

## METABOLIC EVALUATION OF STONE DISEASE

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### ABSTRACT

Urolithiasis is the third most common disease of the urinary tract after infections and diseases of the prostate. Furthermore, there has been an increasing prevalence of calcium stones in the industrialized countries and between 5% and 15% of the population will develop kidney stones during their lifetime.

Calcium stones (calcium oxalate or phosphate) compose the most common stone type. Other stone compositions include uric acid, struvite (magnesium ammonium phosphate), and other miscellaneous components such as cystine.

Advances in minimally invasive techniques have dramatically changed surgical management of stone disease in the last 2 decades. However, medical management of stone disease along with prevention of recurrent stones represents a less invasive and more cost-effective approach. In this concept, an understanding of the pathophysiology of stone formation is the prerequisite for a cost-effective medical evaluation and management as well as the prevention of recurrences.

Although significant knowledge has been gained regarding pathophysiology of stone disease, this has not translated in a similar dramatic change in the medical management and prevention. One reason for this discrepancy may be the fact that the etiology of recurrent calcium stones in many patients remains unclear and/or is multifactorial. Dietary and environmental factors certainly play an important role and long-term control of recurrences can be achieved in many patients with general measures for stone prevention.

In this article, the pathophysiology of stone formation is reviewed, followed by a detailed discussion of the current recommendations for metabolic evaluation. Also, the medical management based on the results of metabolic evaluation is presented at the end.

**Key words:** urolithiasis; metabolic disease; stone; risk factors; calculi

**Braz J Urol, 27: 10-18, 2001**

### INTRODUCTION

Advances in minimally invasive techniques have dramatically changed surgical management of stone disease in the last 2 decades. However, medical management of stone disease along with prevention of recurrent stones represents a less invasive and more cost-effective approach (1, 2). In this concept, an understanding of the pathophysiology of stone formation is the prerequisite for a cost-effective medical evaluation and management as well as the prevention of recurrences. We briefly review the pathophysiology of stone formation followed by a detailed dis-

cussion of the current recommendations for metabolic evaluation. A brief discussion of the medical management based on the results of metabolic evaluation is presented at the end.

### EPIDEMIOLOGY AND RISK OF STONE RECURRENCE

Urolithiasis is the third most common disease of the urinary tract after infections and diseases of the prostate (2). Furthermore, there has been an increasing prevalence of calcium stones in the industrialized countries and between 5% and 15% of the

population will develop kidney stones during their life time (3). The risk of recurrence in first-time stone formers is at least 50% at 10 years (1). However, this risk will increase in those who have already formed recurrent stones or multiple stones. The relative risk of stone formation in Caucasian is four times greater than of African-American, and men three times that of women (4).

The high risk of recurrent nephrolithiasis in the general population emphasizes the importance of a metabolic evaluation and appropriate medical treatment.

## PATHOPHYSIOLOGY

Calcium stones (calcium oxalate or phosphate) compose the most common stone type (3). Other stone compositions include uric acid, struvite (magnesium ammonium phosphate), and other miscellaneous components such as cystine. Although the exact cause of urinary stone disease is unknown, various theories have been suggested. The most commonly accepted theory is the supersaturation, crystallization theory (2). According to this theory, as concentration of solutes in urine increases, the solubility product is reached; above which dissolved solutes can form nuclei of its solid phase (the metastable zone). These nuclei can form homogeneously or heterogeneously. Homogeneous nucleation occurs in pure solutions and requires more thermodynamic energy. Heterogeneous nucleation is believed to initiate crystal formation. The term epitaxy is referred to mixed stone growth by heterogeneous nucleation. The most common example is when uric acid acts as a nidus for calcium oxalate, leading to continued growth. These crystals may attach to the epithelial lining of uniferous tubules and collecting ducts and subsequently grow when ions are in the metastable or oversaturated states. Small stones can grow and either pass spontaneously or become large and lead to obstruction with associated colic, and/or infection. Inhibitors of stone formation in urine represent the opposing force. It appears that an imbalance between crystallization and inhibitors in urine is the driving force for stone formation (1). These inhibitors include magnesium, citrate, pyrophosphate, nephrocalcin,

Tamm-Horsfall mucoprotein, and various peptides that inhibit crystal nucleation, aggregation, and growth. Another factor postulated in stone formation is matrix. Matrix is the organic material found in calculi and is composed of protein. Its content usually varies between 2 to 10% of stones by weights. Whether it functions as a nidus for crystallization, as a urinary inhibitor or an innocent bystander is unknown (2). In summary, stone formation appears to be a multifactorial and complex physical and chemical process. The driving force is the supersaturation of urine with respect to the index crystal. In contrast, inhibitors of crystallization play an important role in preventing stone formation or growth (5).

## Hypercalciuria and Calcium Stones

Hypercalciuria is diagnosed in 30-60% of all patients with nephrolithiasis. This is defined as the urinary excretion of calcium exceeding 4 mg/kg/d in either sex or > 250 mg/d for women and > 300 mg/d for men (2). Selective medical management of calcium stone formers is directed toward the mechanism of the hypercalciuria. Although some controversies still exist as to exact mechanism and classification of hypercalciuria, a commonly used classification is the division into absorptive, resorptive, and renal hypercalciuria (6).

In patients with absorptive hypercalciuria, intestinal hyperabsorption of calcium is the basic abnormality (6). The increase in circulating calcium will enhance renal filtration of calcium and at the same time suppress parathyroid hormone. The combination of these mechanisms will result in hypercalciuria. Absorptive hypercalciuria has been further divided in Types I-III. Type I represents a severe dietary independent form while Type II is a milder form and usually responds to dietary restriction of calcium alone (7). The mechanism of type III absorptive hypercalciuria is different. This is thought to be the result of a phosphate leak resulting in enhanced formation of 1,25 dihydroxyvitamin D, with subsequent increase in intestinal calcium and phosphate absorption (i.e. absorptive hypercalciuria) from the small bowel and mobilization of calcium from bone.

Resorptive hypercalciuria is the result of primary hyperparathyroidism and accounts for only 5%

of cases of hypercalciuria. Excessive parathormone (PTH)-dependent bone resorption and enhanced intestinal absorption of calcium by PTH or PTH dependent synthesis of 1,25-dihydroxyvitamin D<sub>3</sub> results in hypercalciuria. Pure calcium phosphate stones are frequently associated with hyperparathyroidism.

Renal leak hypercalciuria accounts for 5-10% of hypercalciuric calcium stone formers. This is due to impaired renal tubular reabsorption of calcium, which leads to low levels of serum calcium and secondary hyperparathyroidism (6).

Various forms of hypercalciuria can be differentiated based on the biochemical and physiological presentation. While the serum calcium is normal in absorptive and renal hypercalciuria, it is elevated in patients with resorptive hypercalciuria. Parathyroid hormone is primary and secondarily elevated in resorptive and renal hypercalciuria, respectively, while parathyroid hormone is normal or suppressed in absorptive forms. To differentiate primary from secondary parathormone elevation, a course of thiazide treatment (50 mg po BID) for one to two weeks can be prescribed. In patients with primary hyperparathyroidism, the parathormone level will not change while administration of thiazides decreases the parathormone level in cases of secondary hyperparathyroidism such as with renal hypercalciuria. Another cause for secondary hyperparathyroidism is renal failure, which should be included in the differential diagnosis.

All forms of hypercalciuria will result in intestinal hyperabsorption of calcium. However, this is a primary phenomenon in absorptive hypercalciuria and a secondary defect in renal or resorptive hypercalciuria.

## Calcium Stones due to Other Causes

### *Hyperuricosuria and Gouty Diathesis*

This is defined in patients with a urinary uric acid level of > 600 mg/d in women and > 750 mg/d in men. In patients with hyperuricosuric calcium stones, this is in conjunction with a urinary pH > 5.5. Hyperuricosuria is found in 15-20% of calcium stone formers but may be the only metabolic abnormality in up to 10% of patients with calcium stones (8).

Hyperuricosuria may be a result of dietary overindulgence or endogenous overproduction of uric acid. Regardless of the cause, the monosodium urate in an acidic environment acts as a nidus for heterogeneous nucleation of calcium oxalate.

Gouty diathesis is defined as the formation of uric acid or calcium stones in patients with primary gout (8). The basic mechanism is the passage of acidic urine (pH < 5.5), in which the uric acid is insoluble. These patients may form uric acid stones alone or in combination with calcium stones. The mechanism of calcium stone formation is by heterogeneous nucleation of calcium salts.

### *Hyperoxaluria*

Hyperoxaluria is defined as urinary excretion of oxalate of > 45 mg/d. Generally, it has a greater impact on calcium stone formation than an elevation of urinary calcium. Hyperoxaluria may be due to enteric or congenital abnormalities. Enteric hyperoxaluria is due to an intestinal hyperabsorption of oxalate (9). The major cause is ileal disease. This may occur in patients with inflammatory bowel disease, gastric or small bowel resection, or jejunioileal bypass. Two factors may contribute to intestinal hyperabsorption of oxalate. First an increase in intestinal absorption of oxalate may occur as a direct effect of bile salts and fatty acids that increase the bowel mucosal permeability. Furthermore, increased intestinal fatty acids bind to calcium in the intestine thus decreasing the amount of calcium available to complex oxalate and thereby increasing the amount of free oxalate available for absorption.

Congenital hyperoxaluria is much less common. This is an autosomal recessive disease, which may present in two forms. In Type I the primary defect is a deficiency in the enzyme oxoglutarate: glyoxylate carboligase, which will result in increased level of glycolic acid and oxalic acid. Type II is due to a deficiency of the enzyme D-glyceric dehydrogenase. This promotes the conversion of glyoxalate to oxalate (21).

### *Hypocitraturia*

Citrate is the most important inhibitor of urinary stone formation. Citrate decreases urinary cal-

cium salt saturation by forming soluble complexes with calcium and thus prevents precipitation (10). Hypocitraturia is defined as urinary citrate levels < 320 mg/d (11). Acid-base status is the most important factor affecting urinary citrate levels. Acidosis reduces urinary citrate by reducing the synthesis and enhancing proximal tubular reabsorption of citrate. Therefore, hypocitraturia may occur in all conditions associated with metabolic acidosis such as renal tubular acidosis (type I), hypokalemia, physical exercise, and excess sodium intake secondary to bicarbonate loss. However, hypocitraturia may occur as an isolated defect. An iatrogenic cause of hypocitraturia is the use of thiazide diuretics as with absorptive hypercalciuria (11).

#### ***Non-Calcareous Stones***

Non-calcareous stones are less common than calcium based stones. However, knowledge of their pathophysiology is critical for a selective medical approach toward treatment and prevention. Generally, once the diagnosis is made the therapeutic options are straight forward and an extensive metabolic evaluation can be omitted.

#### ***Uric Acid Stones***

Three mechanisms are involved in uric acid stone formation. These include an acidic urine, low volume urine, and hyperuricosuria (8). The most important factor for uric acid stone formation is an acidic urine (consistently with a pH < 5.5). Uric acid is the end product of purine metabolism. Aside from gouty diathesis, uric acid stones may develop secondary to purine over-production such as with myeloproliferative diseases and malignancies. Chronic diarrheal syndromes may also cause uric acid stone secondary to loss of alkali in stool and associated hypovolemia with subsequent acidosis, which will further decrease uric acid solubility.

#### ***Infectious Stones***

Struvite (magnesium ammonium phosphate) or infectious stones are the consequent of urinary tract infection with urea-splitting organisms (12). The degradation of urea in urine by bacterial urease will result in ammonia formation. The ammonia undergoes

hydrolysis to form ammonium and hydroxyl ions. This results in an alkaline urine, which will promote formation of triphosphates from phosphate and the reduction of the struvite solubility. Struvite stones will only precipitate in urinary pH > 7.2. If one could consistently acidify urine, theoretically one could dissolve such stones.

#### ***Cystine Stones***

Cystinuria is an inherited autosomal recessive disorder. It involves a defect in intestinal and renal tubular handling of cystine, ornithine, lysine, and arginine, of which only cystine has clinical relevance (13). This results in excessive cystine excretion in urine which is normally < 50 mg/d. Three types of genetic defects have been identified, with homozygous types excrete cystine up to 700 mg/d. Heterozygous secrete up to 300 mg/d. The main determinant of cystine crystallization is urinary supersaturation. At a cystine concentration above 250 mg/liter, cystine will precipitate out of solution. Cystine solubility is pH dependent. The pKa of cystine is 8.1. With increasing pH, the solubility of cystine increases significantly. At a urinary pH above 7.5, the solubility is doubled.

Other rare types of urinary stones include triamterene (with diuretic use), xanthine, ammonium acid urate, silica, and indinavir stones (secondary to protease inhibitors used in patients with AIDS).

### **BASIC EVALUATION**

All stone-forming individuals should have a thorough history and physical examination. Any previous history of stone disease and treatment should be documented. The family history should include specific questions with regard to gout, cystinuria, and renal tubular acidosis. Systemic diseases such as sarcoidosis, hyperparathyroidism, and myeloproliferative disorders may contribute to stone formation. Enteric hyperoxaluria can occur in inflammatory bowel disease or other disorders associated with malabsorption, such as enteric resection or bypass. Environmental risk factors and dietary factors should be considered. A diet with low fluid intake and high in calcium, oxalate, purines, or sodium should be specifically questioned.

Laboratory evaluation should include urinalysis and culture. Blood chemistry should include calcium, phosphorus, electrolytes, creatinine, uric acid, and parathormone. All patients should have a baseline radiologic evaluation including scout (KUB), an intravenous urography (IVP) or noncontrast computer tomography (CT), or renal ultrasonography. Stone analysis is an integral part of evaluation. An attempt should be made to collect representative stone or stone fragments including those passed after extracorporeal shock wave lithotripsy (ESWL).

## METABOLIC EVALUATION

Aside from the mentioned basic evaluation and laboratory testing, it is not agreed upon whether all stone formers require a more extensive metabolic evaluation (7). Some authors recommend metabolic evaluation in all patients even those with a single stone episode (14). While others suggest that single stone formers without any risk factors do not require further evaluation (1). Accepted risk factors for first time stone formers include stones present in childhood, cystine, uric acid stones, multiple calculi, patients with nephrocalcinosis, stones in a solitary kidney and stones requiring surgical intervention. Moreover, it is important to consider patients' preference. The risk of stone recurrence in a first time stone former is at least 50% at 5 years. This risk should be discussed with all patients to give them the option of a formal metabolic evaluation versus surgical intervention at the time of stone recurrence. It is important to weigh the cost of treatment for recurrent stones against the cost of a limited metabolic evaluation and appropriate prevention. It is obvious that in those circumstances that minimally invasive technology is not readily available or is associated with high cost, a metabolic evaluation with a 24-hour urine collection is cost-effective.

Metabolic evaluation of patients with urolithiasis can be divided into simple and more exhaustive investigations (15). A simple evaluation includes the addition of a 24-hour urine collection to the other blood work as discussed previously. Urine is collected at home while patients are consuming their

normal diet and prescribed medications. It is advisable to postpone the complete metabolic evaluation for at least 1 month after the resolution of ureteral obstruction or infection or after surgical intervention for stone. The 24-hour urine collection is examined for volume, pH, calcium, uric acid, oxalate, citrate, phosphorus, sodium, and creatinine.

In patients at high risk for stone recurrence (family history, early age of onset, nephrocalcinosis, and associated medical conditions) or a recurrent stone former, a more detailed evaluation is indicated. Such patients may require additional 24-hour urine collection with calcium and acid loading tests.

Pak and colleagues have suggested an ambulatory protocol to differentiate subtypes of hypercalciuria (16). This protocol includes two 24-hour urine collections on a normal diet and another 24-hour collection after a week of a calcium and sodium restricted diet followed by an oral calcium load test. However, others criticize the value of calcium load test (1).

A repeat 24-urine collection after initiation of medical treatment for stone disease should be performed to evaluate treatment efficacy and to adjust medications as indicated. Any significant change in diet or medication requires repeat 24-urine collections.

## MEDICAL MANAGEMENT

Metabolic evaluation can only be cost-effective if the results translate to appropriate medical management. Medical management of stone disease is directed toward stone prevention and in certain situations stone dissolution. Some measures are non-specific and are helpful for all stone forming patients regardless of etiology.

### General Measures

All stone formers are encouraged to increase their fluid intake to translate into a urinary output of at least 1.5 liters per day. This will decrease the concentration of urinary solutes. Stone recurrence has been associated with failure to increase urine output. Dietary adjustments may be useful. In some patients

with hypercalciuria, the intestinal absorption of calcium is increased. It has been suggested that decreasing calcium intake will decrease urinary calcium excretion. A low calcium diet may cause increased intestinal absorption of oxalate. Furthermore, bone mineral density has been shown to be below normal in most stone formers and a low calcium diet may further decrease this bone mineral density (17,18). In addition, in a prospective study on dietary calcium intake in a large cohort of men, higher calcium intake was associated with a lower risk of calcium stone formation (19). These data have been supported by a more recent study showing that a cohort of stone formers had a significantly lower calcium intake than a control group (20). Therefore, most authorities believe that a rigid dietary calcium restriction is not advisable and may be harmful (1,2,7,17).

With regard to dietary sodium intake, it is well known that a high sodium intake inhibits tubular reabsorption of calcium, thus increasing calcium excretion. Sodium restriction has been shown to significantly decrease urinary calcium concentration (21, 22). Therefore, high sodium intake should be avoided in all stone formers. A daily sodium intake of < 100 mEq has been suggested.

The main source of oxalate in the urine is endogenous. However, in patients with calcium stones some degree of hyperoxaluria may be observed secondary to intestinal absorption. Therefore, patients may benefit from a low-oxalate diet, avoiding extensive consumption of foods such as spinach, chocolate, nuts, tea, wheat bran, and strawberries (23).

In general, a balanced diet, avoiding extremes is recommended.

Epidemiological studies have shown that the incidence of renal stones is higher in countries in which protein intake is higher (24). A high protein intake will increase urinary calcium, oxalate and uric acid concentrations. The post-prandial acidosis associated with high protein intake may also result in hypocitraturia. Stone patients should avoid excessive protein intake.

In summary, all stone formers benefit from these general measures including increased urinary output to above 1.5 liters/d, restricting sodium intake, and limiting protein intake.

## Specific Treatment

Selective medical treatment is based upon the assumption that the metabolic abnormality identified contributes significantly to stone formation. This however, may not be the case in an individual patient. This is supported by the fact that many patients with a documented urinary abnormality never form stones. Furthermore, many patients are found to have more than one abnormal parameter by 24-hour urinary collection.

In the following, we will briefly review some of the general aspects of the medical management based on the metabolic evaluation.

### *Calcium Stone*

Aside from the nephrolithiasis secondary to hyperparathyroidism, which is treated surgically by parathyroidectomy, medical management may be based on the classification of the hypercalciuric state. Sodium cellulose phosphate has been used as a selective medical management for absorptive hypercalciuria types I and II (2,25). This is a nonabsorbable ion exchange resin, which binds to calcium and inhibits calcium absorption. There are several potential side effect of sodium cellulose phosphate including negative calcium balance, hyperoxaluria and magnesium depletion. Furthermore, sodium cellulose phosphate is relatively costly. These potential side effects have detracted from its routine use in the clinical practice. Therefore, hydrochlorothiazide may be used in combination with potassium citrate as the initial treatment for absorptive hypercalciuria (26).

Thiazide is the most commonly used medication for selective treatment of hypercalciuria. This can be administered in the form of hydrochlorothiazide (25 mg bid,) or trichlorothiazide (4 mg/d). Thiazide acts directly on the kidney to reduce urinary calcium excretion in distal tubules and by causing volume depletion and augmenting proximal tubular reabsorption of calcium. Therefore, thiazide is the treatment of choice for renal hypercalciuria (25). In addition, thiazide may improve bone calcium absorption and results in a positive calcium balance (17). The increase in bone density makes thiazide the preferred treatment for treatment of hypercalciuria in patients at risk for bone disease such as post-menopausal

women, children or those with osteoporosis. With continuous treatment with thiazide (> approximately 5 years), however, the rise in bone density stabilizes and the hypocalciuric effect of thiazide slowly disappears. In this situation, thiazide treatment may be temporarily stopped and sodium cellulose phosphate administered for 6 months; thiazide treatment then may be resumed. Concomitant potassium citrate is necessary in patients on thiazide therapy to avoid hypokalemia and thiazide induced hypocitraturia.

Orthophosphate is indicated in Type III absorptive hypercalciuria due to renal phosphate leak (22). Orthophosphate decreases urinary calcium by decreasing intestinal absorption of calcium (mediated by 1,25 Dihydroxy Vitamin D3). Urinary phosphate is markedly increased during therapy; its use is therefore contraindicated in cases of infectious stones (magnesium ammonium phosphate) (25).

Hyperuricosuric calcium stones can be treated with allopurinol (300 mg per day), which will decrease uric acid synthesis and lower urinary uric acid. Sodium may exaggerate monosodium urate-induced calcium oxalate crystallization, therefore, a moderate sodium restriction 100 meq /d is recommended. Potassium citrate is an effective treatment alternative for these stones. Potassium citrate may reduce the urinary saturation of calcium oxalate and inhibit urate-induced crystallization of calcium oxalate.

Calcium stones due to enteric hyperoxaluria may be treated with administration of calcium after efforts to reduce diarrheal states have been tried. However, a decrease in urinary oxalate may be associated with an increase in urinary calcium concentration, which may obviate the beneficial effect of this therapy. Calcium citrate may theoretically have a role in treatment of enteric hyperoxaluria. Calcium citrate may decrease urinary oxalate by binding to oxalate in the bowel and increase urinary pH by providing an alkali load.

Patients with congenital hyperoxaluria begin stone formation in childhood and develop nephrocalcinosis. Characteristic abdominal plain x-ray appears like a renal nephrogram. A significant number (about 50%) of patients will require dialysis for associated renal failure by the age of 15 years (27).

Pyridoxine as a specific therapy at a dose of 2-15 mg/kg has been used and reduces oxalate excretion. However, the efficacy of this treatment is limited (28). Without definite therapy (combined liver and renal transplant) such patients rarely survive into their 20's.

Hypocitrauric calcium stones may be associated with distal renal tubular acidosis, chronic gastrointestinal disease with diarrhea, secondary to thiazide treatment or idiopathic (25,29). In all these circumstances, potassium citrate, which may be given in crystal, liquid or tablet formulation, is an effective treatment. The initial dose should be 60 mEq in divided doses. Correction of factors contributing to metabolic acidosis will contribute to prevention of hypocitraturic stone recurrences. Potassium citrate will correct the acidosis and hypokalemia in patients with metabolic acidosis. Furthermore potassium citrate will increase the urinary citrate level to normal range in patients with hypocitraturia (25). Patients that are non-compliant or intolerant of pharmacological citrate supplement may increase urinary citrate levels with lemonade consumption.

## Medical Management of Non-Calcalerous Stones

### *Uric Acid Stones*

Urinary alkalization to a pH of 6.5-7 is the most effective treatment for pure uric acid stones (2). This will dissolve the preformed stones and prevent further stone formation or growth. In the past, this was accomplished with sodium bicarbonate or a combination of sodium and potassium alkali therapy. While sodium may cause dissociation or inhibition of uric acid formation, this may contribute to formation of calcium stones (8). Therefore, potassium citrate or potassium bicarbonate are currently the preferred medications for urinary alkalization (25).

### *Struvite Stones*

Surgical management is the preferred approach for preexisting struvite stones. Since infection with urease producing organism is the main mechanism for struvite stone formation, appropriate treatment of UTIs may decrease the chance of stone

growth. Medical therapy can be attempted with the urease inhibitor acetohydroxyamic acid (AHA). This medication will decrease urinary ammonia levels with a subsequent decrease in urinary pH. However, it is associated with significant side effects such as deep venous thrombosis, and gastrointestinal side effects limiting its usefulness (11,30). Theoretically, acidification of urine is an effective means of preventing struvite stone formation and growth. Dissolution of struvite stones with hemiacidrin or Suby's G solution through a low-pressure irrigation system has been described. However, significant side effects including sepsis, hypermagnesemia, and death may occur (11). In general, medical treatment plays a minor role for treatment and prevention of infectious stones (2).

### **Cystine Stones**

Cystine stones form when urinary concentrations reach a critical level. To help dilute cystine, patients have to consume large volumes during the day and night. Increased fluid intake to increase the urine output to at least 2500 ml/day should be encouraged. A urinary pH of 7.5 is ideal to maximally increase solubility of cystine. Medications such as D-penicillamine and alpha-mercaptopyronylglycine (Thiola) can be used to increase the solubility of cystine by forming disulfide complexes. D-penicillamine is associated with significant side effects such as pancytopenia and dermatitis. Therefore, Thiola is the preferred medication (31).

### **CONCLUSIONS**

Advances in endourological techniques along with the introduction of new technologies have revolutionized surgical management of urinary stone disease.

Although significant knowledge has been gained regarding pathophysiology of stone disease, this has not translated in a similar dramatic change in the medical management and prevention. One reason for this discrepancy may be the fact that the etiology of recurrent calcium stones in many patients remains unclear and/or is multifactorial. Dietary and environmental factors certainly play an important role and long-term control of recurrences can be achieved in many patients with general measures for stone pre-

vention. Furthermore, selective medical management is effective in cases of clear metabolic abnormalities. In the future, elucidation of the exact mechanisms responsible for stone recurrences will improve our understanding of stone disease and lead towards a more effective medical management.

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*Received: August 14, 2000*

*Accepted: September 4, 2000*

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