Dietary and medical management of recurrent nephrolithiasis

ABSTRACT

Dietary approaches and medical treatment can prevent recurrence of urinary stones. Some interventions are appropriate for all types of stones, but there are particular risk factors that may need directed therapy.

KEY POINTS

Nephrolithiasis is common and widespread, and its incidence and prevalence are increasing.

Calcium stones are the most common type, and of these, calcium oxalate stones predominate.

The most common risk factors for recurrent calcium stones are low urinary output, hypercalciuria, hyperoxaluria, hypocitraturia, and hyperuricosuria.

Less common types of stones are usually associated with genetic abnormalities, infections, or medications.

Nephrolithiasis is common and often recurs. This review focuses on measures to prevent recurrent stone formation. Some measures apply to all patients, and some apply to specific types of stones.

COMMON AND INCREASING

According to data from the 2007–2010 National Health and Nutrition Examination Survey, the prevalence of nephrolithiasis in the United States was 10.6% in men and 7.1% in women. On average, 1 in 11 Americans will develop kidney stones at least once in their lifetime.1

By race and sex, white men have the highest incidence of nephrolithiasis and Asian women have the lowest. It is less common before age 20 and peaks in incidence in the third and fourth decades of life.

The prevalence has steadily increased in the past few decades (Table 1),1,2 but the reasons are not clear. The trend may be due to changes in diet and lifestyle, increasing prevalence of obesity and diabetes, migration from rural to urban areas, and global warming, with higher temperature resulting in dehydration and high urinary concentration of calcium and other stone-forming salts.3 Nephrolithiasis is now recognized as a systemic disorder associated with chronic kidney disease, bone loss and fractures, increased risk of coronary artery disease, hypertension, type 2 diabetes mellitus, and metabolic syndrome (Table 2).4–7

Without medical treatment, the 5-year recurrence rate is high, ranging from 35% to 50% after an initial stone event.8 Annual medical costs of care for kidney stones in the United States exceed $4.5 billion, with additional costs from missed work. Therefore, this
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condition has a considerable economic and social burden, which underscores the importance of prevention.9

MOST STONES CONTAIN CALCIUM

About 80% of kidney stones in adults contain calcium, and calcium oxalate stones are more common than calcium phosphate stones. Uric acid and struvite stones account for 5% to 15%, and cystine, protease inhibitor, triamterene, 2,8-dihydroxyadenine (2,8-DHA) and xanthine stones each account for less than 1%.10

Stones form when the urinary concentration of stone-forming salts, which is inversely proportional to urine volume, is higher than their saturation point, which is affected by urine pH. Acidic urine (low pH) predisposes to the formation of uric acid and cystine stones, whereas alkaline urine (high pH) favors calcium phosphate stones.

INCREASED FLUID INTAKE FOR ALL

High fluid intake, enough to produce at least 2.5 L of urine per day, should be the initial therapy to prevent stone recurrence.11

Borghi et al12 randomly assigned 199 patients who had a first calcium stone to high oral fluid intake or no intervention and followed them prospectively for 5 years. The recurrence rate was 12% in the treated group and 27% in the control group. Another study, in patients who had undergone shock wave lithotripsy, found a recurrence rate of 8% in those randomized to increase fluid intake to achieve urine output greater than 2.5 L/day, compared with 56% in those assigned to no treatment.13

Without medical treatment, the 5-year recurrence rate is 35% to 50%

Certain beverages increase the risk of stones and should be avoided. Sugar-sweetened noncola soda and punch are associated with a 33% higher risk of kidney stones, and cola sodas are associated with a 23% higher risk.14 Prospective studies have shown that the consumption of coffee, beer, wine, and orange juice is associated with a lower likelihood of stone formation.13,15

Table 3 is a brief summary of the dietary and pharmacologic interventions in the management of recurrent nephrolithiasis.

PREVENTING CALCIUM OXALATE STONES

Major urinary risk factors associated with calcium oxalate stones are hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, and low urine volume.16 Preventing calcium stones therefore depends on reducing the urinary concentration of calcium and oxalate, increasing urinary levels of inhibitors such as citrate, and increasing urine volume.

Reducing calcium excretion

Hypercalciuria has been traditionally defined as 24-hour urinary calcium excretion greater than 300 mg/day in men, greater than 250 mg in women, or greater than 4 mg/kg in men or women.17 It is a graded risk factor, and the cut
points used in published research and clinical laboratories vary substantially. Some institutions use the same value for hypercalciuria in both sexes, eg, greater than 200 mg/day. Excessive sodium intake is the most common cause of hypercalciuria. Systemic conditions such as primary hyperparathyroidism, sarcoidosis, and renal tubular acidosis also cause hypercalciuria but are uncommon. Management depends on the underlying cause and includes dietary modifications and pharmacologic therapy. 

Dietary modifications have a pivotal role in the management of recurrent stones that are due to hypercalciuria.

Dietary calcium should not be restricted, since calcium reduces the excretion of urinary oxalate by decreasing intestinal absorption of oxalate. Guidelines from the American Urological Association recommend a daily calcium intake of 1,000 to 1,200 mg. Moreover, restriction of dietary calcium to less than 800 mg/day (the current recommended daily allowance for adults) can lead to negative calcium balance and bone loss.

Sodium intake also influences hypercalciuria. Calcium is reabsorbed passively in the proximal tubule due to the concentration gradient created by active reabsorption of sodium. A high sodium intake causes volume expansion, leading to a decrease in proximal sodium and calcium reabsorption and enhancing calcium excretion. A low-sodium diet (80–100 mmol/day, or 1,800–2,300 mg/day) is recommended. This enhances proximal sodium and passive calcium absorption and leads to a decrease in calcium excretion.

Dietary protein increases the acid load by production of sulfuric acid and leads to hypercalciuria by its action on bone and kidney. Animal protein has a higher content of sulfur and generates a higher acid load compared with vegetable protein and has been associated with an increased incidence of stone formation, at least in men. Borghi et al reported that the combination of restricted intake of animal protein (52 g/day), restricted salt intake (50 mmol, or 2,900 mg/day of sodium chloride), and normal calcium intake (30 mmol/day, or 1,200 mg/day) was associated with a lower incidence of stone recurrence in men with hypercalciuria compared with traditional

### TABLE 3

**Interventions to prevent recurrent kidney stones**

<table>
<thead>
<tr>
<th>DIETARY INTERVENTIONS</th>
<th>PHARMACOLOGIC INTERVENTIONS</th>
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</thead>
<tbody>
<tr>
<td>All—Increase fluid intake to produce a urine volume of at least 2.5 L/day</td>
<td>Hypercalciuria and recurrent calcium stones—Thiazide diuretics</td>
</tr>
<tr>
<td>Calcium stones and hypercalciuria—Limit sodium intake to 2,300 mg/day; consume at least 1,000 or 1,200 mg/day of dietary calcium; restrict nondairy animal protein to 0.8 to 1 g/kg/day; increase intake of fresh fruits and vegetables</td>
<td>Recurrent calcium stones and hypocitraturia—Potassium citrate</td>
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<tr>
<td>Calcium oxalate stones and relatively high urinary oxalate intake—Limit intake of oxalate-rich foods and maintain normal calcium intake</td>
<td>Uric acid stones or calcium stones with hyperuricosuria—Limit intake of nondairy animal protein to 0.8 to 1 g/kg/day</td>
</tr>
<tr>
<td>Calcium oxalate stones and hypocitraturia—Increase intake of fruits and vegetables and limit nondairy animal protein</td>
<td>Uric acid stones—Do not use allopurinol as first-line therapy, but consider it in refractory cases</td>
</tr>
<tr>
<td>Calcium oxalate stones and hypocitraturia—Increase intake of fruits and vegetables and limit nondairy animal protein</td>
<td>Type 1 hyperoxaluria—Pyridoxine</td>
</tr>
<tr>
<td>Uric acid stones or calcium stones with hyperuricosuria—Limit intake of nondairy animal protein to 0.8 to 1 g/kg/day</td>
<td>Cystine stones unresponsive to conservative measures—Offer a cystine-binding thiol drug, eg, D-penicillamine or tiopronin. Pharmacotherapy should always be used in conjunction with conservative measures of dietary modification and urinary alkalization</td>
</tr>
<tr>
<td>Cystine stones—Limit sodium intake to 2,300 mg/day and protein intake to 0.8–1 g/kg/day</td>
<td>Residual or recurrent struvite stones, and surgical interventions are contraindicated or refused—Consider urease inhibitors, acetoxyhydroxamic acid</td>
</tr>
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low-calcium intake (10 mmol, or 400 mg/day). Patients should therefore be advised to avoid excessive intake of animal protein.

Increasing the dietary intake of fruits and vegetables as in the Dietary Approach to Stop Hypertension (DASH) diet is beneficial and
Nephrolithiasis reduces the risk of stone recurrence, mainly by increasing citrate excretion.24

Pharmacologic therapy in hypercalciuria. Thiazide diuretics are the mainstay of pharmacotherapy for preventing recurrent stones in patients with idiopathic hypercalciuria. They reduce the risk of stone recurrence by about 50%, as reported in a recent meta-analysis that looked at five trials comparing thiazide diuretics with placebo.25 They lower calcium excretion by causing volume depletion, thereby increasing proximal sodium and passive calcium reabsorption.

Chlorthalidone and hydrochlorothiazide are the thiazides commonly used to treat hypercalciuria. The dosage is titrated to the urinary calcium excretion, and a common mistake is to use doses that are too low. They are usually started at 25 mg/day, but often require an increase to 50 to 100 mg/day for adequate lowering of urinary calcium.

Care should be taken to avoid hypokalemia. If it occurs, it can be corrected by adding the potassium-sparing diuretic amiloride (5–10 mg/day), which increases calcium reabsorption in collecting ducts or, in patients with hypocitraturia, potassium citrate-potassium bicarbonate. (Sodium salts should be avoided, since they increase renal calcium excretion.)26

Management of hypercalciuria with metabolic causes, which include primary hyperparathyroidism and chronic acidemia. Patients who have hypercalciuria from primary hyperparathyroidism are treated with parathyroidectomy.27 Chronic metabolic acidosis causes hypercalciuria by loss of bone calcium and hypocitraturia by increasing active proximal absorption of citrate. Potassium citrate or potassium bicarbonate is used to prevent stones in such patients; sodium salts should be avoided.28

Reducing oxalate excretion
Hyperoxaluria has traditionally been defined as urinary oxalate excretion of more than 45 mg/day. However, the optimal cutoff point for urinary oxalate excretion is unclear, as is the optimal cutoff for hypercalciuria. The risk of stone formation has been shown to increase with oxalate excretion even above 25 mg/day, which is within the normal limit.18

Idiopathic hyperoxaluria. High dietary oxalate intake, especially when associated with low calcium intake, leads to idiopathic hyperoxaluria. However, the contribution of abnormal endogenous oxalate metabolism is uncertain. Ingested calcium binds to oxalate in the intestinal tract and reduces both the absorption of intestinal oxalate absorption and the excretion of urinary oxalate.29 High dietary oxalate intake has usually been regarded as a major risk factor for kidney stones.

Taylor and Curhan,30 in a prospective study, reported a mild increase in the risk of stones in the highest quintile of dietary oxalate intake compared with the lowest quintile for men (relative risk [RR] 1.22, 95% confidence interval [CI] 1.03–1.45) and older women (RR 1.21, 95% CI 1.01–1.44). They also demonstrated that eating eight or more servings of spinach per month compared with fewer than one serving per month was associated with a similar increase of stone risk in men (RR 1.30, 95% CI 1.08–1.58) and older women (RR 1.34 95% CI 1.1–1.64). In contrast, spinach and dietary oxalate intake did not increase the risk of nephrolithiasis in young women. The authors concluded that the risk associated with oxalate intake was modest, and their data did not support the contention that dietary oxalate is a major risk factor for kidney stones.

Higher oxalate intake increases urinary oxalate excretion and presumably the risk of nephrolithiasis. Limiting dietary oxalate to prevent stones is recommended if habitually high dietary intake of oxalate is identified or follow-up urine measurements show a decrease in oxalate excretion.31 Foods rich in oxalate include spinach, rhubarb, nuts, legumes, cocoa, okra, and chocolate.

The DASH diet, which is high in fruits and vegetables, moderate in low-fat dairy products, and low in animal protein, is an effective dietary alternative and has been associated with a lower risk of calcium oxalate stones.24 Consuming fruits and vegetables increases the excretion of urinary citrate, which is an inhibitor of stone formation. Also, it has been proposed that the DASH diet contains unknown factors that reduce stone risk.

Taylor et al32 prospectively examined the relationship between the DASH diet and the incidence of kidney stones and found that the
diet significantly reduced the risk of kidney stones. The relative risks of occurrence of kidney stones in participants in the highest quintile of the DASH score (a measure of adherence to the DASH diet) compared with the lowest quintile were 0.55 (95% CI 0.46-0.65) for men, 0.58 (95% CI 0.49-0.68) for older women, and 0.60 (95% CI 0.52-0.70) for younger women, which the authors characterized as “a marked decrease in kidney stone risk.”

Vitamin C intake should be restricted to 90 mg/day in patients who have a history of calcium oxalate stones. Urivetzky et al\(^3\) found that urinary oxalate excretion increased by 6 to 13 mg/day at doses of ascorbic acid greater than 500 mg.

Pyridoxine (vitamin B\(_6\)), a coenzyme of alanine-glyoxylate aminotransferase (AGT), increases the conversion of glyoxylate to glycine instead of oxalate and is used in the treatment of type 1 primary hyperoxaluria (see below).\(^3\) However, its effect in preventing stones in idiopathic hyperoxaluria is not well known, and it has not been studied in a randomized controlled trial. In a prospective study, Curhan et al\(^3\) reported that high intake of pyridoxine (>40 mg/day) was associated with a lower risk of stone formation in women, but no such benefit was found in men.

Enteric hyperoxaluria. About 90% of dietary oxalate binds to calcium in the small intestine and is excreted in the stool. The remaining 10% is absorbed in the colon and is secreted in urine. Hyperoxaluria is frequently seen with fat malabsorption from inflammatory bowel disease, short gut syndrome, and gastric bypass surgery. In these conditions, excess fat binds to dietary calcium, leading to increased absorption of free oxalate in the colon.\(^3\)

Treatment is directed at decreasing intestinal oxalate absorption and should include high fluid intake and oral calcium supplements. Calcium carbonate or citrate causes precipitation of oxalate in the intestinal lumen and is prescribed as 1 to 4 g in three to four divided doses, always with meals. Calcium citrate is preferred over calcium carbonate in stone-formers because of the benefit of citrate and calcium citrate’s higher solubility and greater effectiveness in the presence of achlorhydria.\(^3\) Patients should be advised to avoid foods high in oxalate and fat.

Primary hyperoxaluria is caused by inherited inborn errors of glyoxylate metabolism that cause overproduction of oxalate and urinary oxalate excretion above 135 to 270 mg/day.

Type 1 primary hyperoxaluria is the most common (accounting for 90% of cases) and is caused by reduced activity of hepatic peroxisomal AGT.

Type 2 is from a deficiency of glyoxylate reductase-hydroxypyruvate reductase (GRHPR).

Type 3 is from mutations in the \(HOGA1\) gene, which codes for the liver-specific mitochondrial 4-hydroxy-2-oxoglutarate aldolase enzyme involved in degradation of hydroxyproline to pyruvate and glyoxalate.\(^3\)

High fluid intake to produce a urinary volume of 3 L/day reduces intratubular oxalate deposition and should be encouraged. Potassium citrate (0.15 mg/kg), oral phosphate supplements (30–40 mg/kg of orthophosphate), and magnesium oxide (500 mg/day/m\(^2\)) inhibit precipitation of calcium oxalate in the urine.\(^3\) Pyridoxine, a coenzyme of AGT, increases the conversion of glyoxylate to glycine instead of oxalate and is prescribed at a starting dose of 5 mg/kg (which can be titrated up to 20 mg/kg if there is no response) in patients with type 1 primary hyperoxaluria. About 50% of patients with type 1 respond successfully to pyridoxine, and a 3- to 6-month trial should be given in all patients in this category.\(^3\) AGT is present only in hepatocytes, and GRHPR is found in multiple tissues; therefore, combined liver-kidney transplant is the treatment of choice in patients with type 1 primary hyperoxaluria, whereas isolated kidney transplant is recommended in patients with type 2.\(^4\)

Reducing uric acid excretion

Hyperuricosuria is defined as uric acid excretion of greater than 800 mg/day in men and greater than 750 mg/day in women.

The association of hyperuricosuria with increased risk of calcium oxalate stone formation is controversial. Curhan and Taylor,\(^1\) in a cross-sectional study of 3,350 men and women, reported that there was no difference in mean 24-hour uric acid excretion in individuals with and without a history of stones.

The mechanism by which uric acid leads to calcium oxalate stones is not completely
Do not restrict calcium intake in calcium oxalate stone-formers

Nephrolithiasis

known and could be the “salting out” of calcium oxalate from the urine.42

Dietary purine restriction, ie, limiting intake of nondairy animal protein to 0.8 to 1 g/kg/day, is the initial dietary intervention.43 Allopurinol is the alternative approach if the patient is not compliant or if dietary restriction fails.44

In a study by Ettinger et al,45 60 patients with hyperuricosuria and normocalciuria were randomized to receive allopurinol (100 mg three times daily) or a placebo. The allopurinol group had a rate of calculus events of 0.12 per patient per year, compared with 0.26 in the placebo group.

Increasing citrate excretion

Hypocitraturia is a well-known risk factor for the formation of kidney stones. It is usually defined as a citrate excretion of less than 320 mg/day for adults.

Citrate prevents formation of calcium crystals by binding to calcium, thereby lowering the concentration of calcium oxalate below the saturation point.45

Diet therapy. Patients with calcium oxalate stones and hypocitraturia should be encouraged to increase their intake of fruits and vegetables, which enhances urinary citrate excretion, and to limit their intake of nondairy animal protein.45

The use of citrus products in preventing stones in patients with hypocitraturia is controversial, however, and needs to be studied more.

One study46 demonstrated that lemon juice was beneficial in hypocitraturic nephrolithiasis: 4 oz/day of lemon juice concentrate in the form of lemonade was associated with an increase in urinary citrate excretion to 346 mg/day from 142 mg/day in 11 of 12 patients who participated.

Odvina47 compared the effects of orange juice with those of lemonade on the acid-base profile and urinary stone risk under controlled metabolic conditions in 13 volunteers. Orange juice was reported to have greater alkalinizing and citraturic effects and was associated with lower calculated calcium oxalate supersaturation compared with lemonade.

Lemonade therapy may be used as adjunctive treatment in patients who do not comply with or cannot tolerate alkali therapy. However, we advise caution about recommending citrus products, as they can increase oxalate excretion.

Pharmacotherapy includes alkali therapy. Barcelo et al48 compared the effects of potassium citrate and placebo in 57 patients with calcium oxalate stones and hypocitraturia. Patients treated with potassium citrate had a rate of stone formation of 0.1 event per patient per year, compared with 1.1 in the placebo group.

Many forms of alkaline citrate are available. Potassium citrate is preferred over sodium citrate since the latter may increase urine calcium excretion.49 Treatment is usually started at 30 mEq/day and is titrated to a maximal dose of 60 mEq/day for a urinary citrate excretion greater than 500 mg/day.

Common side effects are abdominal bloating and hyperkalemia (especially with renal insufficiency), and in such cases sodium-based alkali, sodium citrate, or sodium bicarbonate can be prescribed.

PREVENTING CALCIUM PHOSPHATE STONES

Risk factors for calcium phosphate stones are similar to those for calcium oxalate stones (other than hyperoxaluria), but calcium phosphate stones are formed in alkaline urine (usually urine pH > 6.0), often the result of distal renal tubular acidosis. Preventive measures are similar to those for calcium oxalate stones.

Alkali therapy should be used with caution because of its effect on urinary pH and the risk of precipitation of calcium phosphate crystals.50 Use of potassium citrate was found to be associated with increases in both urinary citrate excretion and calcium phosphate supersaturation in hypercalciuric stone-forming rats.51 It is therefore challenging to manage patients with calcium phosphate stones and hypocitraturia. Alkali administration in this setting may diminish the formation of new stones by correcting hypocitraturia, but at the same time it may increase the likelihood of calcium phosphate stone formation by increasing the urinary pH. When the urine pH increases to above 6.5 with no significant change in urine citrate or urine calcium excretion, we recommend stopping alkali therapy.
Preventing Uric Acid Stones

Clinical conditions associated with uric acid stones include metabolic syndrome, diabetes mellitus, gout, chronic diarrheal illness, and conditions that increase tissue turnover and uric acid production, such as malignancies. Other risk factors for uric acid stone formation are low urine volume, low uric pH, and hyperuricosuria.

Abnormally acidic urine is the most common risk factor. Metabolic syndrome and diabetes mellitus reduce ammonia production, resulting in a lower urinary pH, which predisposes to uric acid stone formation. Chronic diarrhea also acidifies the urine by loss of bicarbonate. Similarly, in gout, the predisposing factor in uric acid stone formation is the persistently acidic urine due to impaired ammonium excretion. Uric acid precipitates to form uric acid stones in a low urinary pH even with normal excretion rates of 600 to 800 mg/day and a urinary volume of 1 to 1.5 L.

Therefore, apart from increasing fluid intake, urinary alkalization is the cornerstone of management of uric acid stones. Potassium citrate is the preferred alkali salt and is started at a dose of 30 mEq/day for a goal urinary pH of 6 to 6.5.

Patients with hyperuricosuria are also advised to restrict their protein intake to no more than 0.8 to 1 mg/kg/day.

If the above measures fail, patients are treated with a xanthine oxidase inhibitor, ie, allopurinol or febuxostat, even if their uric acid excretion is normal.

Preventing Struvite Stones

Struvite stones contain magnesium ammonium phosphate and are due to chronic upper urinary tract infection with urea-splitting bacteria such as Proteus, Klebsiella, Pseudomonas, and enterococci. Urea hydrolysis releases hydroxyl ions, resulting in alkaline urine that promotes struvite stone formation. Early detection and treatment are important, since struvite stones are associated with morbidity and rapid progression.

Medical treatment of struvite stones is usually unsuccessful, and the patient is referred to a urologist for surgical removal of the stones, the gold standard treatment. Long-term use of culture-specific antibiotics to prevent new stone growth is not well studied. Medical therapy by itself is preferred in patients who refuse stone removal or cannot tolerate it. Urease inhibitors such as acetohydroxamic acid have been successful in preventing or slowing stone growth, but their use is limited by frequent side effects such as nausea, headache, rash, and thrombophlebitis.

Preventing Cystine Stones

Cystine stones occur in people with inherited defects of renal tubular and intestinal transport of cysteine and dibasic amino acids that cause excessive excretion of urinary cystine, ie, 480 to 3,600 mg/day.

Cystine is formed from two cysteine molecules linked by a disulfide bond. The solubility of cystine is pH-dependent, with increased solubility at higher urinary pH. The goal is to maintain a urinary cystine concentration below its solubility level by keeping the cystine concentration below 243 mg/L and the urine cystine supersaturation (the ratio of the urine cystine concentration to the cystine solubility in the same sample) less than 0.6.

Therapy is aimed at increasing daily urinary volume to 3 L and urine alkalization to pH above 7, in order to increase cystine solubility by 300%.

Overnight dehydration should be prevented, and patients should be encouraged to wake up at least once a night to void and drink additional water. Sodium restriction to 100 mmol/day (2,300 mg/day) and moderate protein restriction to 0.8 to 1 g/kg/day are associated with decreased cystine excretion, but long-term studies demonstrating their benefit in preventing cystine stones are lacking.

A thiol-containing drug, eg, D-penicillamine (0.5–2 g/day) or tiopronin (400–1,200 mg/day), should be added to the conservative measures if they have not been effective for 3 months or if there is history of noncompliance. Thiol-containing drugs have a sulfhydryl group that reduces the disulfide bond, and they form soluble disulfide cysteine-drug complexes with greater ability to solubilize cystine in alkaline urine. They must always be used in conjunction with fluid and alkali therapy.

Both drugs have severe and common adverse effects including leukopenia, aplastic anemia,
fever, rash, arthritis, hepatotoxicity, pyridoxine deficiency, and proteinuria (membranous nephropathy). However, tiopronin seems to have a lesser incidence of side effects.\textsuperscript{62} Regular monitoring of complete blood cell counts, liver enzymes, and urine protein should be done.

Captopril contains a sulfhydryl group, and the captopril-cysteine disulfide is more soluble than cysteine alone. The amount of captopril that appears in the urine is low, and doses of 150 mg/day are usually required to reduce cysteine excretion, which can lead to hypotension. The efficacy of captopril in treating cystine stones is unproven, and this drug is used only if patients cannot tolerate other thiol-containing drugs.\textsuperscript{63}

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\textbf{REFERENCES}


