

# Metabolic studies and calculi analysis in urinary lithiasis, how to stop recurrence?

## Estudios metabólicos y análisis del cálculo en litiasis urinaria, ¿cómo detener la recurrencia?

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### Resumen

La litiasis urinaria es la consulta urológica más frecuente para la sala de emergencias debido al cólico renoureteral. Las complicaciones incluyen hematuria, anuria debido a la obstrucción bilateral o unilateral en el riñón solitario y la sepsis. La recurrencia ocurre en hasta el 50% de los pacientes después de 5 años desde el primer episodio, y aquellos paciente requieren estudios metabólicos y análisis del cálculo. El manejo farmacológico y las modificaciones dietéticas evitarán nuevos episodios. Nuestro objetivo es describir cada trastorno metabólico asociado con su respectivo tipo de cálculo y su manejo basado en la prevención de la recurrencia de la litiasis urinaria.

**Palabras clave:** Litiasis urinaria. Cólico renoureteral. Recurrencia. Prevención. Estudios metabólicos. Análisis del cálculo.

### Abstract

Urinary lithiasis is the most frequent urological consultation to the emergency room due to renoureteral colic. Complications include hematuria, anuria due to bilateral or unilateral obstruction in solitary kidney, and sepsis. Recurrence occurs in up to 50% of patients after 5 years from the first episode, and those will need metabolic studies and calculi analysis. Pharmacological management and dietary measures will prevent new episodes. We aim to describe each metabolic disorder associated with its respective type of calculi, and its management based on prevention of recurrence of urinary lithiasis.

**Keywords:** Urinary lithiasis. Renal colic. Recurrence. Prevention. Metabolic work-up. Calculi analysis.

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## Introduction

Lithiasis of the urinary tract is one of the most frequent urological pathologies, with a prevalence that reaches up to 10% in developed countries in the general population<sup>1,2</sup>. Comparing by sex, up to 16% of men and 8% of women will develop at least one episode of renoureteral colic in their lives<sup>3</sup>. Moreover, of those patients who have presented a first episode, 11 to 39% will present a recurrence in the following 2 to 15 years, a figure that increases to 56% in patients with personal risk factors for urolithiasis<sup>4</sup>.

The prevalence and recurrence of this pathology contributes to a high socioeconomic impact associated with treatment costs and work days lost<sup>5</sup>. In the United States, in the year 2000 alone, the disease burden had an estimated annual cost of 5 billion US dollars, a figure that doubled in 2012 and will be estimated at 15 billion dollars by 2030<sup>6-8</sup>.

Currently, the prevalence of urinary lithiasis has increased from 3.2% in 1980 to 5.2% in 1994 and to 8.8% in 2010<sup>1</sup>. This increase is closely related to dietary changes including a rise in consumption of animal protein, salt, carbonated beverages and high fructose foods<sup>3,4</sup>. Also, climate change and global warming might be contributing.

Several extrinsic and intrinsic factors are associated with urinary tract lithogenesis. Among the extrinsic factors are geographical location and weather, with a higher prevalence of lithiasic disease in arid, dry, and tropical regions<sup>9</sup>. There is also an increased risk in those working in environments with high temperatures (e.g. kitchens and machine rooms) or have sedentary jobs<sup>9</sup>. Diet is another influential factor, since a high consumption of sodium, animal protein, and foods high in fructose/sucrose, as well as low water intake, all increase the risk of calculi<sup>10</sup>.

Consistent with the factors outlined previously, populations located at lower latitudes are at greater risk of urolithiasis than those at higher latitudes<sup>8</sup>. This variation in prevalence according to geographical location has been associated with higher ambient temperature and sun exposure<sup>1</sup>, causing high levels of dehydration. Furthermore, within each region there are variations in disease pattern associated to seasonal changes, presenting a higher prevalence during the summer<sup>1,8</sup>. Thus, with the rising concern of climate change, urolithiasis prevalence is predicted to increase in susceptible populations from 40% in the year 2000 to 56 and 70% for the years 2050 and 2095, respectively<sup>8</sup>.

Moreover, there are modifiable risk factors associated with over half of documented urolithiasis cases: body mass index (BMI) greater than 25 Kg/m<sup>2</sup>, daily fluid intake less than 2 liters, inadequate consumption of fruits and vegetables, and consumption of more than four servings of sugary drinks per week<sup>11</sup>. Nonetheless, these factors may be mitigated by other factors shown to have a protective effect, such as the adequate dietary intake of calcium, potassium and natural diuretic drinks such as coffee and tea<sup>12</sup>, suggesting that lithiasic disease of the urinary tract has a high potential for prevention.

Regarding intrinsic factors, the maximum incidence of urolithiasis has been reported in individuals between 20 and 60 years of age, with an average age of diagnosis of 44.8 years in men and 40.9 in women<sup>1,9</sup>. There is also a documented male predominance worldwide, with an overall ratio of 1.5-2.5 men for each affected woman<sup>8,9</sup>. However, this difference has decreased in recent years from 3.1:1 to 1.3:1 associated with lifestyle homogenization between sexes<sup>1</sup>. Moreover, an increase in metabolic syndrome, obesity and diabetes has also been shown to play an important contributing factor in both sexes<sup>1</sup>.

High-risk patients for this disease are defined as those having an increased chance of recurrence or growth of existing calculi. Therefore, these patients should be considered candidates for preventive pharmacologic therapy (Table 1)<sup>13</sup>. The risk of recurrence depends on both the type of stone and disease severity.

This review of the literature seeks to provide urologists with a comprehensive understanding of the metabolic implications behind urinary stone formation, as well as provide recommendations regarding its study and management beyond surgical interventions. Of note, the factors mentioned above and further detailed in the following pages, generally do not present themselves in these patients with a complete and elaborate disorder, but instead present with a combination of elements that coincide, thus creating a high urolithic risk.

## Calculi formation mechanism

The urolithiasis process begins with the nucleation of crystals and their peripheral aggregation with matrix-forming proteins<sup>9</sup>. Nucleation occurs as solutes reach the point of urinary supersaturation for homogeneous nucleation, or around other structures such as crystals, cell membranes, protein aggregates and foreign bodies for heterogeneous nucleation<sup>6,7</sup>. Stone growth occurs according to the etiology of the stone; the amount of protein is

**Table 1.** Risk factors for recurrent urolithiasis in adults

<b>General</b>	Early episode of urinary lithiasis Family history of nephrolithiasis Calcium phosphate calculi Infectious calculi
<b>Associated comorbidities</b>	Hyperparathyroidism Metabolic syndrome Nephrocalcinosis Gastrointestinal disease: <ul style="list-style-type: none"> <li>– Crohn's disease</li> <li>– Malabsorption</li> </ul> Bariatric surgery Sarcoidosis Spinal cord injury Neurogenic bladder
<b>Genetic</b>	Cystinuria: Type A, B and AB Primary hyperoxaluria Renal tubular acidosis type I 2,8-dihydroxyadenuria Xanthinuria Lesch-Nyhan Syndrome Cystic fibrosis
<b>Anatomical</b>	Renal medullary spongiosis Ureteropelvic obstruction Diverticulum or calyceal cyst Ureteral stenosis Vesicoureteral reflux Ureterocele Horseshoe kidney

inversely proportional to the probability of an underlying metabolic disorder, while the amount of matrix is in turn associated with an infectious disease<sup>6,14</sup>.

The initial histopathologic and macroscopic manifestation of crystal deposition is visualized as Randall's plaques<sup>9,15,16</sup>. These are micro- and macroscopic deposits of calcium that originate in the basement membrane of the loop of Henle, which extend into the interstitium below the urothelium of the renal papilla<sup>17,18</sup>.

## Types of calculi and composition

### I. Calcium stones

Calcium calculi account for 80% of stones in adults (19) we performed an ambulatory metabolic protocol with diagnostic purposes. From the total sample 79% of stones were made of calcium salts (oxalate and phosphate). Its formation begins in the medullary interstitium, where the calcium phosphate molecules are deposited before passing to the papilla and forming the Randall's plaques. Subsequently, the superposition of phosphate and calcium oxalate crystals form the stones themselves<sup>17,20</sup>.

The most frequent composition of urinary stones is calcium oxalate (CaOx), present in either monohydrate (COM) or dihydrate (COD) forms, and characterized by calcium and oxalate excess in depletion of citrate and magnesium<sup>14,16</sup>. The COM calculi are characterized by a smooth surface and occur in hyperoxaluric states<sup>2</sup> metabolic evaluation of stone formers and preventive medical therapy is underutilized. The causes for this are multifactorial. Recent technological advances, including extracorporeal shock-wave lithotripsy (ESWL), while the COD calculi are morphologically characterized by a spiculate surface and tend to occur in hypercalciuric states<sup>2,4</sup> metabolic evaluation of stone formers and preventive medical therapy is underutilized. The causes for this are multifactorial. Recent technological advances, including extracorporeal shock-wave lithotripsy (ESWL). While COD stones are more frequent in young people, the concentration of COM increases progressively with age, reaching a peak between 40 and 70 years<sup>8</sup>. The main reported risk factors for calcium oxalate stones are hyperoxaluria, hypercalciuria and hypocitraturia.

Of note, calcium oxalate and calcium phosphate stones differ in their saturation points, precipitating at acidotic and alkalotic pH, respectively. Increases of urine pH to values higher than 6.5-7.5 lead to greater conversion of monobasic to dibasic phosphate, thus increasing risk of calcium phosphate stones, particularly in the presence of hypocitraturia (described below). Moreover, patients with mixed calcium oxalate/calcium phosphate stones have lower urine citrate and higher pH when compared with calcium oxalate stone formers alone<sup>21</sup>.

### II. Hyperoxaluria

Oxalate is a salt that is obtained both exogenously (directly from food intake) as well as endogenously, after hepatic metabolism of glyoxylate, glycine, hydroxyproline, and ascorbic acid<sup>22</sup>. In a healthy person, only 2 to 10% of the dietary oxalate enters the bloodstream, and the rest is used as energy source by the intestinal microbiota<sup>23,24</sup>. The dianionic oxalate is chelated by the metal cation calcium, this being the main regulator of its intestinal absorption<sup>22,25</sup>. Conditions that increase the absorption of oxalate or its production are thus predisposing factors to develop urolithiasis: dietary habits, enteric diseases and genetic conditions<sup>26</sup>.

Oxalate excretion occurs in the kidneys: the breakdown of ascorbic acid and glyoxylate accounts for 80-90% of losses, and the exogenous oxalate for the

remaining 10-20%<sup>27</sup>. Urinary oxalate is directly proportional to its serum concentration (hyperoxaluria > 40 mg/day)<sup>28</sup>.

The main oxalate sources are plants and their products, especially seeds and leaves<sup>29</sup>. Although oxalate is ubiquitous in diet, its bioavailability varies among different food groups. The highest immediate rise in urinary oxalate happens after consuming spinach, while a delayed rise occurs after consuming products such as chocolate, tea, and cranberry and orange juice<sup>28</sup>.

Ethylene glycol is used primarily as a component in antifreeze and is associated with nephrolithiasis, nephrocalcinosis, renal failure and death<sup>30</sup>. Its provoked or accidental ingestion results in the production of oxalic acid that binds to calcium leading to urine oxalate crystals<sup>31</sup>.

Avoiding foods rich in oxalate, particularly spinach and rhubarb (limiting overall daily consumption to 100 mg/day), and increasing dietary calcium intake (1000-1200 mg/day), may help in the prevention of urinary tract stones associated with hyperoxaluria<sup>23</sup>.

Enteric hyperoxaluria occurs due to extensive intestinal resections with intact colon and inflammatory bowel diseases, such as Crohn's disease<sup>32</sup>. These conditions lead to bowel acidification and an increase in oxalate's permeability through the endothelium lining<sup>30,33,34</sup>. Furthermore, these diseases are associated with bacterial decolonization of *Oxalobacter formigenes*, a Gram negative anaerobic bacillus that resides as part of the body's normal intestinal flora and is responsible for metabolizing excess oxalate, leading to a hyperoxaluric state<sup>32,35</sup>. Also, absence of *Oxalobacter formigenes* leads to greater levels of urinary calcium<sup>36</sup>.

Other oxalate-degrading bacteria include *Enterococcus faecalis*, *Providencia rettgeri*, *Eubacterium lentum*, *Escherichia coli*, *Lactobacillus* spp. and *Bifidobacterium* spp<sup>37</sup>. The extensive use of antibiotics also leads to bacterial decolonization of the gut and increases the risk of urinary lithiasis<sup>37</sup>.

Furthermore, primary hyperoxaluria (PHO) is a genetic disease characterized by urolithiasis and severe renal damage<sup>30</sup>. The most common variant is PHO type I, which occurs due to enzymatic damage of hepatic peroxisomes responsible for oxalate degradation, leading to excessive oxalate renal elimination and injury through nephrocalcinosis and recurrent nephrolithiasis. While PHO type II and III are less severe forms of the disease, their association to stone formation has likewise been reported<sup>30</sup>. Treatment of the cause of hyperoxaluria will prevent secondary urinary lithiasis.

### III. Hypercalciuria

Hypercalciuria (> 300 mg/day) is defined as an increase in urinary calcium excretion, independent on serum calcium levels<sup>38</sup>. While, 99% of the body's calcium stores is found in the skeleton, only 1% remains in the intra and extracellular spaces<sup>39</sup>. This balance relies on the normal interplay between intestinal absorption, renal reabsorption, and bone resorption<sup>39</sup>.

Serum calcium is found in ionized form (48%), bound to proteins (46%) and in fractionated complexes (7%)<sup>39</sup>. These complexes bind to larger molecules, such as citrate and phosphate, and are thus responsible for stone formation<sup>39</sup>. Approximately 60 to 70% of the filtered calcium is reabsorbed in the proximal convoluted tubule, 20% in the loop of Henle and 10% in the distal convoluted tubule<sup>39</sup>. This last portion is the main regulatory site due to the expression of hormone-sensitive receptors, and as such, disruptions in its function is associated with nephrolithiasis<sup>39</sup>.

While calcitriol and parathyroid hormone are hypercalcemic hormones that promote bone resorption, calcitonin is hypocalcemic, and therefore stimulates bone accumulation<sup>40</sup>. Moreover, vitamin D favors calcium fixation at physiological levels and bone resorption at higher doses<sup>40,41</sup>. Primary hyperparathyroidism, prolonged immobilization, multiple myeloma, solid cancers and hyperthyroidism causes unbalanced bone remodeling, a pathological state in which resorption generates a hypercalciuric state<sup>39,41,42</sup>. Moreover, patients with vitamin D hypovitaminosis (be it from inadequate sun exposure, limited oral intake, or impaired intestinal absorption) may develop a secondary hyperparathyroid state, compounding the risk of hypercalciuria and kidney stone formation risk<sup>41,43</sup>. Management of hypercalciuria includes loop diuretics and thiazides to increase renal excretion and bisphosphonates to inhibit bone resorption<sup>39-41,44</sup>.

In patients with underlying intestinal disease and malabsorption, hypercalciuria occurs due to metabolic acidosis and intraluminal calcium sequestration<sup>42</sup>. The sequestration in turn causes hyperoxaluria<sup>30,40</sup>, increasing nephrolithiasis incidence.

Additionally, hypernatremia (> 144 mg/dL) increases calciuria due to the decrease in calcium reabsorption at the level of the proximal convoluted tubule and the loop of Henle<sup>44</sup>. As such, low-sodium diets reduce the risk of urolithiasis in patients with recurrent CaOx stones<sup>44</sup>.

#### I.iii. Hypocitraturia

Urinary citrate binds calcium and/or phosphorus in the renal tubular lumen, decreasing the concentration of free

calcium<sup>45,46</sup>. Thus, hypocitraturia (< 170 mg/day) favors the precipitation of CaOx crystals despite normal levels of urinary calcium<sup>34</sup>. The most frequent causes of hypocitraturia are intestinal malabsorption, renal failure, distal renal tubular acidosis, hypocalcemia, use of thiazides and carbonic anhydrase inhibitors (acetazolamide and topiramate), and urinary tract infections<sup>45,47</sup>.

In distal renal tubular acidosis, impaired urinary acidification leads to increased citrate reabsorption (for the formation of bicarbonate). Furthermore, as a consequence of metabolic acidosis, calcium bone resorption increases, generating a hypercalciuric and hypocitraturic environment that predisposes to CaOx calculi formation<sup>48</sup>. Moreover, a low urinary pH causes the precipitation of calcium phosphate salts, thus further increasing nephrolithiasis<sup>48</sup>.

As metabolic acidotic states in turn lead to decreased citrate excretion combined with an increased calcium and uric acid excretion, a favourable (physiologic) milieu for stone formation is produced<sup>49</sup>. This leads to the consideration of other, often overlooked, conditions associated with mild acidotic states, including (but not limited to) being overweight/obese, diabetic, and metabolic syndrome; all of which constitute intrinsic risk for nephrolithiasis<sup>49–51</sup>.

#### **I.iv. Hypomagnesuria**

In urine, magnesium ions inhibit stone formation by destabilizing CaOx molecules<sup>52</sup>. This inhibitory role (along with the action of citrate), is effective even in states of low urinary pH<sup>52</sup>. In other words, low urinary magnesium increases free oxalate in the urine, increasing stone-formation propensity<sup>53</sup>.

Under normal conditions, 96% of the filtered magnesium is reabsorbed in the tubular system<sup>39</sup>. As such, hypomagnesuria (excretion < 50 mg/day) results directly from hypomagnesemic states. The main causes of hypomagnesemia include gastrointestinal losses (chronic diarrhea and chronic use of proton pump inhibitors) and renal losses (use of loop diuretics, uncontrolled diabetes, hypercalcemia and alcohol consumption)<sup>39,54–56</sup>.

#### **I.v. Hyperphosphatemia**

Hyperphosphatemia, through the formation of Randall's plaques, is a risk factor for the formation of calcium stones<sup>39</sup>. The body's equilibrium of phosphorus is determined by the balance between the excretion of phosphate and the dietary intake<sup>39</sup>. Once in plasma, the phosphate is either transported into the intracellular

space or stored in the skeletal system<sup>39</sup>. In this way, the regulation of this ion is closely related to calcium concentrations: parathyroid hormone decreases renal reabsorption of phosphate in the proximal convoluted tubule and causes phosphaturia<sup>39</sup>. The management of hyperparathyroidism includes phosphate binders, vitamin D analogues, and calcimimetics<sup>39</sup>.

## **II. Uric acid stones**

Hyperuricemia is classified as primary and secondary, and in turn, in hyperproduction and uric acid hypoexcretion<sup>24,57</sup>. In the lithiasic patient, hyperuricosuria may occur due to elevated or normal levels of uric acid in the blood. When associated with hyperuricemia, it is suggestive of gout and metabolic alterations, whereas associated with normouricemia is suggestive of purine-rich diets<sup>24,57</sup>. The hyperuricosuria with normouricemia resolves once the consumption of red meat, alcohol and seafood has decreased.

In addition, hyperuricosuria (> 990 mg / day) causes greater elimination of uric acid decreasing urinary pH and triggering the formations of stones nuclei<sup>24,57</sup>. A pH lower than 5.7 increases the precipitation of CaOx crystals and the aggregation of these on crystals of uric acid, forming stones<sup>24,57,58</sup>. In addition, it has been described that insulin resistance, associated or not with metabolic syndrome, directly affects the ammoniogenesis and the ammonium that previously worked as a urinary buffer, will now acidify it<sup>59</sup> in the normouricemic, normouricosuric patient. Of particular importance in this group, are those patients consuming excess animal protein and specialized diets (e.g. Atkins, keto and other low-carbohydrate/high-protein diets), as animal protein has been shown to boost urinary excretion of oxalate, which then combines with calcium and other compounds to form kidney stones<sup>60</sup>.

The treatment is based on urinary alkalinization with potassium citrate and the decrease of uric acid levels from the restriction of purine-rich animal proteins<sup>58</sup> due to the high capacity of urinary acidification they possess<sup>59</sup> calcium phosphate (US-CaP, and allopurinol<sup>61</sup>.

## **III. Struvite stones**

Struvite stones are composed of phosphate crystals hydrated by magnesium ammonium and calcium apatite<sup>57</sup>. These stones are characterized by rapid growth over a period of weeks to months, forming staghorn calculi that occupy the space of the collecting system and thus often obstructing the urinary tract<sup>57,61,62</sup>.

Urine usually maintains low concentrations of ammonium phosphate, however, an alkalization of urinary pH leads to lower phosphate solubility<sup>9,57,62</sup> and, thereof, a greater urinary availability. This happens because as urease-producing bacteria, such as *Proteus* spp., *Klebsiella* spp., and *Pseudomonas* spp. colonize the urinary tract<sup>57</sup>, urea is metabolized into ammonia and combines with water to form ammonium and thus increases urine pH<sup>63</sup>. The treatment includes surgery and acetohydroxamic acid (reversible inhibitor of urea), which prevents the crystallization of struvite and apatite carbonate<sup>2</sup>.

#### IV. Cystine stones

Cystine is an amino acid that, due to its insolubility at normal urinary pH, precipitates to form crystals in patients with cystinuria<sup>2,64</sup>. Cystinuria is a genetic disease of autosomal recessive inheritance, characterized by the inadequate reabsorption of cystine and other dibasic amino acids in the proximal tubule of the nephron and in the gastrointestinal epithelium, causing recurrent urolithiasis<sup>64</sup>.

This condition has an overall incidence of 1 per 7000 live births and corresponds to 1% of urinary tract stones in adults<sup>65</sup>. The majority of cases of cystinuria are caused by mutations in two genes that code for subunits of the cystine transporter (SLC3A1 and SLC7A9)<sup>64</sup>. The treatment consists mainly in preventing the formation of stones through adequate hydration, dietary restriction of foods rich in methionine (e.g. meat, pork and dairy), decreased salt intake, urinary alkalization and drugs with cystine reuptake (e.g. thiols)<sup>2,64</sup>.

#### Metabolic studies and calculi analysis

After complete resolution of renal colic, a 4- to 6-week waiting period (during which the patient is expected to resume habitual diet) is recommended prior to proceeding with the metabolic study<sup>66</sup>. Metabolic study should include the following aspects: medical history directed to the underlying pathology, nutritional evaluation, and urine and blood studies.

The clinical history includes the following:

- Relevant comorbidities: diabetes mellitus, hyperuricemia, sarcoidosis, hyperparathyroidism, osteoporosis, inflammatory disease or intestinal malabsorption, and previous history of urinary lithiasis (and number of episodes).
- Pharmacological background: consumption of topiramate, acetazolamide, thiazide diuretics, vitamin C or vitamin D supplements, antacids, and proton pump inhibitors.

- Family history of calculi.
- Surgical history that includes intestinal resections and bariatric surgery.

Numerous studies link the growing urolithiasis incidence to BMI. Dietary modifications are essential and a comprehensive nutritional history must be undertaken in order to identify dietary elements which contribute to stone pathogenesis<sup>10</sup>. As mentioned previously, increased body weight is associated with mild metabolic acidosis, increasing stone formation risk and thus necessitating additional nutritional recommendations to promote weight loss in overweight to obese patients<sup>49</sup>.

Nutritional appraisal quantifies daily consumption of lithogenic food components, such as sodium, sugar, animal protein (e.g. purines and uric acid) and oxalate. Likewise, protective factors must be quantified including calcium, water, fruits and vegetables<sup>67</sup>. Once dietary risk factors are identified, targeted nutritional recommendations may be endorsed.

General dietary recommendations should be considered in every patient, including:

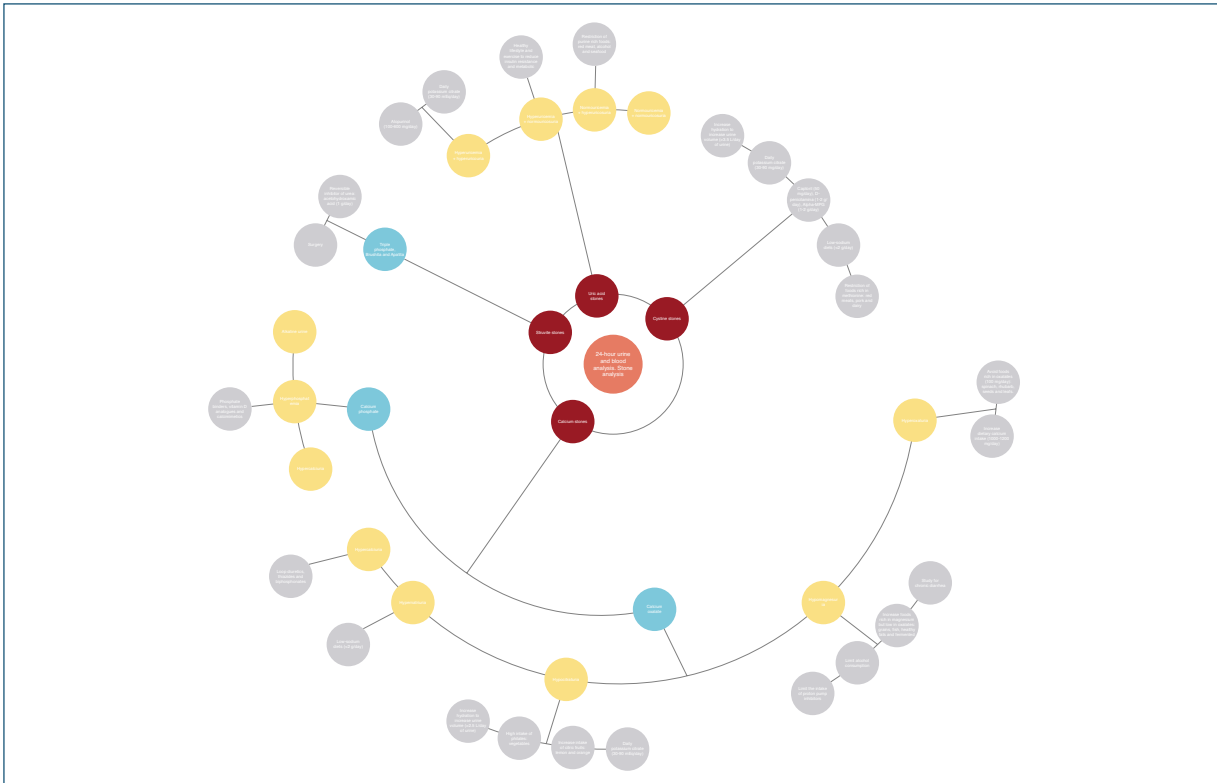
- Increase liquid intake (at least 3 Liters/day to void 2-2.5 Liters/day)
- Dietary calcium: 1000-1200 milligrams/day
- Fiber-rich diet (increase fruits, vegetables, and whole-grain ingestion)
- Include citrate-rich food sources into diet (e.g. citric fruits)
- Decrease consumption of oxalate-rich foods (e.g. spinach)
- Limit salt intake to 5 grams/day or its equivalent in sodium (2 g/day), including added nitrates to most processed food
- Limit daily animal protein consumption to 1 gram per patient's ideal weight (in kilograms).

A thorough metabolic study should include two 24-hour urine collections, blood analysis and physical-chemical analysis of the stone. X-ray diffraction and infrared spectroscopy by Fourier transformation are the recommended tests for the physical study of the calculi<sup>59,68</sup>. These methods permit correct identification of the type of calcium stone present and other associated stone components, such as cystine, xanthine, uric acid, urates, struvite, proteins, lipids, and/or drugs<sup>2,6</sup>.

#### Management in each scenario

#### Conclusions

Urinary lithiasis can be a recurrent disease in patients with risk factors causing high costs to the healthcare



**Figure 1.** Subfoveal, temporal and nasal to foveal choroidal thickness measurement.

system. Is important to look for the etiology of the calculi to focus treatment on the prevention of new episodes. All physicians and urologists should counsel patients with the general recommendations and according to their metabolic studies and calculus analysis.

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## Conflicts of interest

The authors declare that there is no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article.

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