone formation</td>
</tr>
<tr>
<td>Soygür (134)</td>
<td>Potassium citrate vs. no treatment after shock wave lithotripsy</td>
<td>110</td>
<td>RCT</td>
<td>Decreased stone recurrence</td>
</tr>
<tr>
<td>Kang (135)</td>
<td>Mix of potassium citrate, thiazide, allopurinol vs. no treatment after percutaneous nephrolithotomy</td>
<td>226</td>
<td>RCT</td>
<td>Decreased stone recurrence</td>
</tr>
<tr>
<td>Allopurinol treatment</td>
<td>Allopurinol vs. placebo</td>
<td>60</td>
<td>RCT</td>
<td>Decreased stone events</td>
</tr>
<tr>
<td>Ettinger (137)</td>
<td>Thiazide vs. allopurinol vs. both</td>
<td>202</td>
<td>RCT</td>
<td>Decreased stone events vs. pretreatment</td>
</tr>
<tr>
<td>Coe (123)</td>
<td>Other treatment</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dahlberg (139)</td>
<td>d-Penicillamine</td>
<td>89</td>
<td>R</td>
<td>Decreased stone event and dissolution of stones</td>
</tr>
<tr>
<td>Pak (140)</td>
<td>d-Penicillamine or α-mercaptopropionylglycine vs. conservative Rx</td>
<td>66</td>
<td>R</td>
<td>Both drugs equally effective in reducing stone events</td>
</tr>
<tr>
<td>Chow (141)</td>
<td>d-Penicillamine or α-mercaptopropionylglycine vs. conservative Rx</td>
<td>16</td>
<td>NNT</td>
<td>Decreased stone event</td>
</tr>
<tr>
<td>Barber (138)</td>
<td>d-Penicillamine vs. α-mercaptopropionylglycine vs. conservative Rx</td>
<td>27</td>
<td>R</td>
<td>Decreased stone events</td>
</tr>
<tr>
<td>Williams (142)</td>
<td>Acetohydroxamic acid vs. placebo</td>
<td>18</td>
<td>RCT</td>
<td>Decreased stone size</td>
</tr>
<tr>
<td>Griffith (143)</td>
<td>Acetohydroxamic acid vs. placebo</td>
<td>210</td>
<td>RCT</td>
<td>Decreased stone growth</td>
</tr>
<tr>
<td>Griffith (144)</td>
<td>Acetohydroxamic acid vs. placebo</td>
<td>94</td>
<td>RCT</td>
<td>Decreased stone growth</td>
</tr>
</tbody>
</table>

R, Retrospective; RCT, randomized controlled trial; NCT, nonrandomized controlled trial; NNT, nonrandomized, non-placebo controlled trial.
reduce the risk of kidney stone events (57, 129–135). Alkaline treatment is effective in lowering urinary calcium excretion, raising urinary citrate, and reducing urinary CaOx, CaP, and undissociated UA supersaturation (136). Because bone loss and fracture are prevalent in patients with nephrolithiasis, both alkali and thiazide treatments have been shown to increase bone mineral density in the kidney stone-forming population (4). However, no randomized data have been obtained showing decreased fracture rate.

**Allopurinol treatment**

In a randomized controlled trial in hyperuricosuric calcium stone formers, treatment with allopurinol was shown to reduce urinary UA excretion as well as stone recurrence (137). Because multiple metabolic abnormalities may coexist in hyperuricosuric patients, one study has shown that combined thiazide and allopurinol treatment is more effective in reducing stone events compared with either treatment alone (123).

**Other drug treatment for stone prevention**

Although urinary cystine solubility is pH dependent, alkaline treatment alone has limited effectiveness in the management of cystine stone formers. This is due to the high pKa of cystine at 8.0, requiring a large dose of alkali that is difficult to achieve. Furthermore, highly alkaline urine can predispose the patient to CaP stones. The main treatments used in those who suffer from severe cystinuria (>500 mg/d) are thiol-derivatives that split cystine molecules into two cysteines and produce a highly soluble disulfide compound (92). Two such drugs are d-penicillamine and α-mercaptopropionylglycine. In four retrospective, nonrandomized, nonplacebo, controlled trials, both drugs were shown to decrease stone events (138–141). Both drugs share many side effects; however, α-mercaptopropionylglycine may have lower incidence of side effects compared with d-penicillamine (92).

Acetohydroxamic acid is the only drug approved for the treatment of infectious kidney stones. This treatment should only be used if surgical removal of an infectious stone followed by eradication of infection with antibiotics is ineffective. This medication causes an irreversible inhibition of the enzyme urease, therefore attenuating the rise in both urinary pH and NH₄⁺. Three randomized controlled studies have found reduced stone growth with this treatment (142–144). However, compliance is very poor due to severe side effects.

**Clinical Follow-Up**

Follow-up treatment is typically indicated with an annual clinical visit. This evaluation includes medical history, physical examination, and laboratory examination for full serum chemistries and urine profiles.

**Future Directions**

The current management of nephrolithiasis lacks a reliable surrogate marker of kidney stone formation to correlate with stone incidence. The development of practical and novel techniques to easily assess the physicochemical processes involved in crystal growth, aggregation, agglomeration, and attachment will immensely benefit the field. Further effort must also be aimed at understanding the molecular and genetic basis of both calcium and non-calcium kidney stones. Such an effort is necessary for the development of targeted therapy based on the underlying pathophysiological mechanisms of nephrolithiasis. To accomplish these goals, a close interaction between bed and bench investigation is crucial.

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