Renal Stone Disease: Causes, Evaluation and Medical Treatment

review article

Ita Pfeferman Heilberg
Nestor Schor

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

Division of Nephrology, Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil.

RESUMO

Calculose Renal: Causas, Avaliação e Tratamento Médico.
O propósito desta revisão é apresentar uma atualização sobre os fatores de risco ou condições médica comuns associadas com a formação de cálculos renais, os métodos atualmente disponíveis para investigação metabólica, recomendações dietéticas e tratamento médico. A investigação laboratorial para hipercalciúria, hiperuricosuria, hiperoxalúria, cistinúria, hipocitratúria, 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 hipercalciúricos, e o hiperparatiroidismo primário deve ser excluído. O conhecimento atual não endossa as recomendações de restrição de cálcio, já que isto pode levar o hiperaxalúria secundária e desmineralização óssea. Redução da ingesta 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, alopurinol, citrato de potássio ou outras drogas, conforme o distúrbio metabólico. A correção dessas anormalidades 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

Received in 04/14/06
Accepted in 04/19/06

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). Renal 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 unobstructive 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 formers (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-

Table 1. Risk factors for stone formation.

- Anatomic abnormalities: medullary sponge kidney, ureteropelvic junction stenosis, pyelo-ureteral duplication, polycystic renal disease, etc.
- Epidemiological factors and genetic predisposition: dietary risk factors, climate, occupation, family history of stones.
- Excessive excretion of promoters of urinary crystallization: calcium (idiopathic hypercalciuria), oxalate (enteric hyperoxaluria), uric acid (uric acid hyperexcretion).
- Abnormalities of urinary pH: renal tubular acidosis, gouty diathesis, infection stones (struvite stones caused by urea-splitting organisms).
- Reduced excretion of inhibitors of urinary crystallization: hypocitraturia.
- Metabolic syndrome and obesity: pure uric acid stones.
- Low urine volume: reduced intake or increased loss of water.
- Hypercalcemic disorders: primary hyperparathyroidism and other disturbances of calcium metabolism.
- Lithogenic drugs: triamterene, indinavir, sulfadiazine, uricosuric agents.
- Genetic monogenic diseases: primary hyperoxaluria, cystinuria, familial hiperuricosuria, monogenic hypercalciuric stone-forming diseases (X-linked recessive hypercalciuric diseases complex, familial hypomagnesemia with hypercalciuria and nephrocalcinosis, Bartter syndrome types III and IV, autosomal dominant hypocalcemic hypercalciuria, hypophosphatemia associated to hypercalciuria, etc.
- Inflammatory bowel disease and other intestinal malabsorption states.

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 laboratorial 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) in men or 250 mg/day (6.25 mmoL) in women or higher than 4 mg (0.1 mmoL) 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 $1,25(OH)_2D_3$, 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 urinary 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).

Distal Renal Tubular Acidosis (dRTA)

dRTA is characterized by alkaline fasting urine pH associated to hypercloremic hypokalemic metabolic acidosis, hypocitraturia, hypercalciuria and often bone disease (24). Acquired forms may be secondary to different tubulo-interstitial renal diseases, calcium disorders, drugs and toxins, autoimmune diseases (especially Sjögren syndrome), among others. Hereditary forms are mostly associated with nephrocalcinosis (57).

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 lead 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 calciuria is attributed to enhanced reabsorption of calcium on the renal distal convolute tubule but very recent and compelling data show that enhanced passive Ca^{2+} transport in the proximal tubule rather than active Ca^{2+} 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. Indapamide, a thiazide-like agent is also effective.

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

Table 2. Dietary recommendations in renal stone disease.

Adequate dietary calcium intake (calcium and oxalate intakes must be in balance)
Reduce animal protein intake
Reduce salt intake
Increase fruits and vegetables intake (rich in potassium)
Increase fluid intake (at least > 2L/day)

Table 3. Pharmacological treatment of nephrolithiasis according to Metabolic Disturbance.

Hypercalciuria	Hydrochlorthiazide /Chlortalidone/Indapamide (potassium citrate may be added)
Hypocitraturia	Potassium citrate
Hyperuricosuria	Allopurinol or Potassium citrate
Hyperoxaluria (primary)	Pyridoxine
Cystinuria	Alphamercaptoproprionylglycine (tiopronin) or d-penicillamine or angiotensin converting enzyme inhibitor
Distal Renal Tubular Acidosis	Potassium citrate
Low urinary pH	Potassium citrate
Urinary tract infection	Antibiotics

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 mE/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 (*alphamercaptoproprionylglycine* or *tiopronin, d-penicillamine* or *angiotensin converting enzyme inhibitors*) 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

1. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. **Kidney Int 2003**;63(5):1817-23.
2. Moe OW. Kidney stones: Pathophysiology and medical management. **Lancet 2006**;367:333-44.
3. Pak CYC, Resnick MI, Preminger GM. Ethnic and geographic diversity of stone disease. **Urology 1997**; 50(4):504-7.

4. Heilberg IP, Boim MA, Schor N. Biochemical differences between stone formers and normal subjects. In: Segura J, Conort P, Khoury S, Pak C, Preminger GM, Tolley D (eds). **Stone Disease (1st International Consultation on Stone Disease)**. Editions 21. France: Health Publications, **2003**; pp. 61-4.

5. Trinchieri A, Ostini F, Nespoli R, Rovera F, Montanari E, Zanetti G. A prospective study of recurrence rate and risk factors for recurrence after a first renal stone. **J Urol 1999**;162(1):27-30.

6. Sutherland JW, Parks JH, Coe FL. Recurrence after a single renal stone in a community practice. **Miner Electrolyte Metab 1985**;11(4):267-9.

7. Li J, Kennedy D, Levine M, Kumar A, Mullen J. Absent hematuria and expensive computerized tomography: case characteristics of emergency urolithiasis. **J Urol 2001**;165(3):782-4.

8. Abramson S, Walders N, Applegate KE, Gilkeson RC, Robbin MR. Impact in the emergency department of unenhanced CT on diagnostic confidence and therapeutic efficacy in patients with suspected renal colic: a prospective survey. **Am J Roentgenol 2000**;175:1689-95.

9. Shokeir AA, Abdulmaaboud M. Prospective comparison of nonenhanced helical computerized tomography and doppler ultrasonography for the diagnosis of renal colic. **J Urol 2001**;165:1082-4.

10. Teichman JM. Clinical practice. Acute renal colic from ureteral calculus. **N Engl J Med 2004**;50(7):684-93.

11. Grisi G, Satcul F, Cuttin R, Rimondidi A, Meduri A, Dalla Palma L. Cost analysis of different protocols for imaging a patient with acute flank pain. **Eur Radiol 2000**; 10:1620-7.

12. Gandolpho L, Sevillano M, Barbieri A, Ajzen S, Schor N, Ortiz V, et al. Scintigraphy and doppler ultrasonography for the evaluation of obstructive urinary calculi. **Braz J Med Biol Res 2001**;34(6):745-51.

13. Catalano O, Nunziata A, Altei F, Siani A. Suspected ureteral colic: primary helical CT versus selective helical CT after unenhanced radiography and sonography. **Am J Roentgenol 2002**;178:379-86.

14. Coe FL, Evan A, Worcester E. Kidney stone disease. **J Clin Invest 2005**;115:2598-608.

15. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. **N Engl J Med 1992**;327(16):1141-52.

16. Parks JH, Coward M, Coe FL. Correspondence between stone composition and urine supersaturation in nephrolithiasis. **Kidney Int 1997**;51(3):894-900.

17. Levy FL, Adams-Huet B, Pak CY. Ambulatory evaluation of nephrolithiasis: an update of a 1980 protocol. **Am J Med 1995**;98:50-9.

18. Pak CY. Medical prevention of renal stone disease. **Nephron 1999**;81(suppl. 1):60-5.

19. Lotan Y, Cadeddu JA, Roerhborn CG, Pak CY, Pearle MS. Cost effectiveness of medical management strategies for nephrolithiasis. **J Urol 2004**;172:2275-81.

20. 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.

21. Parks JH, Goldfisher E, Asplin JR, Col FL. A single 24-hour urine collection is inadequate for the medical evaluation of nephrolithiasis. **J Urol 2002**;167:1607-12.

22. Yagisawa T, Chandhoke PS, Fan J. Comparison of comprehensive and limited metabolic evaluations in the treatment of patients with recurrent calcium urolithiasis. **J Urol 1999**;161:1449-52.

23. Curhan GC, Willet WC, Speizer FE, Stampfer MJ Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. **Kidney Int 2001**;59:2290.

24. Soriano JR. Renal tubular acidosis: The clinical entity. **J Am Soc Nephrol 2002**;13:2160-70.

25. Vezzoli G, Soldati L, Arcidiacono T, Terranegra A, Biasion R, Russo CR, et al. Urinary calcium is a determinant of bone mineral density in elderly men participating in the InCHIANTI study. **Kidney Int 2005**;67:2006-14.

26. Asplin JR, Bauer KA, Kinder J, Muller G, Coe BJ, Parks JH, et al. Bone mineral density and urine calcium excretion among subjects with and without nephrolithiasis. **Kidney Int 2003**;63:662-9.

27. Gomes SA, Lage A, Lazaretti-Castro M, Vieira JG, Heilberg IP. Response to oral calcium load in nephrolithiasis patients with fluctuating parathyroid hormone and ionized calcium levels. **Braz J Med Biol Res 2004**;37(9):1379-88.

28. Coe FL, Parks JH. **Nephrolithiasis: Pathogenesis and treatment**. 2nd ed. Chicago: Year Book Medical Publishers, **1998**. pp. 109-10.

29. Heilberg IP. Hypercalciuria. In: Martini L (ed). **Encyclopedia of endocrine diseases**. Vol 2. San Diego: Academic Press, **2004**. pp. 530-6.

30. Hodkinson A, Pyrah LN. The urinary excretion of calcium and inorganic phosphate in 344 patients with calcium stone of renal origin. **Br J Surg 1958**;46:10-8.

31. Flocks RH. Calcium and phosphorus excretion in the urine of patients with renal or ureteral calculi. **JAMA 1939**;13:1466-71.

32. Albright F, Henneman P, Benedict PH, Forbes AP. Idiopathic hypercalciuria: A preliminary report. **Proc Roy Soc Med 1953**;46:1077-81.

33. Pak CYC, Kaplan R, Bone H, Townsend J, Waters O. A simple test for the diagnosis of absorptive, resorptive and renal hypercalciuria. **N Engl J Med 1975**;292:497-500.

34. Heilberg IP, Martini LA, Draibe SA, Ajzen H, Ramos OL, Schor N. Sensitivity to calcium intake in calcium stone forming patients. **Nephron 1996**;73:145-53.

35. Martini LA, Heilberg IP, Cuppari L, Medeiros FAM, Draibe SA, Ajzen H, et al. Dietary habits of calcium stone formers. **Braz J Med Biol Res 1993**;26:805-12.

36. Coe FL, Favus MJ, Crockett T, Strauss AL, Parks JH, Porat A, et al. Effects of low calcium diet on urine calcium excretion, parathyroid function and serum 1, 25(OH)2D3 levels in patients with idiopathic hypercalciuria and in normal subjects. **Am J Med 1982**;72:25-32.

37. Frick KK, Bushinsky DA. Molecular mechanisms of primary hypercalciuria. **J Am Soc Nephrol 2003**;14:1082-95.

38. Fuss M, Gillet C, Simon J, Vandewalle JC, Schoutens A, Bergmann P. Bone mineral content in idiopathic renal stone disease and in primary hyperparathyroidism. **Eur Urol 1983**;9(1):32-4.

39. Pacifici R, Rothstein M, Rifas L, Lau KH, Baylink DJ, Avioli LV, et al. Increased monocyte interleukin-1 activity and decreased vertebral bone density in patients with fasting idiopathic hypercalciuria. **J Clin Endocrinol Metab 1990**;71:138-45.

40. Bataille P, Achard JM, Fournier A, Boudailliez B, Westeel PF, el Esper N, et al. Diet, vitamin D and vertebral mineral density in hypercalciuric calcium stone formers. **Kidney Int 1991**;39:1193-205.

41. Pietschmann F, Breslau NA, Pak CY. Reduced vertebral bone density in hypercalciuric nephrolithiasis. **J Bone Miner Res 1992**;7:1383-8.

42. Jaeger P, Lippuner K, Casez JP, Hess B, Ackermann D, Hug C. Low bone mass in idiopathic renal stone formers: magnitude and significance. **J Bone Miner Res 1994**;9:1525-32.

43. Weisinger JR. New insights into the pathogenesis of idiopathic hypercalciuria: the role of bone. **Kidney Int 1996**;49:1507-18.

44. Ghazali A, Fuentes V, Desaint C, Bataille P, Westeel A, Brazier M, et al. Low bone mineral density and peripheral blood monocyte activation profile in calcium stone formers with idiopathic hypercalciuria. **J Clin Endocrinol Metab 1997**;82:32-8.

45. Giannini S, Nobile M, Sartori L, Calo L, Tasca A, Dalle Carbonare L, et al. Bone density and skeletal metabolism are altered in idiopathic hypercalciuria. **Clin Nephrol 1998**;50(2):94-100.

46. Trinchieri A, Nespoli R, Ostini F, Rovera F, Zanetti G, Pisani E. A study of dietary calcium and other nutrients in idiopathic renal calcium stone formers with low bone mineral content. **J Urol 1998**;159:654-7.

47. Heilberg IP, Martini LA, Szejnfeld VL, Carvalho AB, Draibe SA, Ajzen H, et al. Bone disease in calcium stone forming patients. **Clin Nephrol 1994**;42:175-82.

48. Misael da Silva AM, dos Reis LM, Pereira RC, Futata E, Branco-Martins CT, Noronha IL, et al. Bone involvement in idiopathic hypercalciuria. **Clin Nephrol 2002**;57:183-91.

49. Malluche HH, Tschoepe W, Ritz E, Meyer-Sabellek W, Massry SG. Abnormal bone histology in idiopathic hypercalciuria. **J Clin Endocrinol Metab 1980**;50:654-8.

50. Steiniche T, Mosekilde L, Christensen MS, Melsen F. A histomorphometric determination of iliac bone remodeling in patients with recurrent renal stone formation and idiopathic hypercalciuria. **APMIS 1989**;97:309-16.

51. Melton LJ 3rd, Crowson CS, Khosla S, Wilson DM, O'Fallon WM. Fracture risk among patients with urolithiasis: a population-based cohort study. **Kidney Int 1998**;53:459-64.

52. Lauderdale DS, Thisted RA, Wen M, Favus MJ. Bone mineral density and fracture among prevalent kidney stone cases in the Third National Health and Nutrition Examination Survey. **J Bone Miner Res 2001**;16:1893-8.

53. Abate N, Chandalia M, Cabo-Chan AV Jr, Moe OW, Sakhaee K. The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. **Kidney Int 2004**;65(2):386-92.

54. Maalouf NM, Cameron MA, Moe OW, Sakhaee K. Novel insights into the pathogenesis of uric acid nephrolithiasis. **Curr Opin Nephrol Hypertens 2004**;13(2):181-9.

55. McConnell N, Campbell S, Gillanders I, Rolton H, Danesh B. Risk factors for developing renal stones in inflammatory bowel disease. **BJU Int 2002**;89(9):835-41.

56. Nishiura JL, Mendonça COG, Schor N, Heilberg IP. Effect of calcium intake on urinary oxalate excretion in calcium stone-forming patients. **Braz J Med Biol Res 2002**;35:669-75.

57. Cheidde L, Vieira TC, Lima PR, Saad ST, Heilberg IP. A novel mutation in the anion exchanger 1 gene is associated with familial distal renal tubular acidosis and nephrocalcinosis. **Pediatrics 2003**;112(6 Pt 1):1361-7.

58. Shekarriz B, Stoller ML. Cystinuria and other noncalcareous calculi. **Endocrinol Metab Clin North Am 2002**;31(4):951-77.

59. Curhan GC, Willet WC, Rimm EB, Stampfer MJ. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. **N Engl J Med 1983**;328:833-8.

60. Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. **N Engl J Med 2002**;346(2):77-84.

61. Heilberg IP. Update on dietary recommendations and medical treatment of renal stone disease. **Nephrol Dial Tranplant 2000**;15:117-23.

62. de O G Mendonça C, Martini LA, Baxmann AC, Nishiura JL, Cuppari L, Sigulem DM, et al. Effects of an oxalate load on urinary oxalate excretion in calcium stone formers. **J Ren Nutr 2003**;13(1):39-46.

63. Baxmann AC, de O G Mendonça C, Heilberg IP. Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. **Kidney Int 2003**;63(3):1066-71.

64. Martini LA, Cuppari L, Colugnati FAB, Sigulem DM, Szejnfeld VL, Schor N, et al. High sodium chloride intake is associated with low bone density in calcium stone forming patients. **Clin Nephrol 2000**;54(2):85-93.

65. Nijenhuis T, Vallon V, van der Kemp AW, Loffing J, Hoenderop JG, Bindels RJ. Enhanced passive Ca^{2+} reabsorption and reduced Mg^{2+} channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. **J Clin Invest 2005**;115(6):1651-8.

66. Goldfarb DS. Reconsideration of the 1998 NIH Consensus Statement on prevention and treatment of kidney stones: are the recommendations out of date? **Rev Urol 2002**;4(2):53-60.

Address for correspondence:

Nestor Schor
Nephrology Division
Universidade Federal de São Paulo (UNIFESP)
R. Botucatu 740
04023-900 São Paulo, SP, Brazil.
Fax: (11) 5573-9652
E-mail: nestor@nefro.epm.br