

Update – 2022 Canadian Urological Association guideline: Evaluation and medical management of the kidney stone patient

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Introduction

Despite advances in the surgical management of urinary stone disease that have significantly reduced patient morbidity, new stone formation and recurrence remain significant health issues. Data from the United States National Health and Nutrition Examination Survey (NHANES) published in 2020 reported a kidney stone prevalence of 12% in men and 10% among women.¹ Recent data from the US also has noted a cumulative increase in stone incidence from 0.6% to 0.9% between 2005 and 2015.² An increase in stone formation among women has also been observed such that the male to female ratio appears to be decreasing.^{3,4} Evidence is also emerging there may be an increase in the incidence of certain stone compositions such as uric acid, a stone type linked to both dietary and metabolic risk factors.⁵ Furthermore, the association with obesity, metabolic syndrome, diabetes mellitus and stone formation suggests nephrolithiasis should be regarded as a systemic disease.

Recurrence rates after an initial symptomatic stone event are reported to be 30-50% within 10 years.^{6,7} Therefore, patients are generally motivated to explore prevention strategies.¹ 96.8% of recurrent stone formers or those with more than one concurrent stone will have a urinary metabolic abnormality.⁸ Epidemiological data from the US show that only 7% of patients

with a high risk of recurrent stone disease undergo metabolic evaluation by any physician.⁹ 81% of patients interviewed would prefer to take prophylactic medication than undergo another stone episode, and 92% of respondents preferred medication to undergoing surgery.¹⁰ Although patients indicate they would be interested in using medication to prevent future stones, compliance studies suggest otherwise. Close to 50% of patients prescribed pharmacological prevention were non-compliant, especially those on potassium citrate.¹¹ This data stresses the importance of a comprehensive metabolic assessment with implementation of individualized prevention strategies. With directed therapy and proper patient education, patient compliance and therapeutic success may be optimized.

The economic burden of recurrent stone disease is also significant. Estimates of direct costs for patient care and the indirect costs related to lost work time exceed \$5 billion USD.^{12,13} Given the rising rates of obesity and diabetes and their association with stone formation, the cost of managing stone disease is expected to increase to 1.24 billion dollars yearly in the US by 2030.¹⁴

This guideline is an update of the 2016 document and aims to identify patients at heightened risk of stone recurrence, to outline the required investigations to assess these patients, and to provide contemporary advice on dietary and medical interventions of proven benefit in the Canadian context. This current guideline addresses the evaluation and medical prophylaxis of upper urinary tract stones and not bladder stones.

Literature review

The updated content included in this document is based on a review of the English language literature. A PubMed search was conducted encompassing the period from January 1, 2015 to July 1, 2021 to include the following terms: “nephrolithiasis”, “urolithiasis”, “kidney stone”, “renal stone”, or “urinary stone”. In total, 11,640 article titles were reviewed and 293 were identified as potentially relevant for inclusion in the literature assessment for this guideline update. Management recommendations were modified if needed based on the most current literature since the last guideline was published in 2016. Studies were evaluated and recommendations made based on Oxford levels of evidence and grades of recommendation as per the CUA Guidelines Committee’s directive.¹⁵

Indications for metabolic evaluation

Recommendation: Basic metabolic screening should include a urinalysis, with or without a urine culture, serum electrolytes (Na, K, HCO₃), calcium, creatinine, and a stone analysis when available (LE 4, Grade C recommendation).

A first time stone former, without any identifiable risk factors for recurrent stone formation, should undergo a limited metabolic screen to rule out potential systemic disorders such as hyperparathyroidism and renal dysfunction.

Recommendation: An in-depth metabolic evaluation is recommended in patients with risk factors for recurrent stone disease (LE 3, Grade C recommendation).

An in-depth metabolic investigation may be considered for *any* patient who is motivated and interested in completing metabolic testing. There are however, patient populations with clearly known risk factors where an in-depth metabolic investigation is recommended:¹⁶⁻²³

- Children (<18 years of age)
- Bilateral or multiple stones
- Recurrent stones (≥ 2 kidney stone episodes)
- Non-calcium stones (e.g. uric acid, cystine)
- Pure calcium phosphate stones
- Any complicated stone episode that resulted in a severe (if even temporary) acute kidney injury, sepsis, hospitalization, or complicated hospital admission
- Any stone requiring percutaneous nephrolithotomy treatment
- Stones in the setting of a solitary (anatomical or functional) kidney
- Patients with renal insufficiency
- History of systemic disease that increases the risk of kidney stones (e.g. gout, osteoporosis, inflammatory bowel disorders, hyperparathyroidism, renal tubular acidosis, sarcoidosis, diabetes mellitus/metabolic syndrome)
- Occupation where public safety is at risk (e.g. pilots, air traffic controller, police officer, military personnel, firemen)
- Family history of kidney stones

Struvite stones typically form in the setting of recurrent urinary infection, anatomical anomalies, and foreign bodies but occasionally are associated with metabolic abnormalities. Metabolic evaluation may be considered in these patients although the prevention focus should be on addressing the risks mentioned with periodic imaging surveillance if risk factors are not modifiable. The urease inhibitor acetohydroxamic acid (AHA) has been used with limited success and with significant side effects.²⁴⁻²⁶ This agent is not currently available in Canada.

In-depth evaluation

For those patients where an in-depth evaluation is indicated, the work-up should include serum and 24-hour urine tests as well as a thorough dietary history. These tests should include:

Serum:

- Creatinine, sodium, potassium, calcium, albumin, uric acid, and bicarbonate.

- Parathyroid hormone (PTH) level if high or high-normal serum calcium, or if idiopathic hypercalciuria with normocalcemia.
- Vitamin D level if PTH is elevated to rule out secondary hyperparathyroidism

24-hour urine collection:

- Volume, creatinine, calcium, sodium, potassium, oxalate, citrate, uric acid, magnesium
- Cystine if known or suspected cystine stone

Spot urine:

- Urinalysis with urine pH

Previously, it was suggested that PTH testing was only required if serum calcium was elevated.²⁷ However, more recent data suggests that normocalcemic hyperparathyroidism is an important clinical variant that is associated with a high prevalence of nephrolithiasis.²⁸ Screening for primary hyperparathyroidism in a tertiary stone clinic demonstrated a prevalence of 7.1% with 71.7% of those cases having high-normal serum calcium.²⁹ Therefore, we recommend serum PTH if the patient has a high or high-normal serum calcium or in patients with idiopathic hypercalciuria and normocalcemia.

Vitamin D deficiency is common in North American populations and new and evolving data has emerged regarding the impact of vitamin D on stone disease (see Vitamin D section below). Based on this evidence, we recommend that serum vitamin D be measured (if available in your health region) when a patient has an elevated PTH in order to rule out secondary hyperparathyroidism.

Number of 24-hour urine collections

Recommendation: Two 24-hour urine collections are preferred when possible but should be balanced by the practicality and importance of obtaining at least one collection (LE 3, Grade C recommendation).

There is some controversy regarding the number of 24-hour urine collections that are necessary in order to investigate patients.^{30,31} Data suggests that 47.6% of patients had their clinical management changed by an abnormality identified only when two samples were collected.^{32,33} Close to 25% of patients will have a 50% variation in at least one urinary parameter, and 25% of patients will have a 20% difference in three urine parameters.³⁴ As such it is currently recommended that two 24-hour urine collections be obtained. The benefit of two collections should be balanced however, by the practicality and importance of obtaining at least one collection.

Importance of stone analysis

Recommendation: Stones collected by patients or removed at the time of surgical intervention should be submitted for analysis (LE 3, Grade C recommendation).

Identification of stone composition will aid in determining prevention and directing surgical options for future stones. Furthermore, identification of struvite, ammonium urate, uric acid, calcium phosphate, or cystine stones would alter the indication for in-depth metabolic evaluation. If a patient continues to form new stones, a repeat stone analysis should be performed as this may change management. Stone composition changed in 21.2% of patients over time.³⁵

Reports have demonstrated a strong correlation between pure stone composition and metabolic abnormalities.³⁶ Specifically, hypercalciuria was associated with brushite and calcium oxalate dihydrate stones; whereas, hyperoxaluria was found most commonly in calcium oxalate monohydrate stone formers.³⁷ In addition, apatite stones were correlated with both hypercalciuria and hypocitraturia, and uric acid stones were found in patients with low urinary pH.³⁶ Stone composition may be a useful tool to help guide empiric medical therapy for patients who are unable or unwilling to perform an in-depth medical evaluation.³⁷

General dietary measures

Recommendation: When possible specific dietary assessments and recommendations should be made with the involvement of a registered dietician (LE 3, Grade C recommendation).

General dietary and fluid intake advice has been shown to be effective in reducing stone recurrence rates and is warranted for even the first-time stone former without identifiable risk factors. The “stone clinic effect” has shown that counseling on appropriate fluid intake and dietary excesses can significantly reduce stone recurrence.³⁸

The involvement of a registered dietician, if available, in the counseling of patients with recurrent renal stones should be incorporated into the management of these patients. Assessment with a registered dietician is strongly suggested where there is a history of compromised nutritional status, complex medical situations, or patients who need assistance implementing dietary recommendations.^{39,40} Evidence suggests that patients who received specific dietary recommendations based on a comprehensive evaluation had fewer stone recurrences over 3 years than those who only received general dietary advice.⁴¹

Fluid intake

Recommendation: All stone formers should be counseled to achieve a daily urine output of 2.5 liters (LE 2, Grade B Recommendation).

Adequate fluid intake to produce a urine output of 2.5L daily has been shown to reduce the risk of stone formation by 60-80% in several meta-analyses.⁴²⁻⁴⁶ Conversely, studies have shown that poor fluid intake increases lithogenic risk particularly with 1.4L of urine or less.^{45,47-49} Adequate fluid intake in the form of water is suggested as the first line treatment to prevent stones with each 200mL increase in fluid intake reducing the risk of stones by 13%.⁵⁰

Other fluids, including orange juice, caffeinated beverages (or caffeine alone), coffee, wine and beer may have a protective effect against stone formation which must be weighed against other potential health effects.⁵¹⁻⁵⁴ The consumption of low-calorie orange juice has been shown to have a protective effect by increasing urinary citrate levels.⁵⁵ Additionally, sugar sweetened non-colas and colas may increase the risk of stone formation.⁵² Milk does not increase the risk of stones unless consumed in excess. Lastly no conclusive evidence exists regarding the specific properties of water (e.g. water hardness) and lithogenic risk.⁴⁸

Recent studies assessing smart technology including smart water bottles and associated digital applications have shown the accuracy of these technologies to measure fluid intake, however the impact on urine output may be similar to counseling.⁵⁶⁻⁵⁸ A systematic review showed that most interventions can improve fluid intake by approximately 500mL, with the most effective strategies being instruction, and self-monitoring using urine dipstick or 24-hour urine volume.⁵⁹

Counseling regarding fluid intake should clearly state the risk reduction associated with increased fluid intake, explore barriers to fluid consumption such as occupational barriers, taste factors related to water, and urinary voiding difficulties such as overactive bladder and bladder outlet obstruction.^{60,61} Practical ways to increase fluid intake include drinking at set times during the day and hourly during working hours, maintaining a water bottle in all places where significant time is spent, and eating foods higher in water content such as fruits and vegetables.⁶¹ Caution should be exercised when counselling patients with congestive heart failure or chronic renal insufficiency.

Calcium

Recommendation: The goal for dietary calcium intake should be 1000-1200mg/day and if calcium supplementation is required it should be taken at mealtimes (LE 3, Grade B Recommendation).

A public misconception persists that stone formers should restrict calcium in their diet. On the contrary, multiple large, prospective cohort studies have demonstrated higher dietary intakes of calcium are correlated with a lower risk of stone formation in both men and women.^{46,62-64} Previous studies examining the effect of calcium supplementation on stone risk have shown conflicting results; with one study demonstrating a slightly increased risk in stone formation⁶³, and another study showing no change in risk.⁴⁷ The difference in these findings may

be attributed to the timing of the calcium supplement administration, since calcium not consumed at mealtimes in one study may have decreased its ability to chelate oxalate.⁶⁴

The recommended daily intake of calcium is 1000–1200mg separated into 2 doses and ideally with meals. Calcium would preferably be obtained through diet as some studies suggest supplementation may also increase cardiovascular risk.⁶⁵ Where supplementation is required it should be taken with meals as this results in the greatest oxalate sequestration and is not associated with an increased risk of hypercalciuria.⁶⁵

Vitamin D and bone health

Recommendations:

1. **In calcium stone formers with vitamin D deficiency, repletion is appropriate however, monitoring of vitamin D levels and hypercalciuria on repeat testing is necessary** (*LE 2-3, Grade C Recommendation*).
2. **Consider bone mineral density testing in calcium stone formers with evidence of hypercalciuria and/or distal renal tubular acidosis (dRTA)** (*LE 2-3, Grade C Recommendation*).
3. **Treatment of calcium stone formers with either a thiazide diuretic, alkali citrate or ideally both has been shown to reduce stone recurrence risk and increase bone mineral density and should be considered in patients with documented low bone mineral density** (*LE 2-3, Grade C Recommendation*).

Vitamin D deficiency is common among stone formers in northern latitudes, with 80.2% of patients in a Canadian metabolic stone clinic having vitamin D insufficiency.⁶⁶⁻⁶⁸ Patients with low vitamin D levels have been shown to have an increased number of metabolic abnormalities; specifically, secondary hyperparathyroidism which was found in 26% of a Canadian cohort.⁶⁷ Studies examining serum vitamin D levels and urinary calcium excretion are conflicting. Some studies noted an association between higher vitamin D levels and hypercalciuria;^{66,69} whereas others have failed to find a relationship between vitamin D and hypercalciuria,⁷⁰ or stone re-occurrence.⁷¹

The impact of vitamin D supplementation on hypercalciuria and stone risk is unclear. The largest study to date examining the effect of vitamin D in the general population evaluated over 200,000 men and women found no association between vitamin D intake and urolithiasis.⁷² Similarly, a meta-analysis of 10 randomized controlled trials of vitamin D supplementation including 2,010 participants showed no increased incidence of kidney stones.⁷³ Several other large studies have shown an increased risk of stone formation with vitamin D supplementation; however, these studies were confounded by the co-administration of calcium supplementation.⁷⁴⁻

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Previous studies in stone formers with vitamin D deficiency have found mixed effects of vitamin D repletion on urinary calcium excretion. Two prospective cohort studies of vitamin D supplementation in patients with vitamin D deficiency did not show an increase in mean calcium excretion.^{66,77} A recent randomized trial showed no effect of vitamin D administration on urinary calcium excretion or the supersaturation of calcium oxalate or calcium phosphate crystals.⁷⁸

Although we do not recommend routinely testing vitamin D levels (see metabolic evaluation above), chronic depletion of vitamin D may lead to secondary hyperparathyroidism thereby increasing the risk of bone loss and recurrent stones. Consequently, vitamin D levels should be measured in the settings of an elevated PTH level in order to rule out secondary hyperparathyroidism. Repletion of vitamin D in stone formers is appropriate with follow-up monitoring for vitamin D response and the development of hypercalciuria.

The association between low bone mineral density (BMD) and calcium nephrolithiasis has been well investigated. Several studies have demonstrated that calcium stone disease correlates with low BMD, with a higher risk corresponding with increasing levels of hypercalciuria.⁷⁹⁻⁸² Furthermore, the prevalence of osteopenia or osteoporosis is higher in stone formers with concomitant vitamin D deficiency.⁸⁰ Chronic metabolic acidosis in patients with complete distal renal tubular acidosis (dRTA) increases bone resorption and places these patients at very high risk of low BMD; one series demonstrated rates of osteopenia and osteoporosis as high as 43% and 21% respectively.⁸³ Multiple studies have shown an increased risk of fractures in patients with urolithiasis (HR 1.13-2.32).^{84,85}

Dietary recommendations for stone reduction including a low sodium and normal calcium diet have also been shown to improve BMD.⁸⁶ Thiazide diuretics also reduce urinary calcium levels, decrease stone recurrence,^{86,87} improve BMD in stone formers^{85,87,88} and reduce the risk of hip fractures.⁸⁹ In addition, alkali citrate therapy has a positive effect on both stone recurrence and bone health by reducing bone resorption and buffering acid production. Treatment with potassium citrate monotherapy effectively increases BMD in calcium stone formers and is effective in patients with dRTA.^{87,90,91} Several studies have examined combination therapy with both thiazides and potassium citrate and found significant improvements in both BMD and stone recurrence.^{87,92} While more prospective studies are required, combination therapy may be more effective than either monotherapy. Bisphosphate therapy has also been shown to be safe and effective in increasing BMD in patients with urinary stones.⁸⁶

Animal protein

Recommendation: Patients with recurrent calcium or uric acid stones should moderate their animal protein intake and avoid purine rich foods (LE 2-3, Grade C Recommendation).

In some populations, high animal protein is associated with a slight increase in the risk of nephrolithiasis.⁶³ A large, prospective cohort study of men showed that dietary protein consumption was directly associated with the risk of stone formation (RR 1.33).⁶² Similarly, idiopathic calcium stone formers have been noted to have an increased consumption of protein (animal and vegetable) and purine rich foods compared to non-stone formers, resulting in elevated urinary oxalate and calcium, and lower levels of urinary citrate.⁹³

However, other studies have failed to find a strong correlation between animal protein intake and the risk of nephrolithiasis.^{47,48,94} Regardless, diets high in animal protein are associated with increased uric acid excretion, decreased urinary citrate and pH levels predisposing these individuals to uric acid nephrolithiasis.⁹⁵ A vegetarian diet has been demonstrated to reduce the risk of uric acid crystallization by 93% compared to a typical Western diet.⁹⁶

Sodium

Recommendation: Patients with recurrent calcium nephrolithiasis should limit their sodium intake to 1500mg daily and not exceed 2300mg daily (LE 1-2, Grade B Recommendation).

Dietary sodium excess is associated with hypercalciuria,⁹⁷ and high urinary sodium levels increase calcium excretion and decrease urinary citrate.^{35,38} High sodium intake was associated with up to 61% increase in stone risk in a large prospective cohort of women.⁴⁷ Furthermore, reduction in dietary sodium can improve urinary parameters and decrease stone recurrence. In a randomized trial of hypercalciuric calcium stone formers, a low sodium diet resulted in lower urinary sodium, calcium, and oxalate; and resulted in normalization of urine calcium excretion for one third of patients.⁹⁸ An additional randomized trial demonstrated that a low sodium and animal protein diet resulted in fewer stone recurrences compared with a low calcium diet.⁹⁹

Fruits and vegetables

Recommendation: A diet high in fiber, fruits, and vegetables may offer a small protective effect against stone formation (LE 2-3, Grade C Recommendation).

Low dietary intake of fiber, fruit, and vegetables increases the risk of kidney stones in women.¹⁰⁰ In stone forming patients with hypocitraturia, introducing these foods resulted in increased excretion of citrate, potassium, and magnesium and a reduction in the supersaturation of calcium oxalate and calcium phosphate crystals.¹⁰¹

Vitamin C

Recommendation: Vitamin C supplementation of more than 1000mg daily is not recommended due to the associated risk of hyperoxaluria and nephrolithiasis (LE 2-3, Grade C Recommendation).

It is theorized that the excess vitamin C is converted to oxalate and may increase stone risk. In population-based studies intake of over 1000mg of vitamin C daily caused a slight increase in the risk of nephrolithiasis.⁶³ Vitamin C supplementation of 1 to 2g was associated with increased urinary oxalate in stone forming patients.^{102,103}

Metabolic syndrome

Recommendation: Stone disease highly correlates with obesity, diabetes, and metabolic syndrome; and patients should be counselled that proper management of these conditions may reduce their future stone risk (LE 2-3, Grade D Recommendation).

Patients with one or more features of metabolic syndrome have significantly increased risks of heart disease, myocardial infarction, angina, and coronary bypass.¹⁰⁴ Stone disease is also linked to metabolic syndrome, where patients with metabolic syndrome have a 2.13 times increased odds of developing stones.¹⁰⁵ In addition, the risk of stone disease increases with the number of metabolic syndrome traits present.¹⁰⁵

Patients with metabolic syndrome and stones should be counselled to adopt healthier lifestyles, including dietary practices that promote low sodium intake and consumption of fresh fruit and vegetables. The DASH diet (Dietary Approaches to Stop Hypertension) has been shown to be effective in reducing cardiovascular risks as well kidney stone recurrence in three large epidemiological studies.¹⁰⁶

Obesity and diabetes have been shown to be independent risk factors for stone formation, likely secondary to the development of acidic urine promoting uric acid crystal formation.¹⁰⁷⁻¹¹⁰ The underlying insulin-resistance in these patients leads to impaired glutamine metabolism, ammonia production, and ammonium excretion. This results in unbuffered hydrogen ions and a lowering of the urinary pH.¹¹¹ Recent evidence suggests pioglitazone, a thiazolidinedione used in the treatment of type 2 diabetes can reduce insulin-resistance leading to increases in ammonium excretion and more alkaline urinary pH values, which may be protective against stone disease.¹¹²

Oxalate

Recommendations:

1. **Patients with hyperoxaluria should minimize their intake of high-oxalate foods. Vitamin B6 supplementation can be considered to lower urinary oxalate levels, when dietary modification has been unsuccessful (LE 2-3, Grade C Recommendation).**
2. **In patients with enteric hyperoxaluria, elemental calcium or calcium citrate should be given with meals to bind with dietary oxalate to reduce its intestinal absorption (LE 2-3, Grade C Recommendation).**

Hyperoxaluria can result from dietary, enteric, or idiopathic causes and is associated with an increased risk of calcium oxalate stone formation.¹¹³ Treatment of dietary and idiopathic hyperoxaluria with a low oxalate diet has shown mixed results. Most studies have demonstrated that a low oxalate diet reduces urinary oxalate levels; however, this did not consistently result in a decrease in calcium oxalate crystal supersaturation.^{114,115} Multiple studies, including several prospective cohort studies and a randomized controlled trial have shown that vitamin B6 or pyridoxine supplementation (25mg daily) is effective in reducing urinary oxalate levels.¹¹⁶

Enteric hyperoxaluria, is due primarily to the malabsorption of intestinal fats in the ileum. This condition is most frequently found in patients with inflammatory bowel disease with small bowel involvement, short gut syndrome, and after bariatric surgery (not including restrictive bariatric procedures such as vertical banded gastroplasty and sleeve gastrectomy).¹¹⁷ The intestinal fatty acids that are not absorbed cause saponification of calcium and magnesium in the intestinal lumen leading to a decreased amount of calcium available to bind dietary oxalate.¹¹⁷ This results in increased availability and absorption of oxalate and hyperoxaluria. As these conditions are often associated with diarrhea, typical laboratory findings include low urine volume and pH, hypocitraturia, hypocalciuria (unique to malabsorptive disease) and hyperoxaluria.¹¹⁷ Treatment includes reduction of dietary oxalate, increased fluid intake and calcium consumption.¹¹⁸ The calcium can be elemental calcium or calcium citrate as this will help correct the hypocitraturia and low urinary pH as well. Importantly the calcium should be taken with meals for it to bind to the dietary oxalate.¹¹⁸

Pediatric stone disease

Recommendation: All children with stone disease should undergo an in-depth medical evaluation and may benefit from a multidisciplinary approach with Urology and Nephrology (LE 3, Grade D Recommendation).

While pediatric stone disease is uncommon, with 59.5 cases per 100,000 person-years in the United States,¹¹⁹ the incidence is increasing in many developed countries.¹²⁰ The recurrence rate is high, with 50% of patients forming a recurrent stone within three years of the index

stone.¹²¹ Dietary factors, such as sodium and purine intake, low urine volume and climate are thought to play a role in increased stone risk. Obesity may not have the same effect on stone risk in children, as it does in adults.¹²²⁻¹²⁴ Prematurity, medications (e.g. loop diuretics) and genetic factors also increase the risk of pediatric stone disease.

An in-depth metabolic evaluation has historically been recommended in all children. In toilet-trained children, an in-depth evaluation with a 24-hour urine collection is recommended by most experts. In non-toilet-trained children or when a 24-hour urine collection is not possible in a toilet-trained child, a spot or random urine collection may suffice. This would include a urinalysis, and spot urine calcium, oxalate, citrate, cystine, protein and uric acid.¹²⁵ The utility of a full metabolic stone evaluation has been called into question for first-time stone formers, as it changes management in only 11% of patients.¹²⁶

In a population-based US study, metabolic abnormalities in children were as follows: hypercalciuria (62%), hyperoxaluria (18%), hypocitraturia (12%) with hyperuricosuria relatively rare compared to adults (9%).¹²⁰ Low urine volume may be affected by poor intake, access to clean drinking water, diarrhea, and other gastrointestinal illnesses. Recommended fluid intake is 70-100 ml/kg/day.¹²⁷

Hypercalciuria is the most common metabolic abnormality and is often idiopathic. Management includes increasing fluid intake, reducing sodium intake and thiazide diuretics, if refractory. Hypocitraturia can be idiopathic or associated with other metabolic conditions (e.g. dRTA, high meat protein diet).¹²⁸ Hyperoxaluria can be primary (increased endogenous production), dietary or enteric.¹²⁸ Hyperuricosuria is relatively uncommon, as are uric acid stones. Most children with urinary stones will benefit from a multidisciplinary approach with Urology and Nephrology involvement.¹²⁹

Specific prophylaxis based on stone composition

In the following section, “index patients” have been created based on the predominant stone composition. Potential metabolic abnormalities will be described, and specific diet and medical interventions will be highlighted for each clinical scenario.

Index Patient 1: Calcium oxalate or mixed calcium oxalate/calcium phosphate stones

Recommendations:

- 1. Thiazide diuretics decrease urinary calcium and stone recurrence in calcium stone forming patients. (LE 1-3, Grade A-B Recommendation).**
- 2. Alkali citrates are effective in increasing urinary citrate and reducing stone recurrence in calcium stone formers (Level of Evidence 1-3, Grade A-B Recommendation).**

- 3. In calcium stone formers allopurinol is effective in reducing stone recurrence in patients with hyperuricemia but does not provide any benefit in patients with normal serum uric acid levels (LE 1-2, Grade B Recommendation).**
- 4. Empiric treatment with either thiazide diuretics and/or alkali citrates reduces stone recurrence in calcium stone formers with active stone disease who have normal metabolic evaluations (LE 1-3, Grade B Recommendation).**

Patients with calcium oxalate or combined calcium oxalate/calcium phosphate stones may have normal 24-hour urine testing, hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria, low urine volume, or a combination of any of these features.¹³⁰ Based on 24-hour urine results various interventions can be considered (Figure 1).

Elevated urinary sodium can result in hypercalciuria and should be corrected through dietary reduction of sodium intake prior to initiating thiazide therapy.^{31,34,96} In patients with recurrent calcium stones with and without metabolic abnormalities thiazide use decreases urinary calcium and stone recurrence.¹³¹⁻¹³⁸

Dosages used in clinical trials are hydrochlorothiazide (25mg orally, twice daily or 50mg orally, once daily), chlorthalidone (25mg orally, once daily can be increased to 50mg), and indapamide (1.25mg orally, once daily can be increased to 2.5mg). The dose-dependent side effects of thiazide diuretics include hypokalemia, hyperglycemia, hyperlipidemia, hyperuricemia, hypomagnesemia, and hypocitraturia. Combining thiazide diuretics with potassium citrate or potassium chloride prevents hypokalemia and hypochloremic metabolic alkalosis which can lead to hypocitraturia.^{139,140}

Alkali citrate (potassium citrate, potassium magnesium citrate, sodium citrate) have been evaluated in several studies for the prevention of calcium nephrolithiasis. Alkali citrate increases urinary citrate levels and decreases the risk of recurrent nephrolithiasis.¹⁴¹⁻¹⁴⁹ Potassium citrate is the most studied agent with dosages in clinical trials ranging from 30-60mEq in two to three divided doses daily. Gastrointestinal upset is the primary side effect. Overall, potassium citrate is preferred over sodium citrate as the sodium load may increase urinary calcium excretion.¹⁵⁰

Studies regarding hyperuricosuria in calcium oxalate stone disease show mixed results. In a large cross-sectional study, elevated urinary uric acid levels were not associated with calcium oxalate stone formation.¹⁵¹ However, multiple studies have demonstrated treating hyperuricosuria in calcium oxalate stone formers reduces stone recurrence.¹⁵²⁻¹⁵⁴ Hyperuricemia may be treated with a xanthine oxidase inhibitor, most frequently allopurinol at a dose of 200-300 mg daily. Major side effects include rash, gastrointestinal upset, abnormal liver enzyme levels, and prolonged elimination in renal disease.

Empiric preventative treatment with a thiazide diuretic and or alkali citrate can be considered in calcium stone formers with a normal metabolic workup who continue to have active stone disease. Randomized controlled trials in calcium stone formers have demonstrated

that thiazide diuretics were effective in reducing stone recurrence compared to placebo even in patients with normocalciuria.^{132,138} Similarly, a prospective double-blind study demonstrated decreased stone events in calcium stone patients without hypocitraturia treated with potassium-magnesium citrate.¹⁴⁶

Index Patient 2: Pure calcium phosphate stones

Recommendation: Patients with incomplete or complete distal renal tubular acidosis (dRTA) should be treated with alkali citrate therapy (LE 2-3, Grade C Recommendation).

Patients who form pure calcium phosphate stones may have an underlying condition such as dRTA or primary hyperparathyroidism. Suggestive biochemical features and treatment of these disorders are listed in Table 1.

Patients with primary hyperparathyroidism have a significantly increased risk of renal stone disease.^{155,156} Even in patients with normal serum calcium levels an elevated PTH can increase stone risk, and result in decreased BMD.^{157,158} Surgery for primary hyperparathyroidism results in decreased serum calcium, stone formation, and an improvement in BMD.¹⁵⁹

Patients with dRTA may present with recurrent calcium phosphate stones, nephrocalcinosis, systemic acidosis, osteoporosis, failure to thrive, or sensorineural hearing loss.¹⁶⁰ Patients with dRTA generally have severe hypocitraturia and are best treated with an alkali citrate.^{161,162} In patients with dRTA treatment with potassium citrate resulted in correction of systemic acidosis, improvement in urinary parameters, reduced stone formation, and increased BMD.¹⁶³ Potassium citrate has demonstrated superior effects on urinary indices as compared to sodium citrate in patients with dRTA.¹⁵⁰

Incomplete dRTA is a condition characterized by defective urinary acidification similar to complete dRTA, without systemic metabolic acidosis.¹⁶⁴ Patients with incomplete dRTA still have disturbed calcium, citrate and bone metabolism resulting in recurrent stone formation and increased bone turnover.¹⁶⁵ Incomplete dRTA is likely a significantly underrecognized clinical condition due to the lack of a clear consensus on diagnostic criteria; however, the prevalence has been found to be as high as 15% in stone formers.^{166,167} Incomplete dRTA should be suspected in patients with persistently alkaline urine (pH>5.3), low urinary citrate, and low-normal serum potassium and bicarbonate levels.^{164,167} Similar to complete dRTA, the mainstay of treatment is alkali citrate therapy which improves urinary citrate and reduces stone formation.¹⁶²

Index Patient 3: Uric acid stones

Recommendation: In patients with uric acid stones, urinary alkalization to a pH of 6.5 is first-line therapy. Allopurinol may be used as adjunctive therapy in patients with hyperuricemia or hyperuricosuria (*LE 1-3, Grade B Recommendation*).

Uric acid stone formers are at significant risk of recurrence. Uric acid stones may form as the result of several underlying disorders including obesity, diabetes mellitus, gout, excessive bicarbonate loss due to high output bowel disease, myeloproliferative disorders, and tumor lysis syndrome.^{5,168} Uric acid stone formation is most associated with low urinary pH and low urine volume rather than hyperuricosuria.¹⁵¹ The focus of prevention therefore, should be to correct urine pH above 5.5 and increase urine volume (Figure 2).¹⁶⁸ Xanthine oxidase inhibitors such as allopurinol or febuxostat can be used as adjunctive therapy in patients with demonstrated hyperuricemia, hyperuricosuria, or a history of gout after correction of urinary pH.¹⁶⁹

Success with *in situ* uric acid stone dissolution has been demonstrated with alkali citrate, and maybe an underutilized treatment strategy.^{170,171} In a recent prospective study, potassium citrate therapy was successful in dissolving 83% of stones (mean 1.4cm³) after 6 months of treatment.¹⁷²

Index Patient 4: Cystine stones

Recommendation: Cystine stone formers should be counselled to target 3L of urine output daily, restrict their sodium intake, and moderate their protein intake to reduce stone formation. Urinary alkalization of the urine targeting a urine pH of 7-7.5 is the initial therapy. Thiol-binding agents should be considered second line therapy (*LE 3-4, Grade C Recommendation*).

Cystinuria, caused by a deficiency in reabsorbing dibasic amino acids, is a common genetic disorder affecting 1/7000 individuals. Cystine stone formers often present in childhood or as teenagers and maybe plagued by recurrent stone formation and the need for repetitive surgical intervention especially if prophylaxis is not optimized.

Patients with cystinuria should be encouraged to maintain a urine output of at least 3L daily (often demanding oral intake of 3.5–4L of fluid). This is a critical component of prevention in these patients as even with adjunctive medical therapy the success of stone prevention will be poor in patients who do not comply with increased fluid intake.^{173,174} Sodium restriction is advised for all patients with cystinuria.¹⁷⁴ In small studies sodium restriction significantly decreased cystine excretion,¹⁷⁵⁻¹⁷⁷ reflecting the coupling of cystine to parallel sodium transport in the kidney. Elevated dietary protein is associated with increased urinary cystine and a reduction in overall protein intake can decrease urinary cystine levels.¹⁷⁸

The solubility of cystine increases significantly between urine pH of 7.0-7.5. Urinary alkalization is therefore, the initial step in medical therapy with the goal of achieving a urine pH of greater than 7.0.¹⁷⁹ A urinary pH of greater than 7.5 should be avoided as this may promote calcium phosphate stone formation. Acetazolamide may be used as an adjunct to urinary alkalization when potassium citrate alone is ineffective.¹⁸⁰ If alkalizing agents fail to adequately control cystine stone formation thiol binding agents such as penicillamine 1-2g or tiopronin 800-1200mg in daily divided doses may be used.^{173,181-184} Side effects from penicillamine can be significant and include fever, arthralgias, rash, dysgeusia, leukopenia, and proteinuria. Where available, tiopronin, should be prioritized due to its better side effect profile (asthenia, GI distress, rash, joint aches, and mental status changes) compared to penicillamine.¹⁸² A small study evaluated the role of captopril however, significant reduction in stone formation was not achieved and captopril is no longer recommended.¹⁸³ Dietary and medical prevention options are shown in Figure 3.

Long-term compliance in patients with cystinuria can be difficult to achieve¹⁸⁵ and consideration should be given to management of these patients at specialized multidisciplinary clinics with close follow up.

Future directions: Genetic screening in recurrent nephrolithiasis

While not widely available, the genetic screening of patients with recurrent stone disease may have an increasing future role. It is likely that in addition to dietary and lifestyle choices, genetic factors are associated with recurrent nephrolithiasis. 35-65% of kidney stone patients have a family history of nephrolithiasis.^{186,187} Heritability of kidney stones and urinary calcium excretion have been found to be greater than 45% in twin studies.^{188,189} Underlying genetic causes are likely under-diagnosed, even in specialized renal stone clinics. In a study of nephrolithiasis and nephrocalcinosis patients recruited from renal stone clinics, 14.9% were found to have monogenic causative mutations, and 40% were novel.¹⁹⁰

There have been more than 30 identified kidney stone genes representing different mechanisms leading to stone disease.¹⁹¹ These mutations represent renal tubular disorders, abnormal calcium and vitamin D metabolism, and other inborn errors of metabolism. Cystinuria is the most common of these genetic causes.¹⁹⁰

Diagnosing genetic disorders may lead to targeted prevention and provide an opportunity for genetic counselling. Lumasiran, a novel RNAi therapy for primary hyperoxaluria type I, has been developed, shown promising results in phase 3 trials, and was recently approved by Health Canada.¹⁹² A multidisciplinary team approach including urologists, nephrologists, endocrinologists, and clinical geneticists can help coordinate biochemical and genetic testing and facilitate selection of optimal treatment strategies.¹⁹³

Summary

For patients at risk of recurrent renal stones, a detailed medical evaluation and an individualized approach to dietary and pharmacological prevention are important aspects of their care. The frequency of follow up and the need for repeat metabolic testing is not clearly defined in the literature and must therefore also be individualized. In patients where specific medical prophylaxis has been prescribed, re-evaluations with repeat metabolic testing within 6 months and yearly thereafter to monitor treatment efficacy and side effects are recommended.¹⁷ Periodic imaging is also recommended for those harboring small asymptomatic stones.

Urologists, in addition to providing state-of-the-art surgical care to our patients should be capable of providing up-to-date metabolic assessment and optimal prevention strategies as part of a comprehensive approach to stone management.

DRAFT

References

1. Scales CD Jr., Smith AC, Hanley JM, et al. Prevalence of kidney stones in the United States. *Eur Urol* 2012;62:160-5.
2. Tundo G, Vollstedt A, Meeks W, et al. Beyond prevalence: Cumulative incidence of kidney stones in the United States. *J Urol* 2021;205:1704-9.
3. Penniston KL, McLaren ID, Greenlee RT, et al. Urolithiasis in a rural Wisconsin population from 1992 to 2008: narrowing of the male-to-female ratio. *J Urol* 2011;185:1731-6.
4. Scales CD Jr., Curtis LH, Norris RD, et al. Changing gender prevalence of stone disease. *J Urol* 2007;177:979-82.
5. Chou YH, Su CM, Li CC, et al. Difference in urinary stone components between obese and non-obese patients. *Urol Res* 2011;39:283-7.
6. Uribarri J, Oh MS, Carroll HJ. The first kidney stones. *Ann Intern Med* 1989;111:1006-9.
7. Rule AD, Lieske JC, Li X, et al. The ROKS Nomogram for predicting a second symptomatic stone episode. *J Amer Soc Nephrol* 2014;25:2685-7.
8. Amaro, CRPR, Goldberg J, Damasio PC, et al. An update on metabolic assessment in patients with urinary lithiasis. *World J Urol* 2015;33:125-9.
9. Milose JC, Kaufman SR, Hollenbeck BK, et al. Prevalence of 24-hour urine collection in high risk stone formers. *J Urol* 2014;191:376-80.
10. Bensalah K, Tuncel A, Raman JD, et al. How physician and patient perceptions differ regarding medical management of stone disease. *J Urol* 2009;182:998-1004.
11. Dauw C, Yi Y, Bierlein M, et al. Medication nonadherence and effectiveness of preventative pharmacological therapy for kidney stones. *J Urol* 2016;195:648-52.
12. Saigal CS, Joyce G, Timilsina AR, et al. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? *Kidney Int* 2005;68:1808-14.
13. Pearle MS, Calhoun EA, Curhan GC, et al. Urologic diseases in America project: urolithiasis. *J Urol* 2005;173:848-57.
14. Antonelli JA, Maalouf NM, Pearle MS, et al. Use of the National Health and Nutrition Examination Survey to calculate the impact of obesity and diabetes on cost and prevalence of urolithiasis in 2030. *Eur Urol* 2014;66:724-9.
15. Center for Evidence-Based Medicine (CEBM), 2018. Available at: <https://www.cebm.net>. Accessed Dec. 7, 2021.
16. Skolarikos A, Straub M, Knoll T, et al. Metabolic evaluation and recurrence prevention for urinary stone patients: EAU guidelines. *Eur Urol* 2015;67:750-63.
17. Pearle MS, Goldfarb DS, Assimos DG, et al. American Urological Association. Medical management of kidney stones: AUA guideline. *J Urol* 2014;192:316-24.
18. Goldfarb DS, Arowojolu O. Metabolic evaluation of first-time and recurrent stone formers. *Urol Clin North Am* 2013;40:13-20.
19. Maalouf N. Approach to the Adult Kidney Stone Former. *Clin Rev Bone Miner Metab* 2012;10:38-49.
20. Kadlec AO, Turk TM. Update on the evaluation of repeated stone formers. *Curr Urol Rep* 2013;14:549-56.

21. Eisner BH, Sheth S, Dretler SP, et al. Abnormalities of 24-hour urine composition in first-time and recurrent stone-formers. *Urology* 2012;80:776-9.
22. Koyuncu HH, Yencilek F, Eryildirim B, et al. Family history in stone disease: how important is it for the onset of the disease and the incidence of recurrence? *Urol Res* 2010;38:105-9.
23. Tiselius HG, Daudon M, Thomas K, et al. Metabolic work-up of patients with urolithiasis: indications and diagnostic algorithm. *Eur Urol Focus* 2017;3:62–71.
24. Griffith DP, Khonsari F, Skurnick JH, et al. A randomized trial of acetohydroxamic acid for the treatment and prevention of infection-induced urinary stones in spinal cord injury patients. *J Urol* 1988;140:318-24.
25. Griffith DP, Gleeson MJ, Lee H, et al. Randomized, double-blind trial of Lithostat (acetohydroxamic acid) in the palliative treatment of infection-induced urinary calculi. *Eur Urol* 1991;20:243-7.
26. Williams JJ, Rodman JS, Peterson CM. A randomized double-blind study of acetohydroxamic acid in struvite nephrolithiasis. *N Engl J Med* 1984;311:760-4.
27. Eyre KS, Lewis F, Cui H, et al. Utility of blood tests in screening for metabolic disorders in kidney stone disease. *BJU Int* 2021;127:538-543.
28. Pierreus J, Bravenboer B. Normocalcemic primary hyperparathyroidism: A comparison with a hypercalcemic form in a tertiary referral population. *Horm Metab Res* 2018;50:797-802.
29. Boyd CJ, Wood KD, Singh N, et al. Screening for primary hyperparathyroidism in a tertiary stone clinic, a useful endeavor. *Int Urol Nephrol* 2020;52:1651-1655.
30. Pak CY, Peterson R, Poindexter JR. Adequacy of a single stone risk analysis in the medical evaluation of urolithiasis. *J Urol* 2001;165:378-81.
31. Parks JH, Goldfisher E, Asplin JR, et al. A single 24-hour urine collection is inadequate for the medical evaluation of nephrolithiasis. *J Urol* 2002;167:1607–12.
32. Healy KA, Hubosky SG, Bagley DH. 24-hour urine collection in the metabolic evaluation of stone formers: is one study adequate? *J Endourol* 2013;27:374-8.
33. Nayan M, Elkoushy MA, Andonian S. Variations between two 24-hour urine collections in patients presenting to a tertiary stone clinic. *Can Urol Assoc J* 2012;6:30-3.
34. Alruwaily AF, Dauw CA, Bierlein MJ, et al. How much information is lost when you only collect one 24-Hour urine sample during the initial metabolic evaluation? *J Urol* 2016;196:1143–8.
35. Lee TT, Elkoushy MA, Andonian S. Are stone analysis results different with repeated sampling? *Can Urol Assoc J* 2014;8:E317-22.
36. Brinkman JE, Large T, Nottingham, et al. Clinical and metabolic correlates of pure stone subtypes. *J Endourol* 2021;35:1555-62.
37. Goldfarb DS. Empiric therapy for kidney stones. *Urolithiasis* 2019;47:107–113.
38. Hosking DH, Erickson SB, Van den Berg CJ, et al. The stone clinic effect in patients with idiopathic calcium urolithiasis. *J Urol* 1983;130:1115-8.
39. Penniston KL. The nutrition consult for recurrent stone formers. *Curr Urol Rep* 2015;16:47.
40. Damasio PC, Amaro CR, Padovani CR, et al. Influence of clinical therapy and nutritional counseling on the recurrence of urolithiasis. *Acta Cir Bras* 2014;29:400-4.

41. Kocvara R, Plasqura P, Petrik A, et al. A prospective study of nonmedical prophylaxis after a first kidney stone. *BJU Int* 1999;84:393-8.
42. Fink HA, Akornor JW, Garimella PS, et al. Diet, fluid, or supplements for secondary prevention of nephrolithiasis: a systematic review and meta-analysis of randomized trials. *Eur Urol* 2009;56:72-80.
43. Cheungpasitporn W, Rossetti S, Friend K, et al. Treatment effect, adherence, and safety of high fluid intake for the prevention of incident and recurrent kidney stones: a systematic review and meta-analysis. *J Nephrol* 2016;29:211-9.
44. Borghi L, Meschi T, Amato F, et al. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. *J Urol* 1996;155:839-43.
45. Wang X, Xu X, Wu J, et al. Systematic review and meta-analysis of the effect of alcohol intake on the risk of urolithiasis including dose-response relationship. *Urol Int* 2015;94:194-204.
46. Sorensen MD, Kahn AJ, Reiner AP, et al. Impact of nutritional factors on incident kidney stone formation: a report from the WHI OS. *J Urol* 2012;187:1645-9.
47. Curhan GC, Willett WC, Knight EL, et al. Dietary factors and the risk of incident kidney stones in younger women: Nurses' Health Study II. *Arch Intern Med* 2004;164:885-91.
48. Ticinesi A, Nouvenne A, Borghi L, et al. Water and other fluids in nephrolithiasis: state of the art and future challenges. *Crit Rev Food Sci Nutr* 2017;57:963-74.
49. Borghi L, Meschi T, Maggiore U, et al. Dietary therapy in idiopathic nephrolithiasis. *Nutr Rev* 2006;64:301-12.
50. Littlejohns TJ, Neal NL, Bradbury KE, et al. Fluid intake and dietary factors and the risk of incident kidney stones in UK Biobank: a population-based prospective cohort study. *Eur Urol Focus* 2020;6:752-61.
51. Ferraro PM, Taylor EN, Gambaro G, et al. Caffeine intake and the risk of kidney stones. *Am J Clin Nutr* 2014;100:1596-603.
52. Ferraro PM, Taylor EN, Gambaro G, et al. Soda and other beverages and the risk of kidney stones. *Clin J Am Soc Nephrol* 2013;8:1389-95.
53. Wang S, Zhang Y, Mao Z, et al. A meta-analysis of coffee intake and risk of urolithiasis. *Urol Int* 2014;93:220-8.
54. Penniston KL, Steele TH, Nakada SY. Lemonade therapy increases urinary citrate and urine volumes in patients with recurrent calcium oxalate stone formation. *Urology* 2007;70:856-60.
55. Large T, Williams J, Asplin JR, et al. Using low-calorie orange juice as a dietary alternative to alkali therapy. *J Endourol* 2020;34:1082-87.
56. Conroy DE, West AB, Brunke-Reese D, et al. Just-in-time adaptive intervention to promote fluid consumption in patients with kidney stones. *Health Psychol* 2020;39:1062-9.
57. Borofsky MS, Dauw CA, York N, et al. Accuracy of daily fluid intake measurements using a "smart" water bottle. *Urolithiasis* 2018;46:343-8.
58. Wright HC, Alshara L, DiGennaro H, et al. The impact of smart technology on adherence rates and fluid management in the prevention of kidney stones. [Epub ahead of print]. *Urolithiasis* 2021;doi:10.1007/s00240-021-01270-6.

59. Chua TX, Prasad NS, Rangan GK, et al. A systematic review to determine the most effective interventions to increase water intake. *Nephrology* 2016;21:860-9.
60. McCauley LR, Dyer AJ, Stern K, et al. Factors influencing fluid intake behavior among kidney stone formers. *J Urol* 2012;187:1282-6.
61. Meschi T, Nouvenne A, Borghi L. The importance of water and other fluids in the prevention of stone recurrence. In *Urolithiasis 2012* (pp. 745-749). Springer, London.
62. Curhan GC, Willett WC, Rimm EB, et al. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med* 1993;328:833-8.
63. Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow up. *J Am Soc Nephrol* 2004;15:3225-32.
64. Curhan GC, Willett WC, Speizer FE, et al. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann Intern Med* 1997;126:497-504.
65. Radford LT, Bolland MJ, Mason B, et al. The Auckland calcium study: 5-year post-trial follow-up. *Osteoporos Int* 2014;25:297-304.
66. Johri N, Haeger P, Ferraro P, et al. Vitamin D deficiency is prevalent among idiopathic stone formers but does correction pose any risk? *Urolithiasis* 2017;45:535-43.
67. Elkoushy MA, Sabbagh R, Unikowsky B, et al. Prevalence and metabolic abnormalities of vitamin D-inadequate patients presenting with urolithiasis to a tertiary stone clinic. *Urology* 2012;79:781-5.
68. Pipili C, Oreopoulos DG. Vitamin D status in patients with recurrent kidney stones. *Nephron Clin Pract* 2012;122:134-8.
69. Rathod A, Bonny O, Guessous I, et al. Association of urinary calcium excretion with serum calcium and vitamin D levels. *Clin J Am Soc Nephrol* 2015;10:452-62.
70. Eisner BH, Thavaseelan S, Sheth S, et al. Relationship between serum vitamin D and 24-hour urine calcium in patients with nephrolithiasis. *Urology* 2012;80:1007-10.
71. Nguyen S, Baggerly L, French C, et al. 25-Hydroxyvitamin D in the range of 20 to 100 ng/mL and incidence of kidney stones. *Am J Public Health* 2014;104:1783-7.
72. Ferraro PM, Taylor EN, Gambaro G, et al. Vitamin D intake and the risk of incident kidney stones. *J Urol* 2017;197:405-10.
73. Kahwati LC, LeBlanc E, Weber RP, et al. Screening for vitamin D deficiency in adults: Updated evidence report and systematic review for the US preventive services task force. *JAMA* 2021;325:1443-63.
74. Avenell A, Mak Jc, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database Syst Rev* 2014;Cd000227.
75. Prentice R, Pettinger M, Jackson R, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. *Osteoporos Int* 2013;24:567-80.
76. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006;354:669-83.
77. Leaf DE, Korets R, Taylor EN, et al. Effect of vitamin D repletion on urinary calcium excretion among kidney stone formers. *Clin J Am Soc Nephrol* 2012;7:829-34.

78. Ferroni MC, Rycyna KJ, Averch TD et al. Vitamin D repletion in kidney stone formers – a randomized controlled trial. *J Urol* 2016;197:1079-83.
79. Tsuji H, Umekawa T, Kurita T, et al. Analysis of bone mineral density in urolithiasis patients. *Int J Urol* 2005;12:335-9.
80. Tugcu V, Ozbek E, Aras B, et al. Bone mineral density measurement in patients with recurrent normocalciuric calcium stone disease. *Urol Res* 2007;35:29-34.
81. Letavernier E, Traxer O, Daudon M, et al. Determinants of osteopenia in male renal-stone-disease patients with idiopathic hypercalciuria. *Clin J Am Soc Nephrol* 2011;6:1149-54.
82. Pasch A, Frey FJ, Eisenberger U, et al. PTH and 1,25-vitamin D response to a low-calcium diet is associated with bone mineral density in renal stone formers. *Nephrol Dial Transplant* 2008;23:2563-70.
83. Domrongkitchaiporn S, Pongsakul C, Stitchantrakul W, et al. Bone mineral density and histology in distal renal tubular acidosis. *Kidney Int* 2001;59:1086-93.
84. Denburg MR, Leonard MB, Haynes K, et al. Risk of fracture in urolithiasis: a population-based cohort study using the health improvement network. *Clin J Am Soc Nephrol* 2014;9:2133-40.
85. Taylor EN, Feskanich D, Paik JM et al. Nephrolithiasis and risk of incident bone fractures. *J Urol* 2016;195:1482-6.
86. Prochaska M. Bisphosphates and management of kidney stones and bone disease. *Curr Opin Nephrol Hypertens* 2021;30:184-9.
87. Alshara L, Batagello CA, Armanyous S et al. The impact of thiazides and potassium citrate on bone mineral density evaluated by CT scan in stone formers. *J Endourol* 2018;32:559-64.
88. Arrabal-Martin M, Gonzalez-Torres S, Cano-Garcia M et al. Urine calcium and bone mineral density in calcium stone-forming patients treated with alendronate and hydrochlorothiazide. *Urol Int* 2016;97:292-98.
89. Aung K, Htay T. Thiazide diuretics and the risk of hip fracture. *Cochrane Database Syst Rev* 2011;CD005185.
90. Sromicki JJ, and Hess B. Abnormal distal renal tubular acidification in patients with low bone mass: prevalence and impact of alkali treatment. *Urolithiasis* 2017;45:263-9.
91. Vescini F, Buffa A, La Manna G, et al. Long-term potassium citrate therapy and bone mineral density in idiopathic calcium stone formers. *J Endocrinol Invest* 2005;28:218-22.
92. Pak CY, Heller HJ, Pearle MS, et al. Prevention of stone formation and bone loss in absorptive hypercalciuria by combined dietary and pharmacological interventions. *J Urol* 2003;169:465-9.
93. Trinchieri A, Mandressi A, Luongo P, et al. The influence of diet on urinary risk factors for stones in healthy subjects and idiopathic renal calcium stone formers. *Br J Urol* 1991;67:230-6.
94. Hiatt RA, Ettinger B, Caan B, et al. Randomized controlled trial of a low animal protein, high fiber diet in the prevention of recurrent calcium oxalate kidney stones. *Am J Epidemiol* 1996;144:25-33.
95. Breslau NA, Brinkley L, Hill KD, et al. Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism. *J Clin Endocrinol Metab* 1988;66:140-6.

96. Siener R, Hesse A. The effect of a vegetarian and different omnivorous diets on urinary risk factors for uric acid stone formation. *Eur J Nutr* 2003;42:332-7.
97. Damasio PC, Amaro CR, Cunha NB, et al. The role of salt abuse on risk for hypercalciuria. *Nutr J* 2011;10:3.
98. Nouvenne A, Meschi T, Prati B, et al. Effects of a low-salt diet on idiopathic hypercalciuria in calcium-oxalate stone formers: a 3-mo randomized controlled trial. *AJCN* 2010;91:565-70.
99. Borghi L, Schianchi T, Meschi T, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med* 2002;346:77-84.
100. Sorensen MD, Hsi RS, Chi T, et al. Dietary intake of fiber, fruit and vegetables decreases the risk of incident kidney stones in women: a Women's Health Initiative report. *J Urol* 2014;192:1694-9.
101. Meschi T, Maggiore U, Fiaccadori E, et al. The effect of fruits and vegetables on urinary stone risk factors. *Kidney Int* 2004;66:2402-10.
102. Baxmann AC, De OG Mendonca C, Heilberg IP. Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. *Kidney Int* 2003;63:1066.
103. Traxer O, Huet B, Poindexter J, et al. Effect of ascorbic acid consumption on urinary stone risk factors. *J Urol* 2003;170:397-401.
104. Ferraro PM, Taylor EN, Eisner BH, et al. History of kidney stones and the risk of coronary heart disease. *JAMA* 2013;310:408-15.
105. West B, Luke A, Durazo-Arvizu RA, et al. Metabolic syndrome and self-reported history of kidney stones: the National Health and Nutrition Examination Survey (NHANES III) 1988-1994. *Am J Kidney Dis* 2008;51:741-7.
106. Taylor EN, Fung TT, Curhan GC. DASH-style diet associates with reduced risk for kidney stones. *J Am Soc Nephrol* 2009;20:2253-9.
107. Negri AL, Spivacow R, Del Valle E, et al. Clinical and biochemical profile of patients with "pure" uric acid nephrolithiasis compared with "pure" calcium oxalate stone formers. *Urol Res* 2007;35:247-51.
108. Maalouf NM, Cameron MA, Moe OW, et al. Low urine pH: a novel feature of the metabolic syndrome. *Clin J Am Soc Nephrol* 2007;2:883-8.
109. Taylor EN, Curhan GC. Body size and 24-hour urine composition. *Am J Kidney Dis* 2006;48:905-15.
110. Semins MJ, Shore AD, Makary MA, et al. The association of increasing body mass index and kidney stone disease. *J Urol* 2010;183:571-5.
111. Maalouf NM, Cameron MA, Moe OW, et al. Novel insights into the pathogenesis of uric acid nephrolithiasis. *Curr Opin Nephrol Hypertens* 2004;13:181-9.
112. Maalouf N, Poindexter J, Adams-Huet B, et al. Increased production and reduced urinary buffering of acid in uric acid stone formers is ameliorated by pioglitazone. *Kidney Int* 2019;95:1262-76.
113. Holmes RP, Assimos DG. The impact of dietary oxalate on kidney stone formation. *Urol Res* 2004;32:311-316.
114. Noori N, Honarkar E, Goldfarb D, et al. Urinary lithogenic risk profile in recurrent stone formers with hyperoxaluria: a randomized controlled trial comparing DASH (Dietary

- Approaches to Stop Hypertension)-style and low-oxalate diets. *Am J Kidney Dis* 2014;63:456–63.
115. Lieske JC, Tremaine WJ, De Simone C, et al. Diet, but not oral probiotics, effectively reduces urinary oxalate excretion and calcium oxalate supersaturation. *Kidney Int* 2010;78:1178–85.
 116. Mitwalli A, Ayiomamitis A, Grass L, et al. Control of hyperoxaluria with large doses of pyridoxine in patients with kidney stones. *Int Urol Nephrol* 1988;20:353–59.
 117. Witting C, Langman CB, Assimos D, et al. Pathophysiology and treatment of enteric hyperoxaluria. *Clin J Am Soc Nephrol* 2021;16:487–95.
 118. Sakhae K, Griffith C, Pak CY. Biochemical control of bone loss and stone-forming propensity by potassium-calcium citrate after bariatric surgery. *Surg Obes Relat Dis* 2012;8:67–72.
 119. Ward JB, Feinstein L, Pierce C, et al. Pediatric urinary stone disease in the United States: the urologic diseases in America project. *Urology* 2019;129:180–187.
 120. Dwyer ME, Krambeck AE, Bergstralh EJ, et al. Temporal trends in incidence of kidney stones among children: a 25-year population based study. *J Urol* 2012;188:247–252.
 121. Tasian GE, Kabarriti AE, Kalmus A, et al. Kidney stone recurrence among children and adolescents. *J Urol* 2017;197:246–52.
 122. Kuroczycka-Saniutycz E, Porowski T, Protas PT, et al. Does obesity or hyperuricemia influence lithogenic risk profile in children with urolithiasis? *Pediatr Nephrol* 2015;30:797–803.
 123. Bandari J, Dangle PP, Lyon TD, et al. 24-Hour urinary parameters in overweight and obese children with urolithiasis. *J Urol* 2016;196:526–30.
 124. Issler N, Dufek S, Kleta R, et al. Epidemiology of paediatric renal stone disease: a 22-year single centre experience in the UK. *BMC Nephrol* 2017;18:136.
 125. Gillespie RS, & Stapleton FB. Nephrolithiasis in children. *Pediatr Rev* 2004;25:131–9.
 126. Carnes K, Howe A, Feustel PJ, et al. 24-Hour urine collection for first time pediatric stone formers: is it worth it? *J Pediatr Urol* 2021;17:387.
 127. Hernandez JD, Ellison JS, Lendvay TS. Current trends, evaluation and management of pediatric nephrolithiasis. *JAMA Pediatr* 2015;169:961–4.
 128. Marra G, Taroni F, Berrettini A, et al. Pediatric nephrolithiasis: a systematic approach from diagnosis to treatment. *J Nephrol* 2019;32:199–210.
 129. Rodriguez Cuellar CI, Wang PZT, Freundlich M, et al. Educational review: role of the pediatric nephrologists in the work-up and management of kidney stones. *Pediatr Nephrol* 2020;35:383–97.
 130. Parvin M, Shakhssalim N, Basiri A, et al. The most important metabolic risk factors in recurrent urinary stone formers. *Urol J* 2011;8:99–106.
 131. Ohkawa M, Tokunaga S, Nakashima T, et al. Thiazide treatment for calcium urolithiasis in patients with idiopathic hypercalciuria. *Br J Urol* 1992;69:571–6.
 132. Coe FL. Treated and untreated recurrent calcium nephrolithiasis in patients with idiopathic hypercalciuria, hyperuricosuria, or no metabolic disorder. *Ann Intern Med* 1977;87:404–10.
 133. Brocks P, Dahl C, Wolf H, et al. Do thiazides prevent recurrent idiopathic renal calcium stones? *Lancet* 1981;2:124–5.

134. Mortensen JT, Schultz A, Ostergaard AH. Thiazides in the prophylactic treatment of recurrent idiopathic kidney stones. *Int Urol Nephrol* 1986;18:265-9.
135. Laerum S, Larsen S. Thiazide prophylaxis of urolithiasis: a double-blind study in general practice. *Acta Med Scand* 1984;215:383-9.
136. Fernandez-Rodriguez A, Arrabal-Martin M, Garcia-Ruiz MJ, et al. The role of thiazides in the prophylaxis of recurrent calcium lithiasis. *Actas Urol Esp* 2006;30:305-9.
137. Borghi L, Meschi T, Guerra A, et al. Randomized prospective study of a non-thiazide diuretic, indapamide, in preventing calcium stone recurrences. *J Cardiovasc Pharmacol* 1993;22:S78-86.
138. Ettinger B, Citron JT, Livermore B, et al. Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. *J Urol* 1988;139:679-84.
139. Nicar MJ, Peterson R, Pak CY. Use of potassium citrate as potassium supplement during thiazide therapy of calcium nephrolithiasis. *J Urol* 1984;131:430-3.
140. Odvina CV, Preminger GM, Lindberg JS, et al. Long-term combined treatment with thiazide and potassium citrate in nephrolithiasis does not lead to hypokalemia or hypochloremic metabolic alkalosis. *Kidney Int* 2003;63:240-7.
141. Allie-Hamdulay S, Rodgers AL. Prophylactic and therapeutic properties of a sodium citrate preparation in the management of calcium oxalate urolithiasis: randomized, placebo-controlled trial. *Urol Res* 2005;33:116-24.
142. Reddy SV, Shaik AB, Bokkissam S. Effect of potassium magnesium citrate and vitamin B-6 prophylaxis for recurrent and multiple calcium oxalate and phosphate urolithiasis. *Korean J Urol* 2014;55:411-6.
143. Barcelo P, Wuhl O, Servitge I, et al. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J Urol* 1993;150:1761-4.
144. Hofbauer J, Hobarth K, Szabo N, et al. Alkali citrate prophylaxis in idiopathic recurrent calcium oxalate urolithiasis: a prospective randomized study. *Br J Urol* 1994;73:362-5.
145. Mattle D, Hess B. Preventive treatment of nephrolithiasis with alkali citrate—a critical review. *Urol Res* 2005;33:73-9.
146. Ettinger B, Pak CY, Citron JT, et al. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol* 1997;158:2069-73.
147. Robinson MR, Leitao VA, Haleblan GE, et al. Impact of long-term potassium citrate therapy on urinary profiles and recurrent stone formation. *J Urol* 2009;181:1145-50.
148. Lojanapiwat B, Tanthanuch M, Pripathanont C, et al. Alkaline citrate reduces stone recurrence and regrowth after shockwave lithotripsy and percutaneous nephrolithotomy. *Int Braz J Urol* 2011;37:611-6.
149. Soygür T, Akbay A, Küpeli S. Effect of potassium citrate therapy on stone recurrence and residual fragments after shockwave lithotripsy in lower caliceal calcium oxalate urolithiasis: a randomized controlled trial. *J Endourol* 2002;16:149-52.
150. Preminger GM, Sakhaee K, Pak CY. Alkali action on the urinary crystallization of calcium salts: contrasting responses to sodium citrate and potassium citrate. *J Urol* 1988;139:240-2.
151. Curhan GC, Taylor EN. 24-h uric acid excretion and the risk of kidney stones. *Kidney Int* 2008;73:489-96.

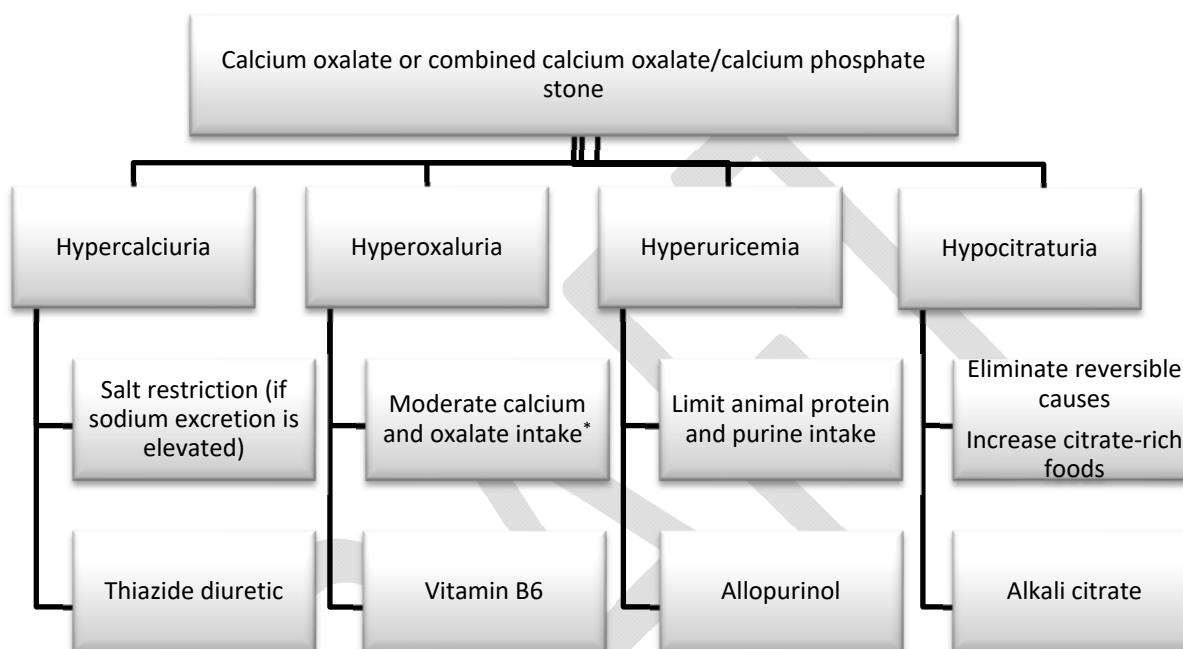
152. Ettinger B, Tang A, Citron JT, et al. Randomized trial of allopurinol in the prevention of calcium oxalate calculi. *N Engl J Med* 1986;315:1386-9.
153. Smith MJ. Placebo versus allopurinol for renal calculi. *J Urol* 1977;117:690-2.
154. Pearle MS, Roehrborn CG, Pak CY. Meta-analysis of randomized trials for medical prevention of calcium oxalate nephrolithiasis. *J Endourol* 1999;13:679–85.
155. Suh JM, Cronan JJ, Monchik JM. Primary hyperparathyroidism: is there an increased prevalence of renal stone disease? *Am J Roentgenol* 2008;191:908-11.
156. Mollerup CL, Vestergaard P, Frøkjær VG, et al. Risk of renal stone events in primary hyperparathyroidism before and after parathyroid surgery: controlled retrospective follow up study. *BMJ* 2002;325:807.
157. Amaral LM, Queiroz DC, Marques TF, et al. Normocalcemic versus Hypercalcemic Primary Hyperparathyroidism: More Stone than Bone? *J Osteoporos* 2012;2012:128352.
158. Tuna MM, Çalışkan M, Ünal M, et al. Normocalcemic hyperparathyroidism is associated with complications similar to those of hypercalcemic hyperparathyroidism. *J Bone Miner Metab* 2015;34:331-5.
159. Silverberg SJ, Shane E, Jacobs TP, et al. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med* 1999;341:1249–55.
160. Ferraro PM, D'Addessi A, Gambaro G. When to suspect a genetic disorder in a patient with renal stones, and why. *Nephrol Dial Transplant* 2013;28:811-20.
161. Sakhaee K, Alpern R, Poindexter J, et al. Citraturic response to oral citric acid load. *J Urol* 1992;147:975-6.
162. Domrongkitchaiporn S, Khositseth S, Stitchantrakul W, et al. Dosage of potassium citrate in the correction of urinary abnormalities in pediatric distal renal tubular acidosis patients. *Am J Kidney Dis* 2002;39:383–91.
163. Preminger GM, Sakhaee K, Skurla C, et al. Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular acidosis. *J Urol* 1985;134:20-3.
164. Dhayat NA, Gradwell MW, Pathare G et al. Furosemide/Fludrocortisone test and clinical parameters to diagnose incomplete distal renal tubular acidosis in kidney stone formers. *Clin J Am Soc Nephrol* 2017;12:1507-17.
165. Osther PJ, Bollerslev J, Hansen AB et al. Pathophysiology of incomplete renal tubular acidosis in recurrent renal stone formers: evidence of disturbed calcium, bone and citrate metabolism. *Urol Res* 1993;21:169-73.
166. Osther PJ, Hansen AB, Rohl HF. Distal renal tubular acidosis in recurrent renal stone formers. *Ban Med Bull* 1989;36:492-3.
167. Donnelly S, Kamel KS, Vasuvattakul S et al. Might distal renal tubular acidosis be a proximal tubular cell disorder? *Am J Kidney Dis* 1992;19:272.
168. Cameron MA, Sakhaee K. Uric acid nephrolithiasis. *Urol Clin North Am* 2007;34:335–46.
169. Goldfarb DS, MacDonald PA, Gunawardhana L, et al. Randomized controlled trial of febuxostat versus allopurinol or placebo in individuals with higher urinary uric acid excretion and calcium stones. *Clin J Am Soc Nephrol* 2013;8:1960-7.

170. Trinchieri A, Esposito N, Castelnovo C. Dissolution of radiolucent renal stones by oral alkalization with potassium citrate/potassium bicarbonate. *Arch Ital Urol Androl* 2009;81:188-91.
171. Pak CY, Sakhaee K, Fuller C. Successful management of uric acid nephrolithiasis with potassium citrate. *Kidney Int* 1986;30:422-8.
172. Elsayy A, Elshal A, El-Naha A, et al. Can we predict the outcome of oral dissolution therapy for radiolucent renal calculi? A prospective study. *J Urol* 2019;201:350-7.
173. Barbey F, Joly D, Rieu P, et al. Medical treatment of cystinuria: critical reappraisal of long term results. *J Urol* 2000;163:1419-23.
174. Mattoo A, Goldfarb DS. Cystinuria. *Semin Nephrol* 2008;28:181-91.
175. Rodriguez LM, Santos F, Malaga S, et al. Effect of low sodium diet on urinary elimination of cystine in cystinuric children. *Nephron* 1995;71:416-8.
176. Lindell A, Denneberg T, Edholm E, et al. The effect of sodium intake on cystinuria with and without tiopronin treatment. *Nephron* 1995;71:407-15.
177. Norman RW, Manette WA. Dietary restriction of sodium as a means of reducing urinary cystine. *J Urol* 1990;143:1193-5.
178. Rodman JS, Blackburn P, Williams JJ, et al. The effect of dietary protein on cystine excretion in patients with cystinuria. *Clin Nephrol* 1984;22:273-8.
179. Claes DJ, Jackson E. Cystinuria: mechanisms and management. *Pediatr Nephrol* 2012;27:2031-38.
180. Sterret SP, Penniston KL, Wolf JS, et al. Acetazolamide is an effective adjunct for urinary alkalization in patients with uric acid and cystine stone formation recalcitrant to potassium citrate. *Urology* 2008;72:278-81.
181. Dahlberg PJ, van den Berg, Kurtz SB, et al. Clinical features and management of cystinuria. *Mayo Clin Proc* 1977;52:533-42.
182. Pak CY, Fuller C, Sakhaee K, et al. Management of cystine nephrolithiasis with alpha-mercaptopropionylglycine. *J Urol* 1986;136:1003-8.
183. Chow GK, Streem SB. Medical treatment of cystinuria: results of contemporary clinical practice. *J Urol* 1996;156:1576-8.
184. Cohen TD, Streem SB, Hall P. Clinical effect of captopril on the formation and growth of cystine calculi. *J Urol* 1995;154:164-6.
185. Pietrow PK, Auge BK, Weizer AZ, et al. Durability of the medical management of cystinuria. *J Urol* 2003;169:68-70.
186. Resnick M, Pridgen DB, Goodman HO. Genetic predisposition to formation of calcium oxalate renal calculi. *N Engl J Med* 1968;278:1313-8.
187. Curhan GC, Willett WC, Rimm EB, et al. Family history and risk of kidney stones. *J Am Soc Nephrol* 1997;8:1568-73.
188. Goldfarb DS, Avery AR, Beara-Lasic L, et al. A twin study of genetic influences on nephrolithiasis in women and men. *Kidney Int Rep* 2018;4:535-40.
189. Goldfarb DS, Fischer ME, Keich Y, et al. A twin study of genetic and dietary influences on nephrolithiasis: a report from the eVentam Era Twin Registry. *Kidney Int* 2005;67:1053-61.
190. Halbritter J, Baum M, Hynes AM, et al. Fourteen monogenic genes account for 15% of nephrolithiasis/nephrocalcinosis. *J Am Soc Nephrol* 2015;26:543-51.

191. Daga A, Majmundar AJ, Braun DA, et al. Whole exome sequencing frequently detects a monogenic cause in early onset nephrolithiasis and nephrocalcinosis. *Kidney Int* 2018;93:204-13.
192. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type I. *N Engl J Med* 2021;384:1216-26.
193. Howles S, Thakker R. Genetics of kidney stone disease. *Nat Rev Urol* 2020;17:407-21.

DRAFT

Figures and Tables

Figure 1. Specific dietary and medical treatments for patients with calcium oxalate or mixed calcium oxalate/calcium phosphate stones.

*Calcium intake 1200 mg daily (with meals), moderation of foods high in oxalate, pair oxalate and calcium containing foods.

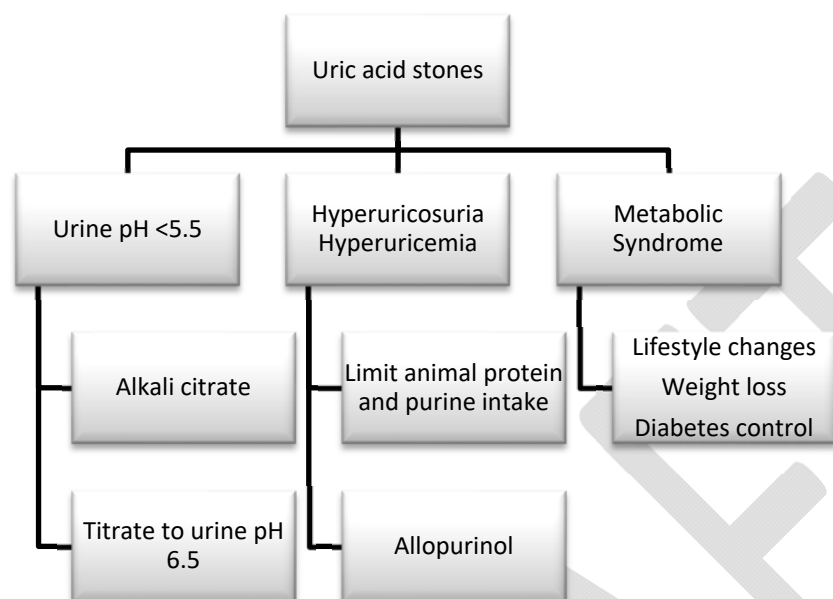
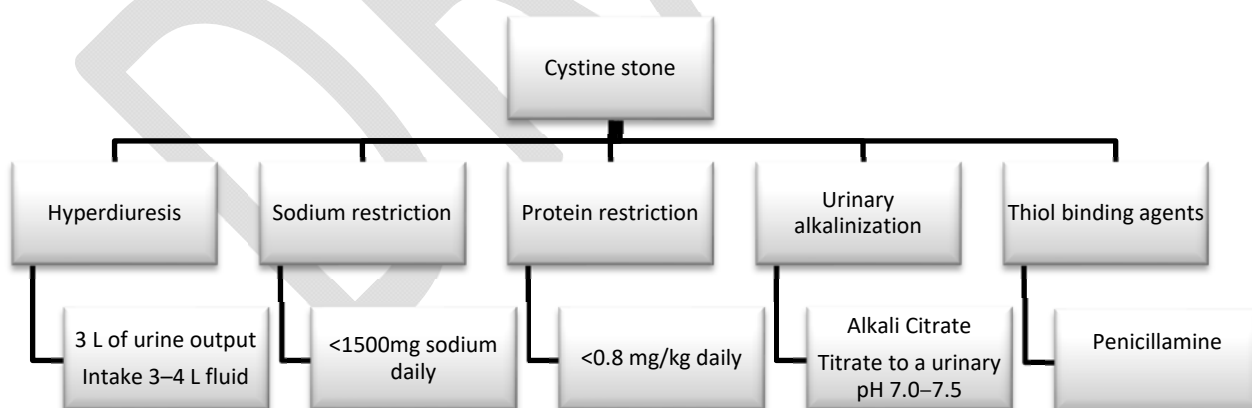
Figure 2. Specific dietary and medical treatments for patients with uric acid stones.**Figure 3.** Specific dietary and medical treatments for patients with cystine stones

Table 1. Characteristic findings, investigations, and treatment of primary/secondary hyperparathyroidism and distal renal tubular acidosis			
Disorder	Suggestive features	Investigations	Treatment
Primary hyperparathyroidism	↑ or ↑N serum calcium ↑ or ↑N serum PTH Hypercalciuria Calcium oxalate or calcium phosphate stone ↓ Bone mineral density	Serum calcium PTH Vitamin D	Treat vitamin D deficiency Referral to endocrinology
Secondary hyperparathyroidism	↑ serum PTH ↓ Vitamin D ↓ or N serum calcium Hypercalciuria ↓ Bone mineral density	Serum calcium PTH Vitamin D	Treat vitamin D deficiency Consider referral to endocrinology
Complete distal renal tubular acidosis	Urine pH >5.8 ↓ serum bicarbonate ↓ serum potassium Pure apatite stone Hypocitraturia Hypercalciuria ↓ Bone mineral density	Serum electrolytes Urine pH 24H Urine Collection	Alkali citrate Thiazide
Incomplete distal renal tubular acidosis	Urine pH >5.3 ↓N serum bicarbonate ↓N serum potassium Pure apatite stone Hypocitraturia Hypercalciuria	Serum electrolytes Urine pH 24H Urine Collection	Alkali citrate Thiazide

PTH: parathyroid hormone, ↑ = high, ↑N = at the high end of normal range; ↓ = low, ↓N = at the low end of normal range.