Renal Stone Disease: Causes, Evaluation and Medical Treatment

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ABSTRACT

The purpose of the present review is to provide an update about the most common risk factors or medical conditions associated with renal stone formation, the current methods available for metabolic investigation, dietary recommendations and medical treatment. Laboratory investigation of hypercalciuria, hyperuricosuria, hyperoxaluria, cystinuria, hypocitraturia, renal tubular acidosis, urinary tract infection and reduction of urinary volume is based on the results of 24-hr urine collection and a spot urine for urinary sediment, culture and pH. Blood analysis for creatinine, calcium and uric acid must be obtained. Bone mineral density has to be determined mainly among hypercalciurics and primary hyperparathyroidism has to be ruled out. Current knowledge does not support calcium restriction recommendation because it can lead to secondary hyperoxaluria and bone demineralization. Reduction of animal protein and salt intake, higher fluid intake and potassium consumption should be implemented. Medical treatments involve the use of thiazides, allopurinol, potassium citrate or other drugs according to the metabolic disturbances. The correction of those metabolic abnormalities is the basic tool for prevention or reduction of recurrent stone formation. (Arq Bras Endocrinol Metab 2006;50/4:823-831)

Keywords: Kidney stones; Nephrolithiasis; Hypercalciuria; Osteopenia; Calcium; Oxalate

RESUMO

Calculose Renal: Causas, Avaliação e Tratamento Médico.

O propósito desta revisão é apresentar uma atualização sobre os fatores de risco ou condições médicas comuns associadas à formação de cálculos renais, os métodos atualmente disponíveis para investigação metabólica, recomendações dietéticas e tratamento médico. A investigação laboratorial para hipercalciúria, hiperuricosúria, hiperoxalúria, cistinúria, hypocitraturia, acidose tubular renal, infecção do trato urinário e redução do volume urinário, é baseada nos resultados das coleções de urina de 24h e amostra isolada para sedimento urinário, cultura e pH. Deve-se obter análises sanguíneas para creatinina, cálcio e ácido úrico. Deve-se determinar a densidade mineral óssea especialmente entre pacientes hypercalciúricos, e o hipoparatiroidismo primário deve ser excluído. O conhecimento atual não endossa as recomendações de restrição de cálcio, já que isto pode levar o hiperoxalúria secundária e desmineralização óssea. Redução da ingestão de proteína animal e de sal deve ser implementada junto com aumento da ingesta de líquidos e do consumo de potássio. Tratamento medicamentoso envolve o uso de tiazídicos, allopurinol, citrato de potássio ou outras drogas, conforme o distúrbio metabólico. A correção dessas anomalias metabólicas é o instrumento básico para a prevenção ou redução da formação recorrente de cálculos. (Arq Bras Endocrinol Metab 2006;50/4:823-831)

Descritores: Cálculos renais; Nefrolitíase; Hipercalciúria; Osteopenia; Cálcio; Oxalato

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Nephrolithiasis is a common clinical disorder affecting up to 5% of the general population in the USA. (1). The prevalence of renal stone disease has been rising in both sexes, being estimated that about 5% of American women and 12% of men will develop a kidney stone at some time in their life (2). Nevertheless, in certain areas of the world, as in the Middle East, the lifetime risk appears to be even higher (3). There has been heightened awareness of renal stone disease in children as well (4). Recurrence rates of 50% after 10 years and 75% after 20 years have been reported (5,6).

Clinical manifestations are characterized by lumbar pain of sudden onset (the location of pain depends on the location of stone in the urinary tract) that may be accompanied by nausea and vomiting, gross or microscopic hematuria. Diagnosis of renal stone in the acute setting is beyond the scope of the present update but in brief, is represented by urinalysis and imaging. Urinalysis often reveals hematuria but the latter is absent in approximately 9% of cases (7). Crystalluria is occasional and the presence of leucocyturia may suggest associated urinary tract infection. Unenhanced helical computed tomography (CT) scan, the most sensitive and specific radiographic test (8,9), is becoming the diagnostic procedure of choice to confirm the presence of kidney and especially of ureteral stones (10). However, high doses of radiation and elevated costs must be considered (11). Since renal ultrasound (US) provides information about obstruction (12) but may miss ureteral stones, the association of US with conventional abdominal X-ray may help (13). R enal colic must be differentiated from musculoskeletal pain, herpes zoster, pyelonephritis, appendicitis, diverticulitis, acute cholecystitis, gynecologic disease, ureteral stricture or obstruction due to blood clot, polycystic kidney disease.

Stone formation usually results from an imbalance between factors that promote urinary crystallization, and those that inhibit crystal formation and growth (14). The main determinants of calcium oxalate (CaOx) supersaturation are oxalate and calcium concentration, while the latter associated to urinary pH determines calcium phosphate supersaturation. Urinary pH itself is the main determinant of uric acid supersaturation (14).

**CAUSES**

Approximately 80% of kidney stones contain calcium, and the majority of them are composed primarily of calcium oxalate. Although most calcium oxalate stones contain some calcium phosphate, only 5% have hydroxyapatite or brushite as their main constituent and 10% contain some uric acid (15). Pure uric acid, cystine and infection stones are less common. Although composition of each stone correlates with supersaturation values in the urine (16), calculi are seldom found without an admixture of many salts and not every passed stone can be retrieved for chemical analysis. In addition, patients may present multiple stones and in case of persistence of small and nonobstructive calculi after spontaneous elimination or surgical removal, the calculi might not present exactly the same admixture as the voided or removed ones. Since the prevention is aimed to avert new stone formation and further growth of the remaining calculi, evaluation of patients should be rather directed toward identifying urinary risk factors for stone formation or recurrence with the goal of devising appropriate, individualized therapy. Table 1 lists the most common causes of renal stone disease. A more detailed view of the pathogenesis mechanisms involved in stone formation is provided in two in-depth reviews, which have recently been published (2,14).

Evaluation of a renal stone patient starts with a detailed history focusing on occupation, dietary and lifestyle habits, previous use of medications, family predisposition, and history of recurrent urinary tract infection and underlying disorders that predisposes to nephrolithiasis. Incidental finding of asymptomatic stones on a radiograph/ ultra-sound may also occur. The majority of calcium oxalate stone forms (SF) suffers from no systemic disease and can be described as idiopathic calcium oxalate SF patients. Metabolic abnormalities responsible for stone recurrence are currently identified in up to 90% of such patients (17) and will be the focus of the present review.

**METABOLIC EVALUATION**

A complete or comprehensive urinary metabolic profile to guide prophylaxis of stone recurrence, consisting of two 24-hr urine samples for stone risk analysis as well as an oral calcium load test has been advocated lately to be time-consuming and expensive (18). In a very recent cost-effectiveness analysis of medical management strategies for nephrolithiasis by the group of Pak and his associates (19), such comprehensive or detailed metabolic evaluation offered no advantage in cost or efficacy over a simple metabolic evaluation (single 24-hr urine collection) with respect to treatment of recurrent stone formers. Therefore, a simple metabolic evaluation con-
sisting of a single 24-hour urine collection for analysis of all urinary stone risk factors may be sufficient (20) for a medical evaluation of urolithiasis. On the other hand, Parks et al. (21) and others (22) reported that only one 24-hour urine specimen may lead to misdiagnosis of common metabolic disturbances.

The routine laboratory investigation among urolithiasis patients includes the determination of urinary parameters involved in stone formation such as urinary calcium, oxalate, magnesium, citrate, uric acid, sodium, potassium and creatinine (23). Spot urine for urinary sediment and culture to rule out urinary tract infection are also part of the investigation. Urinary pH must be determined in a 12-hr fasting sample and a venous blood gas analysis must be obtained to screen for complete forms of distal Renal Tubular Acidosis. When systemic acidosis is not present, an ammonium chloride test is needed (24). A blood sample must be obtained for serum creatinine, calcium (total or ionized), phosphate and uric acid determinations. Bone mineral density has to be assessed mainly among idiopathic hypercalciuria patients, due to the important association of urinary calcium losses with low bone mineral density (25,26). Since primary hyperparathyroidism has to be ruled out, serum PTH can be determined either in the same single blood collection or in a further sample in case hypercalcemia has been detected in the former, in order to reduce costs. However, intermittent high levels of serum calcium may represent mild forms of subtle primary hyperparathyroidism (27). A qualitative colorimetric test in spot urine samples to evidence the presence of high amounts of cystine with sodium nitroprussiate can serve as a screening method for cystinuria.

**Idiopathic hypercalciuria**

It is generally agreed that the oversaturation of urine with calcium is one of the most important risk factors for calcium nephrolithiasis. Primary hyperparathyroidism, the most common primary cause of resorptive hypercalciuria, hence hypercalcemic, is present in less than 1% of nephrolithiasis patients (28) and will be discussed in detail in another chapter in this issue. Conversely, idiopathic hypercalciuria (29) represents the primary metabolic alteration in almost 50% of patients (17). Idiopathic hypercalciuria (IH) is defined by levels of urinary calcium excretion in a 24-hour urine sample exceeding 300 mg/day (7.5 mmol/L) in men or 250 mg/day (6.25 mmol/L) in women or higher than 4 mg (0.1 mmol/L) per kilogram of body weight per day, regardless of gender and age, in the absence of hypercalcemia (14,30). However, levels around 200 mg/day or higher than 150 mg per gram of urinary creatinine can also increase supersaturation in patients with recurrent stones (28). The increased daily urinary excretion rate of calcium among patients with kidney stones was first recognized by Flocks in 1939 (31) and subsequently in 1953, Albright et al. (32) introduced the term Idiopathic Hypercalciuria (IH) to distinguish a group of calcium stone formers (CSF) who exhibited hypercalciuria without hypercalcemia, and did not have a history of excessive vitamin D use, primary hyperparathyroidism, hyperthyroidism, renal tubular acidosis, sarcosidosis, other granulomas or malignancy.

An acute oral calcium load test, described in 1975 by Pak et al. (33), should clearly distinguish between absorptive and renal (renal calcium leak) subtypes of hypercalciuria. In a previous evaluation by our group (34), a 24-hr urinary calcium excretion, under
conditions of a mean usual calcium intake of around 500 mg/day, was determined in CSF patients who previously presented an absorptive or renal response to this test. We observed that the majority of them, 63 and 78% of each group, presented normocalciuria rather than hypercalciuria. Since this apparently normal calcium excretion might have resulted from a combination of high calcium absorption and low calcium intake, those patients where then challenged to a higher calcium intake of 1,500 mg/day given as supplement for one week. Regardless of whether there was a former absorptive or renal-like response to the acute load, the higher calcium intake disclosed the presence of subpopulations sensitive to calcium intake in previously normocalciuric patients. Conversely, most of the hypercalciuric patients, when challenged to a higher calcium intake did not present a further increase in their urinary calcium, showing that under conditions of low calcium intake, as is the case of the Brazilian population (35), patients were already excreting calcium in excess of their intake, hence being considered as dietary calcium-independent. In addition, as the morning urinary fasting calcium/creatinine (Ca/Cr) ratio seemed to be the single parameter which would distinguish between renal and absorptive hypercalciuric patients, with a cutoff value of 0.11, we repeated this determination in 31 patients (34) and found that 87% of them changed their results from values higher than 0.11 to lower values. Taken together, these data suggest that Absorptive and Renal Hypercalciuria should be considered the same rather than two distinct entities, a hypothesis already raised by Coe et al. (36) representing a systemic abnormality of calcium homeostasis probably induced by a dysregulation of 1,25(OH)2D3, leading to alterations in calcium transport in the intestine, kidney and bone (28,37) characterized by increased intestinal calcium absorption and bone resorption, as well as decreased renal tubular calcium reabsorption.

Several series in the literature (38-46), including the one from our group (47), have demonstrated that BMD is reduced in IH patients. Some of them have reported increase of bone resorption markers as well (39,40,42,45,46). A histomorphometric study undertaken by our group in 1994 (47) disclosed a low bone volume, a tendency of low bone formation coupled with increased bone resorption and delayed bone mineralization in male hypercalciuric CSF patients. Other bone biopsy reports showed conflicting data regarding bone resorption, but all of them have suggested low bone formation and a severe mineralization defect in hypercalciuric patients (47-50). The underlying mechanisms responsible for higher bone resorption and/or lower bone formation in this setting are still unclear and the reasons for the mineralization defect remain unknown if one considers that serum levels of calcium, phosphorus and vitamin D are normal in these patients. Anyway, a population-based study has shown a fourfold increase in vertebral fracture risk among urolithiasis patients when compared to the general population (51), and in a large cross-sectional survey (Third National Health and Nutrition Examination Survey, NHANES III), a history of kidney stone was found to be associated with lower femoral neck BMD and more prevalent wrist and spine fractures in men after adjustments for age and body mass index (52).

Whether idiopathic hypercalciuria is the result of a primary bone disorder, a consequence of a persisting negative calcium balance or a combination of both still remains to be determined. Nevertheless, bone status must be evaluated and followed up in patients with IH.

Hyperuricosuria and uric acid nephrolithiasis

Hyperuricosuria is defined by uric acid excretion above 750 and 800 mg/day for women and men, respectively. Its prevalence is highly variable among different series. Hyperuricosuria may be secondary to uricosuric medications, myeloproliferative disorders, primary gout or congenital disorders. A high animal protein (especially purines) may increase uric acid excretion and decrease urine pH. Uric acid supersaturation is strongly controlled by urinary pH. Diarrheas states may predispose to uric acid nephrolithiasis due to low urine volume and urinary pH. Uric acid may provide heterogeneous nuclei for calcium oxalate stone formation. The lower frequency of pure uric acid stones, around 5%, may be ascribed to the usual urine acidity, which favors calcium oxalate crystallization instead. However, recent findings provided by metabolic studies have indicated an association between pure uric acid nephrolithiasis and insulin resistance (53,54). Those patients present abdominal obesity, dyslipidemia, arterial hypertension, elevated fasting glucose levels and lower glucose disposal rate, hyperuricemia, normouricosuria, and low urinary pH (53). The latter may explain stone formation despite of normouricosuria. Potential mechanisms include impaired ammoniagenesis caused by resistance to insulin action in proximal tubule or substrate competition by free fatty acids (54).

Hypocitraturia

Low urinary citrate levels below 320 mg/day, hypocitraturia, occur in approximately 50% of adult SF.
patients (17), isolated or associated with other metabolic disturbances. Hypocitraturia may result from distal renal tubular acidosis, chronic diarrheal syndrome, hypokalemia, urinary tract infection, but mostly it is of unknown etiology, namely idiopathic hypocitraturia. Citrate binds calcium in a soluble salt inhibiting crystallization and slowing stone formation.

**Hyperoxaluria**

Hyperoxaluria can be due to an enzymatic disturbance in oxalate biosynthesis but primary hyperoxaluria type I, the prevailing type, is a rare genetic disorder. Most cases of increased urinary oxalate found in CSF patients are represented by secondary or mild hyperoxaluria, defined by levels of urinary oxalate higher than 45 mg/day, with a reported frequency of around 12%. Secondary hyperoxaluria is due to either increased availability of substrate (ascorbic acid, ethylene glycol, methoxyflurane), reduced degradation of oxalate by intestinal bacteria or intestinal hyperabsorption of oxalate (imbalance between intraluminal calcium and oxalate as in enteric hyperoxaluria or due to a low-calcium diet). Enteric hyperoxaluria induced by fat and bile salt malabsorption is the hallmark of hyperoxaluria due to intestinal hyperabsorption of oxalate (55). The gastrointestinal diseases that have been associated with this entity are those characterized by an absence or nonfunctioning of the small bowel (enteritis, small bowel resection or bypass surgery) and those causing defective absorption of fat or bile acids (chronic pancreatitis, biliary cirrhosis, blind loop syndrome and other diseases). Unabsorbed bile acids and fatty acids form complexes with calcium in the intestinal lumen, limiting the amount of free calcium to bind oxalate, with a consequent increase in intestinal oxalate absorption leading to hyperoxaluria. Dietary calcium restriction may lead to hyperoxaluria through the same mechanism (56).

Other pathophysiological conditions occurring alone in less than 2% of SF patients include distal Renal Tubular Acidosis, Infection Stones and Cystinuria (17).

**Infection stones**

Infection stones form in the setting of upper urinary tract infection with urease-producing bacteria. Those microorganisms hydrolyze urea producing ammonia and hydroxide, increasing urinary pH and phosphate that bind to magnesium to form a "triple-crystal" composed of struvite (magnesium ammonium phosphate) and/or calcium carbonate apatite. Those calculi usually grow as branched stones that occupy a large portion of the collecting system, namely, staghorn calculi.

**Cystinuria**

Cystinuria is a rare autosomic recessive disorder characterized by reduced renal tubular reabsorption of the dibasic aminoacids cystine, ornithine, lysine and arginine (58). Overexcretion of cystine leads to stone formation because its solubility in the urine is very low under normal urine pH.

**TREATMENT**

**Dietary recommendations**

In the past, calcium restriction became a very popular recommendation, based on the high incidence of hypercalciuria. However, a large prospective epidemiological study conducted in healthy men with different levels of calcium intake led to a surprising observation that the lower was the calcium intake, the higher was the incidence of stone formation (59). Such unexpected effect had probably been ascribed to a secondary increase in urinary oxalate due to the decrease binding of oxalate to calcium in the gastrointestinal tract. In 2002, a five-year randomized trial comparing the effect of two diets in hypercalciuric men with recurrent calcium oxalate stones and hypercalciuria, showed that a restricted intake of animal protein and salt, combined with a normal calcium intake, provided greater protection than the traditional low-calcium diet (60). Therefore, there are many reasons why calcium restriction should be avoided in hypercalciuric patients: lack of a clear distinction between absorptive and renal hypercalciuria, induction of secondary hyperoxaluria, predisposition to bone loss due to a negative calcium balance and also because other nutrients like protein, sodium, oxalate and potassium could affect calcium excretion as well (61). With respect to oxalate intake, there have been no studies demonstrating that restrictions in oxalate intake effectively reduce the recurrence of stones. The ability of oxalate-rich foods to augment oxalate excretion depends not only on the oxalate
content but also on its bioavailability, solubility and salt form. Finally, the effect of dietary oxalate on urine oxalate critically depends upon calcium intake since decreasing calcium load in the intestinal lumen will increase the concentration of free oxalate anions available for absorption (56), as mentioned above. In a previous evaluation of our group (62), a 2-fold increase in oxalate intake produced a significant 20% increase in oxaluria not observed when Ca was consumed simultaneously. Therefore, calcium and oxalate must be maintained in balance during meals. As urinary oxalate is also derived from the breakdown of ascorbic acid, the use of vitamin C supplementation poses some threat to calcium oxalate SF patients. We have observed a significant increase in mean urinary oxalate in SF patients receiving either 1 g or 2 g of supplement (63). The nutrient that clearly has universal effects on most of the urinary parameters involved in stone formation is protein. High protein intake of animal origin, especially red meat, contributes to hyperuricosuria (purine overload), hyperoxaluria (higher oxalate synthesis), hypocitraturia (higher citrate tubular reabsorption) and hypercalciuria (higher bone resorption; lower tubular calcium reabsorption to buffer the acid load provided by meat; elevated calcium filtered load; nonreabsorbable calcium salts). Moderate protein restriction is able to reduce urinary oxalate, phosphate, hydroxyproline, calcium, and uric acid and to increase citrate excretion, as reported (60). The effect of sodium chloride (NaCl) intake on increasing calcium excretion is well established. Every 100 mmol increase in dietary sodium results approximately in a 25 mg rise in urinary calcium. The adverse effects of a high salt intake also contribute to bone loss. In a previous evaluation by our group (64), a multiple regression analysis has suggested that a high NaCl intake (≥ 16 g/ day) was the single variable that was predictive of risk of low bone mineral density in 85 CSF patients (odds ratio: 3.8) after adjustments for age, weight, body mass index, duration of stone disease, calcium and protein intakes and urinary calcium citrate and uric acid. Low potassium intake may increase the relative risk for stone formation (59) due to an increase in urinary calcium and a decrease in urinary citrate.

Table 2 summarizes the general dietary recommendations for SF patients. Whenever possible, they should be tailored to the specific underlying metabolic disturbance and also to the individual dietary habit, to ensure compliance.

**DRUG TREATMENT**

**Thiazide diuretics**

Thiazide lowers urine calcium resulting in a fall in calcium oxalate and calcium phosphate supersaturation. Reduction of calcium is attributed to enhanced reabsorption of calcium on the renal distal convolute tubule but very recent and compelling data show that enhanced passive Ca²⁺ transport in the proximal tubule rather than active Ca²⁺ transport in distal convolution explains thiazide-induced hypocalciuria (65). Doses of either chlorthalidone or hydrochlorothiazide should be no more than 25 mg/ day to avoid adverse effects.

**Allopurinol**

Allopurinol blocks uric acid production, reducing heterogeneous nucleation of calcium oxalate by both uric acid and monosodium urate. In addition, the adsorption of normally occurring macromolecular inhibitors of calcium oxalate crystallization by uric acid or monosodium urate could be possibly averted when using this drug. However, Allopurinol (100 to 300 mg/ day) is indicated only when hyperuricosuria is the only metabolic abnormality. On the other hand, alkali therapy with potassium citrate may also be beneficial, since raising urinary pH will help solubilizing uric acid converting it into potassium urate.

**Potassium citrate**

Potassium citrate reduces urinary saturation of calcium salts by complexing calcium and reducing ionic calcium concentration. Due to its alkalinizing effect, it also increases the dissociation of uric acid, lowers the amount of poorly soluble undissociated uric acid, reducing the propensity to form uric acid stones. The induced decline of urinary calcium during the early period of treatment represents a potential additional

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**Table 2.** Dietary recommendations in renal stone disease.

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<th>Recommendation</th>
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<td>Adequate dietary calcium intake (calcium and oxalate intakes must be in balance)</td>
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<tr>
<td>Reduce animal protein intake</td>
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<tr>
<td>Reduce salt intake</td>
</tr>
<tr>
<td>Increase fruits and vegetables intake (rich in potassium)</td>
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<tr>
<td>Increase fluid intake (at least &gt;2L/day)</td>
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advantage of the drug. Therefore, potassium citrate seems to be effective in conditions of hypocitraturia, hypercalciuria, or hyperuricosuria and also in distal RTA patients, due to the need of alkalinization in the latter. Potassium citrate is preferable to sodium citrate in the prevention of urolithiasis, in doses ranging from 30 to 60 mEq/day. However, adverse effects of gastrointestinal origin including epigastric pain, abdominal distention or diarrhea are common. Promising results with the use of other citrate salts such as potassium-magnesium, not yet approved by the Food and Drug Administration, have also been shown.

**Other therapeutic agents**

Potassium-acid phosphate and magnesium hydroxide were shown to have little or no effect on prevention of stone formation. A neutral potassium phosphate preparation was shown to be better than placebo in reducing calcium excretion and raising urinary inhibitors of stone formation, hence inhibiting CaOx crystal agglomeration and spontaneous nucleation on brushite. Pak et al. (18) also suggested a nonselective therapy, based on evidences from some of the pharmacological trials, about the beneficial and protective effects of drugs in stone recurrence rates observed in patients not categorized according to different urinary derangements hence not being influenced by the baseline urinary chemistry. Overall, potassium citrate represents the most suitable drug for such unselective treatment because of its indications for hypocitraturic, hypercalciuric, hyperuricosuric and dRTA patients. On the other hand, identification of abnormal risk factors for urinary stones is still important to rule out secondary causes of nephrolithiasis, such as cystinuria, hyperoxaluria, renal tubular acidosis and infection stones (18). Among all of these examples, cystinuria, the rarest, represents the single entity for which an actual specific therapy with cystine-binding thiol drugs to solubilize cystine (alphamercaptopropionylglycine or tiopronin, d-penicillamine or angiotensin converting enzyme inhibitor) would be warranted, despite the need for a vigorous increase in the amount of fluid intake and alkalinizing therapy with potassium citrate as well. Treatment of primary hyperoxaluria consists of pyridoxine, which facilitates the conversion of glyoxylate to glycine. In cases of mild, non-genetic secondary hyperoxaluria, in addition to dietary manipulation, there have been new therapeutic perspectives concerning the use of intestinal colonization with the oxalate-degrading bacteria Oxalobacter formigenes or other lactic-acid bacteria (66). The single contraindication for potassium citrate would be urinary tract infection because of the alkalinizing properties of the compound. Antibiotics should rather be prescribed in such cases. Complete removal of struvite infection stones (staghorn calculi) is an important goal to eradicate causative organisms, relieve obstruction, prevent further stone growth and associated infection and preserve kidney function. The use of acetohydroxamic acid, a bacterial urease inhibitor, may help to reduce struvite calculi growth but the prevalence of adverse reactions is very high. The treatment of Primary Hyperparathyroidism is surgical.

Table 3 lists the most common pharmacological agents prescribed according to the metabolic disturbance as discussed earlier. The results of the majority of clinical trials about medical treatment are summarized in recent update articles (2,14,61). A reconsideration of the 1988 National Institute of Health (NIH) Consensus Statement on prevention and treatment of kidney stones had been well covered elsewhere (66).

**REFERENCES**


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