

Evaluation and Management of Kidney Calculi

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Introduction. The recent change in the view towards nephrolithiasis from a benign isolated disease to a disorder associated with numerous systemic and chronic conditions has added to the importance of a more thorough and timely diagnostic and therapeutic intervention.

Materials and Methods. Both original and review articles found via the PubMed search on recent evaluation and management strategies of urinary calculi were reviewed. These resources were integrated with the authors' knowledge of the field.

Results. The emerging evidence attests to the association of nephrolithiasis with many morbid and fatal diseases, such as coronary heart disease, ischemic stroke, hypertension, chronic kidney insufficiency, malignancies, and bone loss, as well as the economic burden of urinary calculus on health system and work force.

Conclusions. Findings of this review justify a timely and comprehensive workup and dietary-therapeutic measures in order to prevent, treat, and control the associated complications of this condition.

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EVALUATION

History and Physical Examination

In patients with risk factors for kidney calculus formation, such as past history or family history of kidney calculus, lithogenic metabolic disorders (eg, metabolic syndrome, gout, malignancy, or granuloma-induced hypercalcemia), endocrine disorders (eg, hyperparathyroidism, Cushing syndrome), or those who use lithogenic medications, attention should be paid to early detection of crystalluria and subclinical urinary calculi. On the other hand, in patients with documented urinary calculus, screening for signs and symptoms of associated comorbidities, such as metabolic syndrome, cardiovascular and neurovascular diseases, kidney impairment, urothelial malignancies, and underlying inflammatory bowel diseases, could be useful in early detection and prevention of complications.

Laboratory Workup

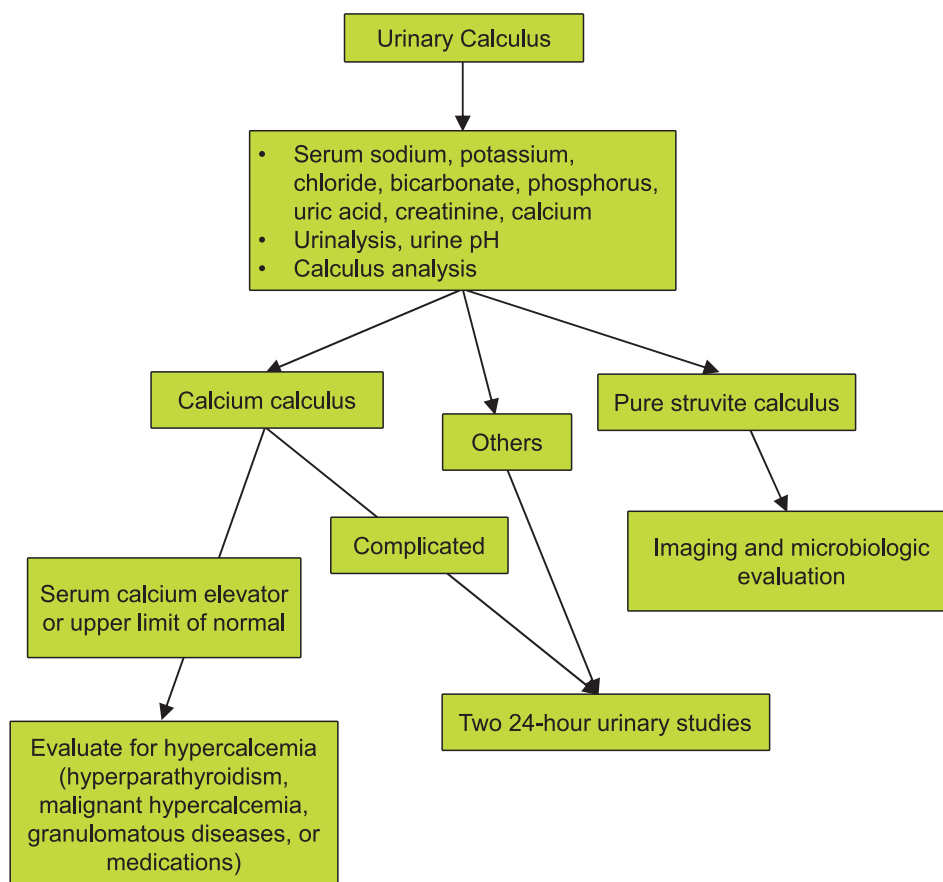
A basic metabolic workup recommended

for the first urinary calculus includes complete blood count; serum levels of sodium, potassium, chloride, bicarbonate, phosphorus, calcium (or ionized calcium), creatinine, and uric acid; urinalysis with urine pH, and calculus analysis.¹ Patients with complicated calculi (outlined in Table 1),¹ need a more detailed workup. The Figure illustrates a diagnostic algorithm in patients with nephrolithiasis.

Calcium calculi. Patients with complicated calculi (Table 1) require 2 rounds of 24-hour urine

Table 1. Complicated Calculi

Complicated Calculi
Recurrent, multiple or bilateral calculus of any kind
Noncalcium calculi
Calculi in patients < 18 years old
Calculi during pregnancy
History of calculi in 1 or more of the first-degree relatives
Systemic disease with increased risk of urinary calculi (gout, inflammatory bowel disease, and distal renal tubular acidosis)
Calculi in patients with solitary kidney, kidney insufficiency, or an anatomical abnormality



Diagnostic algorithm in patients with nephrolithiasis.

collection while following their usual diet. The sample should be collected when the patient is off any lithogenic medications.¹ Low urine volume; high levels of urine calcium, uric acid, and oxalate levels; low urine citrate level; and extreme urine pH disturbances (pH < 5.5 or pH > 6.7) predispose an individual to calcium calculus formation.

Thirty percent to 60% of adults with nephrolithiasis have hypercalciuria. Hypercalciuria is defined as a 24-hour urine calcium excretion greater than 250 mg/d in women and greater than 300 mg/d in men.² In more than 90% of patients with hypercalciuria, no primary cause can be found, and thus labeled as "idiopathic hypercalciuria."²⁻⁴ Citrate is a urine calcium crystallization inhibitor. Hypocitraturia, defined as excretion of less than 320 mg of citrate in 24-hour urine, was observed in 20% to 60% of calcium calculus formers.^{5,6} Since molar ratio of oxalate to calcium in urine is about 1:2, changes in urinary oxalate concentration exert more significant changes in relative supersaturation of calcium oxalate than changes in urine calcium

concentration. Ten percent to 50% of calcium calculus formers demonstrate greater than 40 mg/d urinary oxalate excretion.⁷

Finally, both acidic and alkaline urine predispose to calcium nephrolithiasis. Uric acid supersaturation in a urine pH of 5.5 and less may lead to calcium oxalate crystallization.⁸ On the other hand, a urine pH greater than 6.7 increases supersaturation of calcium phosphate, which may lead to formation of hydroxyapatite.^{9,10} Alkaluria (urine pH > 5.5) in the setting of metabolic acidosis suggests distal renal tubular acidosis.

Uric acid calculi. Interestingly, the primary urinary abnormality in most patients with idiopathic uric acid calculus is an excessively acidic urine (pH < 5.5) and low urine volume, rather than hyperuricosuria.¹¹ Less commonly, patients with hyperuricosuria and a normal urine pH may develop calculi that are composed of calcium oxalate with or without urate.¹²

Cystine calculi. Patients with homozygote cystinuria excrete more than 400 mg/d and form

cystine calculi. However, if the urine sample is not alkalinized (pH > 6.5) immediately after voiding and before measurement of cystine, it precipitates and thus underestimates soluble urine cystine level.¹³ Solid-phase assay is a more reliable method.¹⁴ Cystine crystals are added to the patient's urine in the presence of thiol drug. After incubation for 2 days, the remaining crystals are collected. In a supersaturated urine, the excessive cystine precipitates, so the solid phase grows which is called "negative cystine capacity."¹⁵

Struvite calculi. Frequent bacteriological examination of urine and imaging studies is warranted, especially early after the surgery.¹⁶

Calcium phosphate calculi. Distal renal tubular acidosis and hyperparathyroidism should be ruled out as the primary etiology.

Monitoring Kidney Function

Although research is required to elicit a cause-and-effect relationship between urinary calculi and chronic kidney disease, the association of nephrolithiasis and development of chronic kidney impairment is well established. For this reason, clinicians should consider routine monitoring of kidney function (including urine albumin-creatinine ratio, serum creatinine, and estimated glomerular filtration rate) in patients with nephrolithiasis.

Screening for Malignancies

The association of urinary calculus with urothelial malignancies should encourage physicians to consider a routine follow-up urinalysis for hematuria, kidney function test, and cytology, depending on the degree of suspicion in high-risk patients (Table 2).^{17,18}

Table 2. Patients With Urinary Calculus and High Risk of Developing Urothelial Cancer

Risk of Urothelial Cancer
Long standing calculus disease (> 6 years) plus:
• Constant pain
• Hematuria (microscopic or gross)
• Impaired kidney function
• Urinary tract infection
• Female sex

Radiologic Workup

Diagnostic imaging. Imaging is indicated in patients with suspicious ureteral calculus with frequent and severe flank and abdominal pain. The decision on the imaging of choice should be tailored according to one's risk factors and underlying conditions. In general a noncontrast helical computed tomography (CT) scan of the abdomen and pelvis (calculus protocol) is the imaging of choice for diagnosing renal calculus with more than 95% sensitivity and more than 96% specificity.^{19,20} The only exception being in children and in young females with a possibility of pregnancy that ultrasound would be the first-line imaging modality of choice. The American Urology Association (AUA) recommends the following approach for different conditions.²¹⁻²³ (Table 3):

- In patients with a body mass index less than 30 kg/m², a low-dose noncontrast CT (4mSv) is preferred, as it maintains both sensitivity and specificity at greater than 90%, while it limits the potential side effects of ionizing radiation exposure. For people with body mass index greater than 30 kg/m², a regular-dose CT is recommended, in order to achieve the acceptable sensitivity and specificity.

Table 3. Imaging of Choice for Patients With Urinary Calculus*

Imaging	Indication
Helical CT scan without contrast	BMI > 30 kg/m ² : high dose BMI < 30 kg/m ² : low dose
CT urography with contrast (alternatively IVU)	Medication Metabolite calculi (eg, indinavir)
Ultrasonography	First choice in IBD patients and pregnant women (combined with transvaginal ultrasonography) Evaluate for obstruction, hydronephrosis and renal restrictive indexes
KUB and/ or Ultrasonography	Identifying noncalcified calculi that the KUB alone might miss Yearly routine follow-up
KUB	When CT is not available (ambulatory setting) Once the diagnosis is made, it can be used in tracking the calculus, better imaging of calculus shape, and establishing the radio-opacity of the calculus.

*CT indicates computed tomography; BMI, body mass index; IVU, intravenous urography; IBD, inflammatory bowel disease; and KUB, plain radiography of the kidney, ureters, and bladder.

- For indinavir-induced calculi, intravenous contrast-enhanced CT urography is the modality of choice.
- Although ultrasonography is not very sensitive in diagnosing urinary calculi, it is the modality of choice in pregnant women or in estimating the degree of urinary obstruction, hydronephrosis or renal resistive indexes (a marker for elevated urinary tract pressure and determining the choice of intervention). In patients with inflammatory bowel diseases, who are predisposed to recurrent renal colic and abdominal pain (gastrointestinal and genitourinary associated pain), ultrasonography is the first modality of choice, in order to spare them from excessive radiation exposure.^{24,25}
- The combination of ultrasonography with kidney, ureters, and bladder plain radiography (KUB) helps in identifying nonopaque calculi that the KUB alone might miss.
- When CT scan is not available (eg, ambulatory setting), KUB is useful considering the fact that 75% to 90% of urinary calculi are radiopaque.
- Plain radiography is generally recommended for tracking growth and passage of a calculus, once diagnosis was made. It also establishes the radio-opacity of a calculus, when the location of calculus is well known, and usually yields a better image of the shape of the calculus than a CT scan does.

Pregnancy

As mentioned earlier, nephrolithiasis in pregnant women is considered complicated calculus that requires a detailed and early workup.²⁶ Workup includes blood chemistry, two 24-hour urine samples, and appropriate imaging studies with special consideration to the fetus. The reason for a lower threshold of exploration is: higher rate for complications like urinary tract obstruction and urosepsis, due to anatomical and hormonal induced urinary tract changes, and subsequent kidney damage to the mother; higher risk of premature labor induced by colicky renal pains²⁷; and higher possibility of underlying anatomical or metabolic abnormalities when a pregnant woman develops nephrolithiasis justifies an earlier and a more detailed workup. In general, the incidence of nephrolithiasis in pregnant women is lower than in general population, likely secondary to the fact

that physiologic increase in urinary crystallization inhibitors outweighs the lithogenic (hypercalcuria and hyperuricosuria) and anatomical changes that occur during the pregnancy.²⁶

Due to the teratogenic and carcinogenic hazards of radiation to the fetus, ultrasonography remains the first modality of choice in evaluating pregnant women with nephrolithiasis.²⁸ However, due to physiologic dilatation of ureter in pregnant women, the sensitivity and specificity of renal ultrasonography is lower compared to general population (34% and 86% versus 98% and 74%, respectively).²⁹ A transvaginal ultrasonography can be adjunctive modality in differentiating the physiologic gestational ureteral dilation and hydronephrosis from a pathologic obstruction.³⁰⁻³² If the result of an ultrasonography is unrevealing, magnetic resonance urography with a half Fourier single-shot turbo spin-echo protocol without contrast yields comparable accuracy to CT scan and should be considered as the second modality of choice.³³⁻³⁵ As the last resort, a low-dose CT (fetal radiation dose 4 mGy versus 25 mGy) could be considered.³⁶⁻³⁸ It is highly sensitive and specific and should it be implemented, physician should try to postpone it until the second or third trimester of pregnancy, when minimal radiation related teratogenicity and carcinogenicity occurs.²⁷

Alternatively, KUB or a limited intravenous urography yields reasonable sensitivity (94%) and specificity (100%) with minimal radiation exposure (0.2 rads that is equivalent to 1.4 mSv for KUB and 0.4 to 1.0 rads that is equivalent to 2.8 to 7.0 mSv for limited intravenous urography).³⁹⁻⁴⁰

Follow-up Imaging

General guidelines. The most sensitive way to track the passage or detect the growth of a new or an existing calculus is imaging. Current guidelines recommend KUB (rather than CT scan) for radio-opaque calculi, and ultrasonography for radiolucent calculi, 1 year after the diagnosis of nephrolithiasis.⁴¹

Guidelines for urogenital malignancies. The association of nephrolithiasis with transitional cell carcinoma and squamous cell carcinoma of urogenital epithelium was demonstrated in a nation-wide cohort study in Sweden (25-year follow-up). The dominant cancer type in patients with nephrolithiasis was transitional cell carcinoma

(71.7% to 90.3%), followed by squamous cell carcinoma (5.3% to 17.4%).¹⁸ The incidence of malignancy was higher in women or patients with concomitant urinary tract infection (more than twice for each group). A multicenter prospective study with adequate sample size is required to determine a clear indication for cancer screening in patients with calculus disease. However, at this point, data from the retrospective study by Raghavendran and coworkers¹⁷ and the Swedish National Cancer Institute¹⁸ provide an empiric guide for the timing and the need of ordering a contrast enhanced CT scan with CT urography. According to these studies, high-risk patients are women and those with long-standing calculus disease (> 6 years), especially those who experience constant pain, hematuria (microscopic or gross), impaired kidney function, and urinary tract infection (Table 2).^{17,18}

MEDICAL MANAGEMENT

Approximately, 10% to 20% of calculi that are larger than 5 mm, painful, obstructive, and located in the proximal part of the ureter or are infected require surgical intervention. In this article, we review the most recent preventive and passage-facilitating medical interventions.

Several studies have shown the effectiveness of medical therapy in calculus management. One study showed that medical therapy resulted in remission rate of more than 80% and overall reduction in calculus formation rate of more than 90% in patients with nephrolithiasis.⁴² As a general rule, increased fluid intake is effective for all kinds of urinary calculi and urine alkalization for acidic-related or hypocitraturic-related urinary calculi.

Additionally, in patients with ureteral calculi in whom watchful waiting nonsurgical therapy has failed to pass the calculus over 6 weeks' period, a trial of medical expulsion therapy is indicated in order to avoid potential complications.^{43,44} Five meta-analyses studies have shown the efficacy of smooth muscle relaxant drugs tamsulosin (an alpha-adrenoreceptor antagonist) and nifedipine (a calcium channel blocker) on facilitating the passage of calculi.⁴⁵⁻⁴⁹ Blockade of alpha1 receptors exerts its effect through reducing the basal tone, and amplitude and frequency of peristaltic contractions that results in decreasing luminal pressure and increasing the rate of fluid transport.⁵⁰ The calculus expulsion depends on many factors, such as, the

size of the calculus (< 10 mm), location (more favorable on the right side and distal ureter), and associated obstruction.⁵¹⁻⁵³ However, a recent multicenter randomized controlled trial on 1136 patients found no difference in outcome between those who received 4 weeks of tamsulosin, 400 µg/d, nifedipine, 30 mg/d, or placebo.⁵⁴

Calcium Calculi

Table 4 shows an overview of dietary recommendation for calcium oxalate calculus formers.

Dietary versus supplementary calcium. A retrospective analysis on 7982 postmenopausal Caucasian women, assessing their dietary or supplemental calcium intake, fractional calcium absorption, and history of nephrolithiasis, showed that those with higher dietary calcium intake were 21% to 44% less likely to report a history of nephrolithiasis. The higher amount of dietary calcium intake (> 565 mg/d) was associated with 45% to 54% less likelihood of finding a history of nephrolithiasis. Four hundred and ninety women (6.1%) who reported a history of nephrolithiasis were on no or low-dose calcium supplementation. On the other hand, for each 10% increase in fractional calcium absorption, there was a 24% increase in the likelihood of having a history of nephrolithiasis. The study demonstrated that increasing dietary calcium intake is associated with lower fractional calcium absorption.⁵⁵ This phenomenon could be explained by the fact that sufficient amount of calcium in the intestine binds to oxalate and excretes it in the stool, preventing free oxalate from absorption and subsequent urinary excretion that predispose calcium oxalate calculus formation. The strength of the study was its relatively large sample size as well as looking at the true clinical endpoint, which was the existence

Table 4. Recommended Dietary Modifications for Calcium Oxalate Calculus Formers

Recommendation	Diet
Recommended	Fluid Phytate Dietary calcium Potassium
Limited	Oxalate Sucrose and Fructose Calcium supplements Sodium Animal protein?

of a clinical calculus and not urinary calcium level. The limitations were the uniform demography of patients and retrospective nature of it.

The combined results of 3 cohort studies (total of 56 years' follow-up) in a wide variety of demographic populations showed lower incidence of urinary calculi (defined as calculi accompanied by pain or hematuria) in individuals who consumed higher amounts of dairy or nondairy calcium diet, independent of age, body size, intake of fluid, thiazide use, and other calculus risk factors. There was a significant decrease in the incidence of urinary calculi as the amount of dietary calcium increased.⁵⁶ The results of this study and 2 others showed a slight increase in the risk of nephrolithiasis (relative risk, 1.17 to 1.20) in those who consumed supplemental calcium.^{57,58} This could be explained by the timing of calcium tablets ingestion, not associated with other lithogenic components of foods like oxalate, leaving calcium free in the intestine for absorption and subsequent excretion in the urine.

Considering the abovementioned findings, unless the dietary calcium exceeds 2 g/d, patients with calcium oxalate nephrolithiasis should be encouraged to consume sufficient amounts of dietary (dairy or nondairy) calcium (1000 mg/d to 1200 mg/d) and avoid calcium supplements. This would not only lower the risk of recurrent kidney calculus formation, but also protects the bone density in patients with idiopathic hypercalciuria and a negative calcium balance.⁵⁹⁻⁶²

Thiazide diuretics. Mild volume depletion induced by thiazide diuretics leads to a compensatory increase in the active sodium reabsorption in the proximal tubule with up to 50% concomitant

passive reabsorption of calcium.^{63,64} Administration of thiazide diuretics has resulted in up to 90% reduction in the development of new calculi.⁶⁵⁻⁶⁸ It is recommended that patients with normal serum calcium and high or relatively high urine calcium excretion and recurrent calcium calculus formation (or high-risk first time calculus formers) receive thiazide diuretics. It is also suggested to replace calcium tablets with a thiazide diuretic in patients who have an indication for calcium supplementation (eg, osteoporosis) and a history of calcium calculus, if urine calcium level shows a significant rise 1 month after starting the calcium supplement (Table 5).⁶⁹ Moreover, in order to maximize the hypocalciuric effects and to minimize renal potassium losses during thiazide treatment, one should significantly restrict sodium intake.^{41,63}

On thiazide therapy, we recommend monitoring urine calcium and sodium and serum potassium levels, before and after initiation of therapy. Maintaining serum potassium in normal range prevents the potential complications associated with hypokalemia including its adverse effect on calcium calculus formation due to causing hypocitraturia. According to one's comorbidities, potassium supplements or potassium-sparing diuretics should be considered to achieve normokalemia; however, triamterene should be avoided since triamterene calculi have been reported.⁴¹

Potassium citrate. The agent of choice for urine alkalization is potassium citrate, given the fact that it contains potassium, which is a well-known crystallization inhibitor, while the sodium component of sodium citrate or sodium bicarbonate carries the deleterious lithogenic effect of increasing

Table 5. Comprehensive Overview on Thiazide Therapy in Prevention of Nephrolithiasis

Type of Calculi	Indication	Thiazide	Dietary Precaution	Post-thiazide Monitoring	Adjunctive Therapy to Maintain Normokalemia
Calcium oxalate	Recurrent calculi with normal serum calcium and high or relatively high urine calcium	Hydrochlorothiazide, 25 mg, twice a day, or Chlorthalidone, 25 mg to 50 mg, once a day	Decrease sodium intake (1.8 g/d to 2.3 g/d)	Serum potassium, urine calcium	Potassium citrate (potassium chloride if urinary pH > 6.5)
Calcium phosphate	Hypercalciuria	Chlorthalidone 25 mg to 50 mg, once a day	Decrease sodium intake (1.8 g/d to 2.3 g/d)	Serum potassium, urine calcium	Spironolactone (avoid triamterene)
	High-risk first time calculus formers*	Indapamide, 2.5 mg, once a day			Amloride
	Recurrent calcium calculus formers with normal metabolic profile or appropriately addressed				

*Those with a solitary kidney, hypertension or large calculus burden, or refractory to other risk-modifying measures

calciuria. In patients with urinary pH greater than 6.5, potassium chloride is preferred due to the concern related to overalkalization precipitating calcium phosphate crystals.⁷⁰

The preventive effect of potassium citrate is through increasing urinary citrate and potassium levels, and by alkalizing urine. Three randomized clinical trials have shown significant reduction in the recurrence rate of calcium calculi in patients with hypocitraturia.⁷¹⁻⁷⁴ Another study showed that adding potassium citrate (10 mEq to 20 mEq, 3 times per day) in patients who continued to form calcium calculi, despite adequate hypocalciuric response on thiazide therapy, significantly decreased the chance of calculus recurrence.⁷⁵ This beneficial response was attributed to a raise in urine pH and urine citrate level.

In summary, potassium citrate should be offered to recurrent calcium calculus formers with low urine pH or hypocitraturia, and to those who continue to form urinary calculi despite thiazide-controlled urine calcium. Finally, it would be appropriate to prescribe potassium citrate and thiazide therapy (alone or in combination) in recurrent calcium calculus formers whose metabolic profile has been normal or appropriately addressed (Table 6).^{41,65,66,72}

Allopurinol. In a double-blinded study, 60 patients with history of urinary calculi and hyperuricosuria (> 800 mg/d) but a normal urine calcium level received allopurinol (100 mg, 3 times per day) or placebo. An 18% reduction in calcium oxalate nephrolithiasis was observed in the group that received allopurinol.⁷⁶

Patients with inflammatory bowel disease are more likely to suffer from calcium oxalate and uric acid calculi. Frequent diarrhea with resultant dehydration, metabolic acidosis and hypokalemia causing hypocitraturia, and fat malabsorption causing enteric hyperoxaluria, plus corticosteroid

and bed-rest-related hypercalciuria are accounted for this observation.⁷⁷⁻⁷⁹ The synergistic effect of allopurinol on 6-mercaptopurines and azathioprine in inflammatory bowel disease patients with poor response to these immunomodulators (those who favor shunting the metabolism of thiopurines to 6-methylmercaptopurine nucleotide, which is an inefficacious and hepatotoxic metabolite, rather than 6-thioguanine nucleotide, which is the therapeutic metabolite, benefit from adding allopurinol and closely monitoring complete blood count.^{80,81}

Therefore in inflammatory bowel disease patients with calcium or uric acid calculi, cautious addition of Allopurinol to thiopurine poor responders (ratio of 6-methylmercaptopurine nucleotide to 6-thioguanine nucleotide > 20) optimizes the underlying lithogenic abnormality and should be considered by the clinicians, when appropriate.

Dietary sodium. Sorensen and colleagues conducted a secondary analysis on 78 293 postmenopausal women who had no history of nephrolithiasis, to evaluate the relationship between dietary calcium, sodium, and protein, and the incidence of nephrolithiasis. During the follow-up, 1952 women (2.5%) reported an incident of kidney calculus.⁸² After adjusting for age, ethnicity, education, geographic region, calcium supplementation, and current estrogen use, higher sodium intake was associated with 11% to 61% increase in the rate of calculus incidence. This effect was most pronounced in women with the highest daily sodium intake of greater than 3249 mg (8.2 g salt). This finding confirmed an earlier report suggesting a 30% increased risk of kidney calculi in women with the higher sodium intake.⁵⁷

Physiologically, calcium is reabsorbed passively in the proximal tubule down the favorable concentration gradient created by the reabsorption of sodium and water. Therefore, excessive sodium

Table 6. Overview of Potassium Citrate Administration in Different Types of Calculi

Type of calculus	Indication	Urinary pH goal	Dose
Calcium	<ul style="list-style-type: none"> • Low urinary pH or hypocitraturia • Added to thiazide despite normal urine calcium level on thiazide • Recurrent calculus formers whose metabolic profile is normal or has been normalized (alone or combined with thiazide) 	5.5 to 6.5	10 mEq to 20 mEq, 2 to 3 times per day
Uric acid	All	6.0 to 7.0	10 mEq to 20 mEq, 3 times per day
Cystine	All	7.0 to 7.5	15 mEq to 30 mEq, 3 times per day

intake results in an increase in urinary sodium and calcium.⁸³ Restricting dietary sodium to 1.8 g/d to 2.3 g/d (4.5 g/d to 5.8 g/d of salt) can enhance proximal sodium and calcium reabsorption, leading to a reduction in calcium excretion.^{61,84}

Dietary animal protein. Although metabolism of animal protein that is rich in sulfur-containing amino acids results in acid-load-induced hypocitraturia, hypercalciuria, and hyperuricosuria,⁶² clinical trials have failed to show an independent beneficiary effect of animal protein restriction in reducing calcium calculus recurrence rate.^{61,82,85} Observational studies have demonstrated controversial results of the deleterious effect of animal protein intake in men but not in women.^{57,86,87} These findings make avoidance of excessive animal protein intake a prudent measure.

Vitamin C intake. High doses of vitamin C increase urinary oxalate excretion and occurrence of symptomatic calcium oxalate calculi.⁸⁸⁻⁹⁰ It is recommended that patient with calcium oxalate calculus limit their vitamin C consumption to less than 2 g/d (and preferably < 1 g/d).

Vitamin D intake. Although the role of vitamin D in formation of calcium calculi is not clear, we recommend that clinicians should not be reluctant to replace vitamin D in vitamin D-deficient calculus formers. In 2012, Leaf and colleagues studied on 29 patients with a history of nephrolithiasis and vitamin D deficiency who had a urinary calcium excretion between 150 mg/d and 400 mg/d. The urinary calcium excretion was measured after 8 weeks of ergocalciferol therapy (50 000 IU/wk). Although remarkable increase in vitamin D level was observed in all of the patients, the mean 24-hour urinary calcium excretion did not change significantly. However, 11 participants showed 20 mg/d or greater increase in urinary calcium excretion. These participants also had an increase in urine sodium excretion, which likely reflected dietary variability.⁹¹

In 2013, a cross-sectional analysis of 25-hydroxyvitamin D serum level in 16 286 participants in the Third National Health and Nutrition Examination Survey showed no difference between calculus formers and noncalculus formers. Also, higher 25-hydroxyvitamin D concentration was not associated with increased odds of previous kidney calculi (odds ratio, 0.99) after adjustment for age, sex, race, history of hypertension, diabetes

mellitus, body mass index, diuretic use, and serum calcium level. Furthermore, after dividing 25-hydroxyvitamin D concentrations into quartiles, or into groups using higher cutoffs (eg, 40 ng/mL and 50 ng/mL), there was still no significant difference in calculus formation rate among different groups. The results of this study suggested that calculus formers did not have an increased vitamin D store in the form of serum 25-hydroxyvitamin D concentration, and that higher serum concentration of 25-hydroxyvitamin D did not appear to increase the risk of kidney calculus disease.⁹²

Considering the abovementioned findings and the hypothesis of vitamin D gene overexpression in response to small amount of 1,25-dihydroxyvitamin D in calcium calculus formers,⁹³ we recommend replacing vitamin D (without calcium) in calcium calculus formers who have low levels of serum 25-hydroxyvitamin D, in order to prevent the complications of vitamin D deficiency and bone loss.

Fluid intake. Fluid intake is important both in the passage and prevention of all types of calculi. An analysis on patients with urinary calculi showed that most people are willing to implement this measure as opposed to dietary modification or taking medications.⁹⁴ The recommended fluid intake is to reach more than 2.5 L of urine per day.⁴¹ No randomized trials have been conducted on the type of the fluid of choice, observational studies suggest that coffee, tea, orange juice, lemonade, and alcoholic beverages might be protective, while grape juice and sugar-sweetened sodas might increase the risk of calculus formation.^{86,95-97}

Uric Acid Calculi

Extremely acidic urine (pH < 5.5) is the most common finding in uric acid calculus formers,¹¹ while hyperuricosuria and low urinary volume are less frequently observed.⁹⁸ Impaired renal ammonium excretion, independent of dietary manipulation, and increased acid production by intestine and aerobic metabolism have been blamed as the underlying cause of acidic urine production in this population.⁹⁹⁻¹⁰¹

Medical treatment in uric acid calculus formers plays a pivotal role, since dissolution of such calculi is highly possible without the need for invasive intervention.¹⁰² Urine alkalization (urine pH of about 6.0 to 7.0) through using potassium citrate and increased fluid intake should be the first line

recommendation in the treatment of uric acid calculi.^{41,103} Allopurinol (300 mg/d) is prescribed only for patients who continue to make uric acid calculi despite urinary alkalinization and high fluid intake.⁷⁰ The primary goal of using xanthine oxidase inhibitors in patients with recurrent or tophaceous gouty arthritis and uric acid calculi is gout and not prevention of uric acid calculi. Clinicians may consider cautiously adding allopurinol in inflammatory bowel disease patients with uric acid calculi, who have responded poorly to thiopurines, with the primary goal of correcting the underlying diarrhea induced metabolic acidosis and volume depletion.^{80,81}

Cystine Calculi

Like uric acid calculi, the first line in managing cystine calculi is alkalinizing urine with potassium citrate, increasing fluid intake, and restricting salt and protein intake.⁴¹ Fluid intake should be increased in order to keep the urine cystine concentration below 243 mg/L.¹⁰⁴ Cystine-binding thiol drugs should be prescribed in patients with a large calculus burden; those who keep forming calculi on conservative treatment; patients who fail to achieve the desirable urinary pH (7.0 to 7.5) on medical treatment; those who fail to lower urine cystine concentration below 243 mg/L (for example, a patient who excretes 1 g of cystine per day would require more than 4 L of urine output to achieve such a goal); and patients with persistent cystine crystals in urinalysis despite conservative management.^{14,15,105}

Alpha-mercaptopyrionylglycine (tiopronin) is preferred over D-penicillamine due to fewer adverse events and possibly more effectiveness.¹⁰⁶

Struvite Calculi

Urinary tract infection with urease producing organism may result in the development of magnesium ammonium phosphate and/or calcium carbonate apatite calculi (struvite calculi). Since antimicrobial therapy alone is usually unsuccessful and there is a potential of developing urosepsis and end stage renal failure, surgical intervention should be implemented as soon as possible.

Clinicians should apply frequent urinary and imaging screening in the postoperative care of patients with small residual calculus particles in order to monitor and assure persistent sterile urine

and absent calculus growth. Finely pulverized calculus material is susceptible to sterilization by appropriate antimicrobial therapy.¹⁰⁷

In patients with residual calculus fragments that persisted eight weeks after extracorporeal shock wave lithotripsy, it was shown that appropriate long-term antibiotic treatment and administration of 40 mEq to 60 mEq of potassium citrate per day increased rate of calculus clearance.¹⁰⁸ Although struvite calculi form in alkaline urine (pH > 8), potassium citrate is speculated to be helpful by inhibiting the growth of other crystals and fragments (like calcium oxalate) that might impede the passage of struvite's fragments and facilitate spontaneous passage of the residues.

The use of urease inhibitors like acetohydroxamic acid in combination with antibiotics should only be considered in patients with residual or recurrent struvite calculi after surgical options have been exhausted or is not feasible and in those in whom the risk for calculus recurrence or progression remains high. However, the extensive side effect profile of this medication limits its use.^{108,109}

FUTURE DIRECTION

Public and professional steps must be taken in increasing awareness towards a comprehensive and on time evaluation and medical management of nephrolithiasis in order to prevent or minimize the morbidity and expenses associated with this common condition.

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CONFLICT OF INTEREST

None declared.

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