

## Medical Management of Kidney Stones: a review



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### ABSTRACT

The incidence of kidney stone disease has been rising in past decades. The prevalence has doubled in both genders, and the prevalence ratio is shrinking from 3.4 to 1.3 between males and females. This condition greatly impacts individuals, the health care system, and socioeconomic levels. Kidney stone diseases are related to various risk factors and medical conditions. A detailed diagnosis through history taking, urinalysis, metabolic evaluation, and stone analysis is important to direct the therapy approach. The therapy in managing kidney stone diseases comprises dietary and pharmacological treatment. In addition to general advice on sufficient fluid intake, citrate intake, maintaining ideal body weight, and restricting sodium and animal protein, the therapy should be adjusted based on the specific type of stones.

**Keywords:** Kidney stones; medical management; kidney stone dietary therapy; kidney stone pharmacological therapy.

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### INTRODUCTION

The incidence of nephrolithiasis, widely known as kidney stones, has risen rapidly in recent decades. Between 1994 and 2012, the prevalence had doubled, from 6% to 11% among the male population and 4 to 7% in the female population. In addition, the prevalence ratio between genders is also shrinking from 3.4 to 1.3, implying that both genders are starting to possess a similar risk of developing kidney stones.<sup>1,2</sup>

A complex process of crystal nucleation, aggregation and/or secondary nucleation, fixation within the kidney, more accumulation, and secondary nucleation involved in stone formation. These processes are affected by the concentration of stone constituents appearing in tubular fluid, urine pH, and substances that consist in the urine. A high concentration of stone constituents in the urine leads to urine supersaturation which induces crystallization. Low urine volume and the presence of uric acid will promote the stone formation, while the presence of citrate will inhibit stone formation. Urine pH can encourage or inhibit stone formation, depending on the stone's type. Due to heterogeneous crystallization, highly acidic urine promotes uric acid, cystine stone formation, and calcium oxalate crystallization. Highly alkaline urine

may also promote secondary nucleation of calcium oxalate by precipitation of calcium phosphate. A urine pH of 5.5-7.0 is considered to have the least risk for stone formation.<sup>3,4</sup>

Several factors contribute to kidney stone formation. Body mass index (BMI), dietary habits, metabolic conditions, daily behavior, and even genetic disorder are some examples of risk factors for kidney stone formation. Moreover, kidney stone disease is linked to other systemic conditions such as hypertension, chronic kidney disease (CKD), and osteopenia or osteoporosis. Thirty percents of idiopathic kidney stone patients with recurrent calcium stones also have osteoporosis.<sup>5</sup> Patient's medication such as sulfadiazine, triamterene, acetazolamide, and calcium or vitamin C supplementation is also a possible factor for kidney stone formation, specifically known as drug-induced calculi.<sup>6</sup>

The high prevalence of stone diseases in working-age adults significantly impacts the individual, healthcare, and socioeconomic burdens. The direct costs to treat patients with urinary stones and the indirect costs due to work time loss exceed USD 5 billion.<sup>2</sup> Furthermore, kidney stones are also a problem in managing the disease. More than 50% of kidney stones are recurrent within the

first five years.<sup>7</sup> Considering the burdens that kidney stones bring on various scales, preventive strategies are desirable. However, the preventative approach is proved ineffective sometimes, if not often, in the long run. The main cause is the low and diminishing compliance over time.<sup>8</sup> Therefore, medication and diet therapy become important aspects of kidney stone disease management.<sup>9</sup>

Knowing which type of stones are occurring in each patient is helpful for physicians in directing the medication approach. Although calcium oxalate and calcium phosphate stones are the most frequently diagnosed type of kidney stones, it is not always the case. More than 100 chemical components and 100 different etiologies may be involved in stone formation. Each one might have a different pathophysiological process.<sup>6,7</sup> This literature review aims to explain the medical approach to managing kidney stone disease effectively. Related risk factors and diagnostic approaches will be discussed in this review in addition to medication and dietary therapy.

### EVALUATION OF KIDNEY STONE DISEASES

#### Risk Factors to Kidney stone diseases

Evaluation of kidney stone disease starts as early as assessing the patient's detailed

medical condition and history. It is aimed to diagnose kidney stone disease accurately as well as to screen for risk factors. Below is the information that should be assessed from the patient's history:<sup>7</sup>

- **Stone history.** This information includes the number of episodes, any surgical intervention before assessment, and composition of past stones.
- **Medical history.** Assessing medical history is meant to identify risk factors and systemic conditions related to kidney stone formation, such as obesity, type 2 diabetes, gout, and genetic disorders.
- **Family history** of kidney stone diseases
- **Dietary history.** The food history includes high sodium intake, excessive animal protein intake, calcium intake, low fluid intake, lack of fibers consumption, and food rich in oxalate.
- **Medication history.** The medication history includes certain drugs associated with stone formation, including calcium supplements, vitamin C, carbonic anhydrase inhibitors (e.g., acetazolamide), and protease inhibitors.

From detailed history, physicians will be able to assess the risk factors of kidney stones formation and predict the type. The risk factors to stone formation can be divided into general and stone type-specific risk factors.

### General Risk factors

#### Metabolic syndrome

Growing epidemiologic evidence indicates that each trait of metabolic syndrome (MS) increases the risk of stone formation. A study by West et al. shows that four or all MS traits are associated with a two-fold increase in odds of stone disease compared to a person without MS. The traits of MS are central obesity, diabetes mellitus (DM), dyslipidemia (high LDL and triglyceride level and low HDL level), and hypertension.<sup>10</sup>

One of the risk factors for kidney stones is obesity. Obesity through studies is highly correlated with the incidence of kidney stones which can be associated with other risk factors. The risk factors are

high content of oxalate compounds, uric acid, sodium, and phosphorus in the urine and low citrate levels in the urine.<sup>11</sup> Urine will tend to be more acidic in patients with metabolic syndrome in the form of obesity along with insulin resistance.<sup>10</sup>

The relative risk of kidney stone disease in individuals with DM compared to without DM is 1.31 in men, 1.38 in older women, and 1.67 in younger women.<sup>10</sup> Insulin resistance, the underlying mechanism of DM type 2 and the key factor of MS, may cause defects in renal ammonia production, thus lowering urinary pH. On the other hand, hyperinsulinemia is reported to increase urinary calcium excretion.<sup>12</sup> Since low urinary pH is a risk factor to uric acid stone formation, MS is highly related to uric acid stone disease, although calcium stone formation is also possible due to hypocitraturia in MS.<sup>10</sup>

Stoller et al. found that esterified cholesterol accounted for 14% to 16% of total cholesterol in stones. The cholesterol component may result from plasma leakage of free cholesterol in vasculature.<sup>10</sup> A study by Toricelli et al. showed that all three lipid profiles (LDL, triglyceride, and HDL) were associated with the risk of stone formation. Remodeling LDL with insulin resistance and elevated HDL anti-inflammatory mitigation of insulin resistance was speculated to explain the relationship. However, it could not be fully explained. Masterson JH et al., on the other hand, found that in dyslipidemia, only low HDL levels increased the risk of stone disease despite the level of LDL and triglyceride. HDL level below 45 for men and below 60 for women increased the risk of stone diseases.<sup>13</sup>

Hypertension seems to have a bidirectional relationship with kidney stone formation. Cappuccio et al. found that hypertensive patients are twice more likely to have a history of kidney stone disease (OR 2.11). Borghi et al. found that patients with hypertension were 5.5 times more likely to develop kidney stone diseases.<sup>10</sup>

#### Fluids

Fluid intake is inversely associated with stone formation. Increasing fluid intake decreases the concentration of calcium, oxalate, phosphorus, and uric acid in

the urine. The daily fluid intake goal needs to be individualized based on a target urine output of at least 2.5 L daily regardless of the underlying metabolic abnormalities.<sup>10,14</sup>

#### Sodium

Dietary salt in food is a risk factor for calcium stones due to hypercalciuria conditions. High salt intake will increase the sodium content in the blood, thereby inducing the kidneys into a hypovolemic state, reducing sodium reabsorption in the proximal tubule. Impaired sodium absorption causes calcium absorption in the distal nephron to be damaged. The calcium reabsorption is also independent of volume status. Consumption of salt 3.5 grams/day risk 1.63 times the occurrence of hypercalciuria.<sup>1</sup>

In addition, urinary citrate excretion also decreased due to high sodium intake. The citrate content in urine has a role as an inhibitor of stone formation. The increase in salt consumption every 5 grams will reduce the citrate concentration in the urine by 50 mg/day.<sup>1</sup> A synergistic effect can also appear when combined with a diet high in animal protein, which will cause intracellular and extracellular acidosis conditions so that citrate excretion is disrupted. A high sodium diet increases the risk of cystine stones and greater urinary saturation of brushite and monosodium urate.<sup>7</sup>

#### Stone-specific risk factors

##### Calcium stones

As mentioned above, hypercalciuria and hypocitraturia are risk factors for developing calcium stones. Besides these, hyperuricosuria and hyperoxaluria also increase the risk of calcium stone formation. Hypercalciuria may arise from disturbances in gastrointestinal, renal, or bone handling of calcium. Dietary calcium restriction was recommended in the past. However, recent studies suggest that it is ineffective in preventing recurrence. Consequently, strict dietary calcium is no longer advised. Hypocitraturia impairs the inhibition of calcium oxalate and phosphate stone formations. Renal citrate excretion is regulated primarily by the systemic acid-base balance. Acidosis decreases renal tubular production

and excretion of citrate, while alkalosis increases it. Medical conditions such as distal Renal Tubular Acidosis (dRTA), chronic diarrhea, and certain drugs (e.g., carbonic anhydrase inhibitors) are known to cause hypocitraturia.<sup>7,10</sup>

There are several suggested mechanisms of hyperuricosuria in causing calcium oxalate stone formation. One of them is through the growth of crystals (epitaxy). An addition of crystalline sodium urate accelerated the crystallization of calcium oxalate. In addition to epitaxy, uric acid promotes calcium oxalate crystallization through a salting mechanism. The salting-out mechanism increases the concentration of electrolytes so that the solubility of non-electrolytes will decrease and precipitate out of the solution. Uric acid compounds tend to be more soluble than calcium oxalate compounds. That is because uric acid compounds tend to be electrolytes than calcium oxalate compounds which will not make calcium oxalate.<sup>14,15</sup>

Urine with an oxalate excretion value exceeding 40 mg/day is called hyperoxaluria.<sup>7</sup> Hyperoxaluria conditions will increase urinary calcium oxalate saturation, thereby increasing the risk of calcium oxalate stone formation. Increased urinary oxalate levels are also influenced by factors such as genetic disorders (primary hyperoxaluria), calcium and oxalate intake from food, the anatomical and functional integrity of the gastrointestinal tract, and the presence of oxalate-degrading bacteria.<sup>16</sup>

### Uric acid stones

Low urine pH is a major factor in the formation of uric acid stones. The acidic condition of the urine pH causes uric acid to be titrated into insoluble uric acid compounds, which leads to urine supersaturation. Uric acid solubility increased 11 times at pH 6.5 compared to pH 5.0. The risk of uric acid stone formation is greater in patients with a history of primary gout, obesity, diabetes, or metabolic syndrome. However, there was no increase in urinary uric acid excretion. In addition to the influence of acidic urine pH, reduced urine volume also affects the formation of uric acid stones.<sup>7,17</sup>

### Cystine stones

Cystinuria is a major factor in the formation of cystine stones. Cystinuria is an inherited autosomal recessive disorder that causes defects in amino acid transport in the intestines and kidneys. This transport defect results in excessive excretion of cystine, orthine, lysine, and arginine in the urine. However, cystine tends to precipitate in the urine and form stones because the solubility of cystine in urine is very poor.<sup>7</sup>

### Struvite stones

Struvite stones are also known as triple phosphate stones or infection stones. The incidence of infection is related to upper urinary tract infection by urease-producing bacteria such as *Proteus* or *Klebsiella*. Normally, ammonium is less saturated in urine, but the presence of infectious conditions increases ammonia production. Rising ammonia levels will cause the urine to become alkaline so that the solubility of phosphate compounds in the urine decreases. The precipitated phosphate then forms stones that combine with ammonium, magnesium, and carbonate compounds, so that the rock content consists of magnesium ammonium phosphate (struvite) and calcium carbonate-apatite.<sup>18</sup>

### Imaging

The stone burden can be evaluated through radiographic imaging. In addition, imaging can also inform anatomical or medical conditions in recurrent stone conditions. The stone burden can provide an overview of the patient's metabolic activity and provide a direction for the aggressiveness of therapy. The occurrence of the first stone on initial imaging can be a condition for the event of recurrent stones. The presence of staghorn stones reflects the presence of an infection, besides anatomic abnormalities such as medullary sponge kidney conditions or metabolic conditions such as primary hyperparathyroidism or dRTA can be expected due to nephrocalcinosis at the time of imaging.<sup>8,11</sup>

### Urine analysis

Urine analysis can provide a lot of useful information regarding the composition

of kidney stones, both by dipstick and microscopic examination. Certain crystals are pathognomonic of a particular stone composition (e.g., hexagonal crystals, which indicate cystine stones or coffin-lid crystals, which indicate struvite stones). Some parameters such as urinary pH, sodium, oxalate, uric acid, and citrate are valuable in assessing kidney stone diseases, especially in-depth metabolic evaluation. The best specimen should be obtained from a 24-hour urine collection. Unfortunately, only 7% of symptomatic kidney stone disease patients and 17% of patients with recurrent stones undergo the analysis. Pyuria and bacteriuria indicates infection stones. If an infection marker appears in the urinalysis, urine culture should be done.<sup>7</sup>

### Metabolic evaluation

In-depth metabolic testing is important in patients with recurrent stones and first-time stone formers with a high risk of recurrence.<sup>7</sup> However, even the first-time stone-former without any identifiable risk factors for recurrent stone formation should also undergo a limited metabolic evaluation to rule out potential systemic disorders, such as hyperparathyroidism or kidney dysfunction. The limited metabolic evaluation includes a urinalysis (with or without culture), serum electrolytes (including HCO<sub>3</sub> and calcium), and serum creatinine.<sup>2</sup> In-depth metabolic evaluation, on the other hand, comprises more detailed blood tests, urine analysis, as well as detailed dietary history.

In-depth metabolic evaluation is recommended for patients with certain risk factors as follows:<sup>2</sup>

- Children (<18 years old)
- Bilateral or multiple stones
- Recurrent stones (Defined as two or more kidney stone episodes in the past)
- Non-calcium stones
- Pure calcium phosphate stones
- Any stone episode complicated with severe acute kidney injury, sepsis, or complicated hospitalization
- Any stone requiring PCNL
- Stones of a solitary kidney
- Renal insufficiency
- History of kidney stones and systemic diseases (e.g., osteoporosis, gout,

hyperparathyroidism, RTA, intestinal disorders, etc.)

- Occupation where public safety is at risk

Any patient interested in having their 24-hour urine analyzed and blood tested may also undergo in-depth analysis. However, according to the testing result, one should also be willing to alter their diet or start medication.<sup>2</sup>

**In-depth blood testing**

An in-depth evaluation from blood testing may identify certain medical conditions associated with stone disease. Electrolytes (sodium, potassium, chloride, calcium, and bicarbonate), creatinine, albumin, and uric acid are some parameters being tested on this evaluation based on AUA recommendation.<sup>2</sup>

- Elevated uric acid may indicate gout is associated with uric acid or calcium oxalate stones.
- Low potassium and bicarbonate with high chloride indicate dRTA, which is a risk of calcium oxalate and calcium phosphate stones.
- Parathyroid hormone (PTH) is tested if the calcium level is considered high, whether normal or abnormal. A high level of PTH is suggestive of primary hyperparathyroidism. This condition is associated with calcium phosphate stone or nephrocalcinosis.
- Vitamin D is tested if the calcium level is considered low or PTH is elevated to evaluate the possibility of secondary hyperparathyroidism.

**In-depth urine analysis**

In in-depth urine analysis, 24-hour urine collection should be obtained. The current recommendation is that two 24-hour urine collections be brought. However, if it is not practical, at least one collection should be used. Among the parameters of 24-hour urine collection, creatinine should be evaluated first since it reflects whether the urine has been collected properly or not. Creatinine levels should be consistent with lean body weight, sex, and muscle mass. The typical urine creatinine level for males is between 18-24 mg/kg, while females are 15-20 mg/kg.<sup>2,7</sup> Parameters measured in this analysis are volume, electrolytes (including calcium, bicarbonate, and

**Table 1. Identification of Metabolic Abnormalities Using Standard Metabolic Evaluation (Modified from Lipkin and Preminger).**

Urinary finding	Implicated dietary disturbances
Total volume < 2 L/day	Low fluid intake, excessive sweating
Sodium > 200 mEq/day	Excessive salt intake
Oxalate > 45 mg/day	High intake of oxalate-rich food or; Very low calcium intake
Calcium > 250 mg/day	High intake in calcium
Uric acid > 600 mg/day	High animal protein intake
Sulfate > 30 mmol/day	Excessive animal protein intake
Citrate < 500 mg/day	High intake of salt and/or animal protein

magnesium), oxalate, uric acid, and citrate. Any abnormal finding is often attributed to dietary or environmental disturbances, as shown in table 1. Cystine should be tested if cystine stone is suspected or based on stone analysis.

Urinary pH is also an important part of the metabolic workup of patients with nephrolithiasis because it can help physicians direct the management approaches to stone prevention. Low pH suggests uric acid stones. On the other hand, high pH indicates calcium phosphate or struvite stones. The pH electrode method's evaluation of 24-hour urine collection is the gold standard for metabolic evaluation in urinary stone diseases. However, it is inconvenient and time-consuming, especially in outpatient settings. Therefore, spot measurement using dipstick becomes an alternative in this situation. Regardless, the dipstick measurement's accuracy varies depending on the pH value a patient had at the time of size. Dipstick measurement provides less accurate value for urinary pH > 6.5. Therefore, the result should be cautioned, especially in patients with alkaline urine.<sup>19</sup>

**Stone analysis**

To identify the etiologies and chemical components of the stone, chemical or physical methods can be used. However, chemical processes are often inaccurate and unsatisfying, despite their low cost. Chemical analysis, for example, fails to adequately identify rare purine stones, which resulted from a genetic disorder, or drug-induced calculi. Furthermore, they cannot quantify the amount of each component in mixed stones or differentiate various crystalline phases in calcium oxalate or calcium phosphate stones, which is important considering each one

is related to different pathophysiological conditions.

**Physical method stone analysis**

Physical methods show more satisfying results compared to chemical processes. Among the techniques, X-ray diffraction (XRD) and Fourier Transform Infrared Spectroscopy (FTIR) are the most used methods. These methods identify each component and provide the proportion of each within the stone.<sup>6</sup>

These methods can identify calcium and non-calcium stones such as cystine, xanthine, uric acid, struvite, proteins, lipids, and drugs. Accurate identification of each component, including the minor ones, is clinically relevant to explain the stone formation (lithogenic) process from different conditions.<sup>6</sup>

Physical methods also provide information on the crystalline phase of kidney stone formations. The same chemical composition of the stones might have a different crystalline phase, implying another lithogenic condition. Take, for example, Calcium Oxalate Monohydrate (COM) and Calcium Oxalate Dihydrate (COD). COM stones may imply a hyperoxaluric state while COD stones are related to hypercalciuria in most cases. Those stones can be distinguished physically both from the surface and the section.<sup>6</sup>

Physical stone analysis can provide accurate metabolic conditions or risk factors involved in stone formation with blood and urine biochemistry. This information is sometimes hard to be identified only by standard metabolic investigation. For instance, a stone analysis shows a stone made of 2,8-dihydroxyadenine. This result leads to identifying adenine phosphoribosyltransferase enzyme

**Table 2. Relations observed between stone main component and etiology (modified from Cloutier J, et al.).**

Main component	Common causes
Calcium Oxalate Monohydrate (COM)	Hyperoxaluria, low diuresis, malformative uropathy
Calcium Oxalate Dihydrate (COD)	Hypercalciuria
Uric acid	Low urinary pH, diabetes, metabolic syndrome
Various urates	Hyperuricosuria, alkaline urine, UTI
Ammonium urate	Hyperuricosuria, diarrhea
Carbapatite	Hypercalciuria, UTI, dRTA
Struvite	UTI by urease-splitting bacteria
Brushite	Hypercalciuria, PHPT, phosphate leak
Cystine	Cystinuria
Protein	Proteinuria, drugs, chronic pyelonephritis, ESRF

deficiency which would not be detected on routine metabolic investigation.<sup>6</sup> Table 2 provides the main components of the stone and their common causes.

## MEDICAL APPROACH TO KIDNEY STONE DISEASES

While there is general advice to follow in treating kidney stones, different types of stones are related to various risk factors and medical conditions. Hence, the medical approach for each stone must be tailored according to each risk factor encountered. Table 3 provides the general steps in treating kidney stone disease and recommendations to be followed for specific conditions.

Maintaining a high fluid intake is a universal recommendation to prevent kidney stones from forming. Fluid intake in one day is recommended around 2.5 - 3 liters or output 2.5 liters of urine. Meta-analysis studies show that a daily intake of 2 liters of fluid or adequate fluid intake to produce 2.5 liters of urine can reduce the risk of developing kidney stones by 61%.<sup>2,7</sup>

Caffeinated beverages (such as coffee and tea), and alcohol have been shown to have some or no benefit in various trials. Three large cohort studies found that coffee, tea, beer, wine, and orange juice were associated with a reduced risk of incident stone formation. On the other hand, lemonade is a dietary source rich in citrate and has increased urinary citrate and urine volume. However, caution must be taken because sugar-sweetened drinks and punch were associated with an increased risk of stone formation.<sup>2,7</sup>

## Calcium stones

Calcium stones are formed by various predispositions such as hypercalciuria, low urine volume, hyperoxaluria, and hypocitraturia. In addition, the presence of urinary tract abnormalities also predisposes to stone formation, so correction is needed in the form of drugs and/or diet as a treatment strategy to prevent recurrent stones. The prevention strategy will also be adjusted to the composition of the type of stone. Calcium stones have the most diverse causes compared to other kinds of stones. That causes the treatment of calcium stones to have variations in the type of diet and medication.<sup>7</sup>

## Dietary therapy

Various dietary factors also have a role in the adjunctive therapy of calcium stones and adequate fluid intake as the main therapy. The nutritional factors include calcium intake, fish oil, oxalate, vitamins, sodium, animal protein, and citrate.

## Calcium

Calcium supplementation can increase the risk of stone formation compared to no supplement intake. There has been speculation regarding the timing of taking calcium supplements with the risk of stone formation. Calcium supplements taken together with food will form a complex with oxalate compounds in the intestinal lumen. The appearance of this complex reduces the absorption of oxalate and compensates for the increase in urinary calcium. That will have a protective effect on the risk of stone formation.<sup>7</sup>

The AUA and the EAU, in consideration of the evidence, recommend: (1) patients at risk for recurrent calcium stones should consume 1000 - 1200 mg of dietary calcium daily; (2) daily intake of calcium is obtained from food rather than supplements; and (3) if it is necessary to take calcium supplements, then the supplements are given together with food.<sup>7</sup>

## Fish oil

Studies show that a diet rich in fish protein with omega-3 content in native Greenlanders has a lower risk of developing kidney stones than westerners.<sup>20</sup> The fish that are good sources of fish oil are salmon, tuna, mackerel, and sardines.<sup>7</sup> The study reviewed the medical records of 29 patients who were treated with a conservative diet and fish oil supplementation (1200 mg/day) for the incidence of hypercalciuric calcium stones. After ten months of follow-up, the study results showed that the average urinary calcium decreased significantly from 329.27 mg to 247.47 mg/day. In addition, there was a significant decrease in urinary oxalate and calcium oxalate supersaturation. However, the application of the results of this study has weaknesses, namely, the lack of a control group and the unstandardized fish oil used in the study.<sup>20</sup>

## Oxalate

Reducing intake of oxalate-rich foods is advised for recurrent calcium oxalate stone formers with high urinary oxalate levels.<sup>7</sup> The Academy of Nutrition and Dietetics Nutrition Care Manual recommends a restriction of oxalate to less than 40-50 mg/day. Patients should avoid foods such as animal organs, spinach, rhubarb, and peanuts. Boiling vegetables has been found to decrease oxalate content by 30%-87%.<sup>7,21</sup>

Certain conditions can also lead to hyperoxaluria. In primary hyperoxaluria, a situation where the oxalate level is high due to enzymatic defects in the oxalate biosynthetic pathway, a strict dietary oxalate restriction is recommended.<sup>7</sup> In hyperoxaluria condition caused by chronic diarrhea (enteric hyperoxaluria), besides strictly reducing intake of oxalate-rich foods, fat intake should also be reduced. In these patients, calcium supplements

may be beneficial.<sup>7</sup>

### Probiotic

Colonization of normal intestinal flora, such as *Oxalobacter formigenes*, can affect urinary oxalate concentrations. *Oxalobacter formigenes* use oxalate as their energy source. Loss of colonization of *O. formigenes* in the intestine will result in decreased degradation of oxalate in the intestinal lumen and decreased enteric oxalate secretion. A case-control study showed that median urinary oxalate levels were not significantly different between positive and negative patients for *O. formigenes* colonization. Still, there was a strong inverse relationship with the risk of recurrence. However, Batagello et al. suggest that there are associations between the gut microbiota, the balance of oxalate, and urinary stone disease that go well. The successful development of bacteriotherapy to inhibit urinary stone disease will need to incorporate the functional microbiota concept and changes to diet and lifestyle that affect it.<sup>7,16</sup>

### Vitamins

Vitamin C is a factor associated with high oxalate levels in the urine. Metabolic studies suggest that vitamin C supplementation increases urinary oxalate excretion. That is because ascorbic acid in the body will be metabolized into oxalate. A recent observational study states that consumption of vitamin C more than 1000 mg/day has a 40% higher risk of developing kidney stones in men than consumption of vitamin C, according to the Dietary Reference Intake (DRI).<sup>7</sup>

Vitamin B6 (pyridoxine) reduces urinary excretion of oxalate. Cohort studies have shown an inverse relationship between pyridoxine intake and the risk of developing kidney stones. In addition, retrospective studies suggest that the combination of pyridoxine with dietary modification can reduce urinary oxalate levels.<sup>7</sup>

### Citrate

Citrus fruits have high alkaline content and provide a citrate response. The high content of potassium citrate in orange juice has shown the most consistent effect of citrate. Grapefruit juice produces only

a slight increase in urinary citrate and increased urinary oxalate. Lemonade remains controversial, with some studies showing increased urinary citrate and not others. However, these two juices have not been evaluated in an RCT using stone recurrence rate as the primary outcome.<sup>7</sup>

Epidemiological studies show that people with “dietary approaches to stop hypertension” (DASH) rich in fruits and vegetables have a lower risk of developing kidney stones. In addition, in a cross-sectional study of 3426 people with and without kidney stones, multivariate test results showed that the group similar to the DASH diet had 16% higher 24-hour urinary citrate excretion. In addition, increasing fruit and vegetable intake was found to decrease calcium oxalate saturation by 52%.<sup>7</sup>

### Sodium

In a randomized trial of 210 patients with hypercalciuria and calcium stones, a low-sodium diet resulted in lower urinary sodium, urinary calcium, and oxalate excretion, resulting in the normalization of urinary calcium excretion for one-third of patients. Proximal tubular calcium reabsorption is increased on a low sodium diet (2,000-3,000 mg/day), resulting in a decrease in supersaturation of calcium oxalate.<sup>2,18</sup>

### Protein

Animal protein has been shown to affect urine pH, calcium, and uric acid, which will affect stone formation. The sulfur-containing amino acid content in animal protein will provide an acid load, causing low urine pH, hypocitraturia, and hypercalciuria. A high-protein diet (>2.0 g/kg/day) can lower urine pH, so a moderate to low protein diet (0.8-1.4 g/kg/day) is recommended. In addition, animal protein is also a rich source of purines, while the end product of its metabolism is uric acid. That will cause hyperuricosuria, which predisposes to the crystallization of calcium oxalate. In this regard, the AUA guidelines for medical management of kidney stones and the EAU guidelines on urolithiasis recommend limiting consumption of non-dairy animal protein (including all forms of meat, including beef, poultry, and fish).<sup>7</sup>

## Pharmacologic Therapy

### Thiazide

The AUA guidelines recommend that thiazide and potassium citrate therapy be offered to patients with recurrent calcium stones and high fluid intake and dietary recommendations. Thiazide and potassium citrate therapy provide additional benefits on Bone Mineral Density (BMD). Thiazide therapy and potassium citrate can reduce the side effects of kidney stone formation in osteoporosis/osteopenia patients. Alshara L et al. demonstrated a positive impact of thiazides and potassium citrate on bone mineralization. The results of the study showed that 50 mg HCT and/or 20 mEq potassium citrate were found to have the best effect in increasing BMD compared to other doses.<sup>5</sup>

Thiazides have a hypocalciuric effect that will balance positive calcium to suppress parathyroid hormone and reduce bone resorption, which will increase BMD improvement. The impact on BMD was associated with no increased risk of stone formation in patients taking vitamin D and calcium supplements. Therefore, thiazides may reduce the side effects of long-term treatment of calcium and vitamin D supplementation.<sup>5</sup>

### Potassium citrate

RCT studies have shown that potassium citrate is associated with a reduced risk of recurrent calcium stones in patients with hypocitraturia or dRTA. Potassium citrate acts as an inhibitor in forming new stones in hypocitraturia calcium kidney stone disease. The common risk factors for recurrent stones are hypocitraturia and low urine pH (urine pH <5.5). In addition, potassium citrate effectively increases urine citrate and urine pH, reducing the risk of recurrence of recurrent calcium stones. Administration of potassium citrate significantly lowers urinary calcium oxalate saturation without increasing calcium phosphate crystallization. The average dose of potassium citrate is 20 mEq twice daily given with food.<sup>5,22</sup>

Potassium citrate can provide an alkaline load that buffers the bone resorption effect of excess acid and reduces PTH secretion, preventing bone loss. Potassium citrate alone was more beneficial for BMD than

HCT alone or in combination.<sup>5</sup> Potassium citrate is thought to exert an alkaline load that buffers endogenous acid production, thereby inhibiting bone resorption. Its hypocalciuric effect and sustained stimulation of osteoblast activity also lead to an increase in bone mass.<sup>5</sup>

### Pyridoxine supplementation

In primary hyperoxaluria type I, the liver-specific enzyme alanine glyoxylate aminotransferase deficiency, requires pyridoxine as a cofactor. A prospective uncontrolled open-label trial in which 12 patients with primary hyperoxaluria type I were given pyridoxine incrementally up to a dosage of 20 mg/kg/day showed a 25.5% mean relative reduction in urinary oxalate, with benefit seen in 50% of patients.<sup>7</sup>

### Allopurinol

Hyperuricosuria is detected in 15-20% of calcium stone formers. Allopurinol, which has an effect in lowering serum and urinary uric acid, has been shown in randomized trials to reduce stone recurrence rates in hypercalciuric and normocalciuric recurrent calcium oxalate stone formers. Allopurinol is typically initiated when dietary measures to reduce urinary uric acid fail. The typical allopurinol dosage is 200–300 mg daily in single or divided doses. The most common adverse effect associated with allopurinol is an allergic reaction, such as skin rash or a life-threatening condition (Stevens-Johnson syndrome). Allopurinol can also raise liver transaminases. Hence, periodic monitoring of liver enzymes is recommended.<sup>7</sup>

### Pure calcium phosphate stone

Patients with pure calcium phosphate stones may have an underlying condition predisposing them to this type of stone formation, such as dRTA, primary hyperparathyroidism, chronic urinary tract infection, hypercalciuria, and/or hyperphosphaturia.<sup>2</sup>

Patients with primary hyperparathyroidism have a significantly increased risk of kidney stone disease. An elevated parathyroid hormone can increase kidney stone risk and decrease bone mineral density even with normal serum calcium levels. Surgery for primary

hyperparathyroidism results in decreased stone formation, a decrease in serum calcium, and improved bone mineral density.<sup>2</sup>

Patients with dRTA generally have underlying hypocitraturia and are treated with citrate. Potassium citrate is preferred because it has superior effects compared to sodium citrate. Patients with recurrent urinary tract infection and calcium phosphate stone formation may have bacterial persistence of a urease-producing organism causing increased urinary pH and brushite stone formation. Hence, the infection should be treated appropriately and stone material removed to avoid reinfection.<sup>2</sup>

### Uric acid stone Dietary therapy

Low urinary pH is the primary risk factor for idiopathic uric acid nephrolithiasis, although low urine volume and hyperuricosuria can also contribute.<sup>7</sup> The most important intervention for the prevention of uric acid stones is alkali therapy to raise urinary pH through diet modification and/or pharmacologic agents, increasing urinary volume, and less importantly, the reduction of uric acid excretion since at pH 6–6.5, most uric acid in solution will be highly soluble.<sup>7,23</sup>

Weight loss is also important in managing uric acid kidney stones, specifically in preventing metabolic syndrome. A low-calorie DASH diet or more balanced plans should be recommended, but not the Atkins diet high in animal protein.<sup>17</sup>

Protein consumption must be avoided because it leads to increased uric acid, decreased pH, and citrate. In patients with recurrent uric acid kidney stones, limiting the intake of animal protein below 150 g daily (<0.8 g/kg/body mass/24 h) and avoiding purine-rich foods is suggested.<sup>2,23</sup> Several studies have shown increased urine acidity in stone formers and healthy patients compared to vegetable proteins and protein-limited diets.<sup>20</sup> Shellfish such as squid, clams, and shrimp contain a very high level of purine. Purine will convert to xanthine and then to uric acid, which leads to hyperuricosuria, increasing the risk of uric acid stones; thus should be avoided.<sup>20</sup>

A diet rich in fruits and vegetables is recommended because it increases urine citrate content and pH. It is expected to help prevent uric acid stone formation.<sup>17</sup> Numerous short-term studies of urinary chemistry measures have demonstrated the impact of citrus juices (grapefruit, orange juice, lemonade, and limeade) on urinary pH and citrate levels in nephrolithiasis patients. Among some conflicting results, orange juice decreased insoluble uric acid excretion. Baia et al. have shown that melon, a noncitrus source of potassium and citrate, also increase urinary citrate excretion and urinary pH equivalent to that provided by orange.<sup>17</sup>

### Pharmacological therapy Potassium citrate

Potassium citrate effectively provides an alkali load that raises urinary pH and can prevent and dissolve uric acid stones. Although no RCTs have assessed the effectiveness of potassium citrate in preventing uric acid stones, still the AUA guideline recommends potassium citrate as first-line treatment for the prevention of uric acid stones, with a target pH of about 6.<sup>7</sup> Drug-induced urinary alkalinizations can be achieved with 20–80 mEq/day of potassium citrate. Compared to sodium citrate, potassium citrate provides a decline in urinary calcium significantly, in addition to an increase in urinary pH. Thus, potassium citrate is preferable because it could also prevent the complication of calcium kidney stones. An observation by Sakhaee et al. concluded that the citraturic action of potassium citrate was largely through the alkali load.<sup>17</sup>

Despite the benefit, compliance to potassium citrate can be difficult, especially for older people, because of gastrointestinal intolerance. A randomized, double-blind crossover study showed that sodium bicarbonate might be an effective alternative for hypocitraturia calcium oxalate stone formers who cannot tolerate or afford the cost of potassium citrate.<sup>17</sup>

### Carbonic anhydrase inhibitors

Acetazolamide could also be potentially used to raise urinary pH. The drug effectively increased the urinary pH in uric acid stone formers who were already

taking potassium citrate. Still, caution must be taken when prescribing acetazolamide, because of poor tolerance and the risk of inducing calcium phosphate stones.<sup>17</sup>

### Allopurinol

Allopurinol may provide additional benefit for patients who keep forming kidney stones despite adequate alkalinization or in whom the target urinary pH is not achieved. Allopurinol significantly decreases hyperuricemia and hyperuricosuria. However, its use for uric acid stone formers should be initiated after correcting urinary pH and is limited to patients with primary gout or high urinary uric acid levels and calcium stones. Another issue is the conditions associated with increased cell turnover/purine states, such as hemolytic disorders, lymphoproliferative disorders, and other malignancies. Allopurinol prophylaxis should be routinely given when the tumor lysis syndrome is suspected to prevent the risk of urate nephropathy and uric acid stones.<sup>7</sup>

### Uricosuric drugs

Uricosuric drugs such as probenecid, losartan, high-dose salicylates, and radiocontrast agents should be avoided in uric acid stone formers.<sup>17</sup>

### Cystine stone

Cystinuria is a rare inherited autosomal recessive condition. Cystine stone-formers often present in childhood or teenagers, experiencing recurrent stone formation and the need for repetitive surgery, especially if prevention is not optimized. The primary goal of treatment in patients with cystinuria is to reduce the urinary cystine concentration to a level below the solubility limit (about 250 mg/L).<sup>2</sup>

### Dietary therapy

As in other kidney stone diseases, high fluid intake, sodium restriction, and animal protein restriction are important for cystine stone patients. Increased fluid intake is essential to reduce the cystine concentration, and patients with cystinuria are encouraged to drink enough fluid to produce a urine volume of at least 3 L daily.<sup>2,7</sup> To fulfill the high fluid intake, the patient is recommended to wake up

at least once per night to void and drink additional water.<sup>23</sup> The success of stone prevention will be poor in patients who do not comply with increased fluid intake, even with adjunctive medical therapy.

Restriction of animal protein intake decreases cystine excretion. A study of seven homozygous patients with cystinuria who were given a low protein diet compared to a high protein diet found that the lower protein diet was associated with significantly lower urinary cystine excretion than the higher protein diet.<sup>7</sup>

### Pharmacological therapy

Urinary pH of 7.0 to 7.5 increases the solubility of cystine significantly.<sup>7</sup> Urinary alkalinization is an important step in medical therapy for cystine stones to achieve a urinary pH of greater than 7.0. Thus, potassium citrate is beneficial for patients with cystinuria who continue to make stones despite dietary measures and high fluid intake. However, a urinary pH greater than 7.5 should be avoided because it may lead to calcium phosphate stone formation. Acetazolamide may be used as an adjunct to urinary alkalinization when potassium citrate alone is ineffective.<sup>2</sup>

### Thiol containing drugs

Patients who are unable to fulfill the fluid intake and urinary alkalinization may be given thiol-containing drugs to increase the solubility of cystine. These drugs include tiopronin, D-penicillamine, and captopril.<sup>7</sup>

The first-line drug is tiopronin which dosing starts at 200 mg two or three times daily and is titrated to achieve a urine cystine concentration of less than 250 mg/L. Adverse effects include fever, gastrointestinal upset, asthenia, rash, joint aches, loss of taste, thrombocytopenia, aplastic anemia, proteinuria, and changes to mental status.<sup>7</sup>

D-penicillamine has a worse side effect than tiopronin, including pancytopenia, nephrotic syndrome, and dermatitis. Dosing typically starts at 250 mg two or three times daily and is titrated to effect. One study reported adverse effects in 64.7% of patients taking tiopronin compared with 83.7% of D-penicillamine. Although it has been used to treat cystinuria, captopril is thought to have an insufficient therapeutic

effect on the recommended dosage.<sup>7</sup> Urinary supersaturation of cysteine or cystine capacity may be used to monitor thiol drug therapy and used to determine minimum effective dosage for individual patients.<sup>2</sup>

### Struvite stone

A retrospective review in 2013 from Iqbal et al. suggests that patients with struvite stones need aggressive endourologic and medical treatment with continued clinical and radiologic surveillance. They concluded that preventive medical therapy in stone-free patients after PCNL offers the best likelihood of avoiding stone recurrence or stone adverse events.<sup>24</sup>

The standard therapy for struvite stone is surgical stone removal. Culture-specific antibiotic therapy for preventing recurrent infections is essential for eradicating the causative organisms, including *Proteus* spp, *Staphylococcus aureus* and *S epidermidis*, and *Klebsiella*.<sup>2,7</sup>

Acetohydroxamic acid, a potent urease inhibitor, can decrease the risk of struvite stone formation. RCTs have been shown to reduce stone growth and prolong the time interval to stone growth. However, 22-62% of patients on chronic therapy experienced minor side effects, and 15% developed deep vein thrombosis. The side effects include tremor, palpitations, edema, proteinuria, headache, rash, alopecia, anemia, gastrointestinal discomfort, and thromboembolic phenomena. Due to these limitations, acetohydroxamic acid is reserved for patients at high risk of recurrent struvite stone formation and those unable to undergo surgical stone removal.<sup>7</sup>

### Drug stone

Urinary stones may be induced by stone-provoking drugs such as drugs with properties of producing crystal from their metabolites or interfere with urine metabolites. These drugs include sulfadiazine, triamterene, indinavir, ceftriaxone, acetazolamide, calcium supplementation, and vitamin C supplementation. Acetazolamide, although beneficial in increasing urinary pH, might also induce acidosis, hence lower kidney excretion and results in hypocitraturia. Certain antibiotics can



**Table 3. Recommendation and medication for various abnormalities in kidney stone diseases (modified from Morgan et al. and Han et al.).**

Abnormality	Dietary therapy	Pharmacological therapy
General guidelines	<p><b>Fluids</b> Target urine output &gt; 2.5L/day</p> <p><b>Sodium restriction</b> &lt; 2300 mg/day or; &lt; 100 mEq/day (1 teaspoon)</p> <p><b>Sufficient intake of citrus</b> (e.g., lemon, lime, oranges)</p> <p><b>Avoid</b> black tea, carbonated, or sweetened beverages</p> <p><b>Moderate protein intake</b> 0.8-1.4 g protein/kgBW/day or; &lt;150 g/day (about the size of a palm per portion)</p>	none
Hypercalciuria	<p><b>Sodium restriction</b> &lt; 2300 mg/day or; &lt; 100 mEq/day (1 teaspoon)</p> <p><b>Normal calcium intake</b> 1000-1200 mg/day</p> <p><b>Fish oil</b> 1200 mg of Omega-3/day</p>	<p><b>Thiazide</b> Hydrochlorothiazide 25 mg BID or 50 mg/day</p>
Hypocitraturia	<p>Sufficient intake of citrus (e.g., lemon, lime, oranges)</p> <p>Sufficient intake of fruits and vegetables</p> <p>Moderate protein intake</p>	<p><b>Potassium Citrate</b> 20 mEq/day divided in 2- 3 doses</p>
Hyperuricosuria	<p>Moderate protein intake</p> <p>Maintain normal body weight (BMI)</p>	<p><b>Allopurinol</b> 200-300 mg/day in single or divided doses</p>
Hypernatruria	<p><b>Sodium restriction</b> &lt; 1500mg/day</p>	None
Hyperoxalouria	<p><b>Limit</b> oxalate rich foods such as spinach, nuts and berries</p> <p><b>Normal calcium intake</b> 1000-1200 mg/day</p>	<p><b>Pyridoxine (Vitamin B6)</b> Initial dose of 50 mg/day, can be increase gradually up to 200 mg/day</p>
Low pH	<p><b>Moderate protein intake</b> 0.8-1 g protein/kgBW/day or; &lt;150 g/day (about the size of a palm per portion)</p> <p>Sufficient intake of fruits and vegetables</p>	<p><b>Potassium Citrate</b> Titrate to pH 6.0-7.0</p>
Uric acid stones	<p>Lifestyle modification</p> <p>Maintain normal body weight</p> <p>Diabetes control</p> <p>If hyperuricosuria, limit protein and purine intake</p>	<p><b>Potassium Citrate</b> Titrate to pH &gt; 6.0-7.0 (no more than pH 7.0 as it increases risk of phosphate stone formation) <b>+ allopurinol</b> If hyperuricosuria is not managed by a low protein and purine diet</p>
Cystine stones	<p><b>Hyperdiuresis</b> Drink &gt; 4L/day Target urine output &gt; 3L/day</p> <p><b>Cystine urine</b> &lt; 200mg cystine/L</p> <p>Sodium restriction</p> <p>Moderate protein intake</p>	<p><b>Potassium citrate</b> (add acetazolamide if target not achieved)</p>
Struvite stones	Surgery	<p><b>Stone is not resolved by surgery</b> Acetohydroxamic acid 250 mg TID (Possible side effects: phlebitis and hypercoagulability)</p>

also eliminate or reduce oxalate-degrading bacteria, resulting in hyperoxaluria. Most of the cases may be treated by discontinuation of the drug and hydration. Throughout the therapy, any side effects from pharmacological treatment should be monitored. Thiazide decreases potassium level in blood and induces glucose intolerance; Allopurinol can lead to elevated liver enzymes; and potassium citrate may cause hyperkalemia.<sup>7,23</sup>

Following dietary and pharmacologic therapy of various risk factors and stone types, a 24-hour urine evaluation should be done six months after. The assessment is aimed to see if there has been any improvement in the urinary environment (growth or recurrence). The evaluation should be repeated annually or earlier, depending on the response observed. The 24-hour urine evaluation can be stopped if a stone-free state is obvious. On the other hand, stone analysis should be repeated in patients who do not respond to therapy. Imaging can be done one year after treatment. In unstable cases, imaging can be done earlier, depending on the situation.<sup>7</sup>

## CONCLUSION

Kidney stone disease is a rising problem and significantly impacts individuals, healthcare, and socioeconomic burden. Hence, an effective approach to evaluating and managing kidney stone disease is necessary. The evaluation of kidney stone disease is done through detailed risk factors and medical condition assessment, imaging, metabolic analysis, and stone analysis. A thorough assessment is important to determine the treatment. The treatment of kidney stone disease consists of dietary and pharmacological therapy tailored to each specific condition or type of stones such as hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria, uric acid, cystine stone, or struvite stone. Despite the particular situation, all kidney stone formers should follow the general recommendation to have sufficient fluid intake, maintaining ideal body weight, citrate intake, sodium and animal protein restriction.

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