

## Metabolic Evaluation of Stone Disease Patients: A Practical Approach

DAVID A. LIFSHITZ, M.D.,<sup>1</sup> ARIEH L. SHALHAV, M.D.,<sup>2</sup> JAMES E. LINGEMAN, M.D.,<sup>1</sup>  
and ANDREW P. EVAN, Ph.D.<sup>3</sup>

### ABSTRACT

In the last three decades, minimally invasive techniques have progressed significantly, replacing traditional open surgery as the mainstay of stone disease surgical treatment. The challenge for the next millennium remains medical prevention of calcium urolithiasis, a field where less dramatic progress has been achieved during the same period of time. The purpose of this article is to provide the practicing urologist with current practical guidelines for the assessment and management of calcium urolithiasis patients. The recommendations are based on the latest available information regarding the pathogenesis, medical treatment options, and decision-making rationale when managing these challenging patients. Every urolithiasis patient should undergo a basic evaluation, which is considered the minimal essential diagnostic work-up, in order to rule out obvious, treatable systemic causes of urinary stone disease. All patients should be advised about conservative nonspecific preventive measures. High-risk stone patients should have a more extensive metabolic evaluation based on two 24-hour urine samples. Treatment protocols for each patient are tailored individually according to the metabolic evaluation findings.

### INTRODUCTION

**R**ENAL STONE DISEASE accounts for about 7 to 10 of every 1000 hospital admissions in the United States.<sup>1</sup> Between 5% and 15% of the population will develop kidney stones during their lifetime.<sup>2</sup> Four of every five patients with stones are men, and in both sexes, the peak age of onset is during the third and fourth decade of life. There has been an increase in the prevalence of calcium stones in industrialized countries.<sup>3</sup>

Kidney stones cause considerable suffering and have a substantial economic impact. In 1993, the total annual cost for urolithiasis treatment in the United States was estimated to be \$1.83 billion.<sup>4</sup> Surgical treatment including lithotripsy is not a substitute for medical prevention, which has been proven to be effective in reducing stone recurrence.<sup>5</sup> Medical prevention based on appropriate evaluation and treatment of metabolically active stone disease could save nearly \$2200 per year per patient in related treatment costs.<sup>6</sup> An understanding of the factors leading to stone formation and a structured patient evaluation are the bases for effective medical prevention.

### RISK OF STONE RECURRENCE

The risk of recurrence in a large series of first-time stone formers has been reported to be about 67% at 9 years<sup>7</sup>; by 25 years, 75% of patients have formed a second stone.<sup>8</sup> However, recurrence rates are higher in patients who have already had recurrent stones and patients forming multiple stones, among whom the rate can reach 50% in 3 years.<sup>9</sup>

### PATHOGENESIS OF STONE DISEASE

Kidney stones are generally composed of calcium salts, uric acid, magnesium ammonium phosphate, or cystine (Table 1). Most calcium oxalate stones also contain a small amount of hydroxyapatite, and 10% to 12% contain some uric acid.

Kidney stones result from a complex physical and chemical process. However, two major opposing forces are the key factors (Fig. 1). On one hand, urinary supersaturation (SS) provides the driving force for stone formation, and on the other

<sup>1</sup>Methodist Hospital Institute for Kidney Stone Disease, Indianapolis, Indiana. Departments of Urology<sup>2</sup> and Anatomy,<sup>3</sup> Indiana University School of Medicine, Indianapolis.

TABLE 1. FREQUENCY OF VARIOUS TYPES OF STONES

Stone Type	Percent of Total
Calcium oxalate	58.8
Mixed Ca oxalate/Ca phosphate	11.4
Uric acid	10.1
Struvite	9.3
Calcium phosphate	8.9
Cystine	0.7
Miscellaneous	0.8

Data from reference 10.

hand, urine inhibitors provide a protective effect. Stones form in urine that is supersaturated with respect to the ionic components of the specific stone. Supersaturation means that the concentration of a stone-forming salt, such as calcium oxalate, exceeds its solubility in a solution (the solubility product). Once this concentration is reached, nuclei of its solid phase can form. Saturation is often expressed as the ratio of dissolved material to its solubility concentration: a solution that contains exactly the solubility product has an SS of 1. In urine, SS may rise to between twofold and eightfold, depending on the crystal involved, without new solid-phase formation, a range termed the "metastable zone." At SS values above the metastable zone upper limit (termed the "formation product"), crystal nuclei will form spontaneously, grow, and aggregate (Table 2). With respect to SS, each solute acts as if alone, so a solution may be supersaturated simultaneously with respect to multiple phases.<sup>11-13</sup> The urinary SS of a particular crystal component correlates directly with the stone type that the individual develops.<sup>14</sup> Solute concentration is a function of how much of the particular ion is excreted in the volume of urine. Thus, increased urinary ion concentration and decreased urine volume will both increase free ion activity and favor stone formation and growth. In some cases, high SS is the only apparent reason for stones. Cystinuria is one example; a defect in a renal tubule transport leads to high urine cystine levels that cause concentrations to exceed solubility, leading to stone formation. This subject is discussed in more detail elsewhere in this issue. Uric acid stones are another example. Undissociated uric acid has a solubility of about 96 mg/L, and if urine pH falls near the  $pK_a$  of 5.35, uric acid stones may form. Struvite is yet another material critically dependent on SS. Bacteria that produce the enzyme urease raise urine pH and ammonium ion levels, leading to spontaneous crystallization of magnesium ammonium phosphate. Struvite stones are the subject of another article in this issue.

In the more common calcium stone former (approximately 70% of all kidney stones), the situation is more complicated. The urine of most normal people is supersaturated with respect to calcium oxalate, so in principle, such stones can form in all people. However, kidney stones form only in a small percentage of people with supersaturated urine, probably because of the presence of urine inhibitors of crystallization. Some individuals may form stones primarily because of a lower than normal concentration of a urine inhibitor. Some urinary inhibitors have been identified and include both organic and inorganic substances (Table 3). Urinary citrate is an example of a clinically important inhibitor. Because citrate forms a soluble com-

plex with calcium, lowering urinary citrate excrete is equivalent to increasing the urine concentration of calcium.<sup>17</sup>

An imbalance between SS and urine inhibitors is necessary for crystal nucleation. However, additional factors are required for stone formation *in vivo*. In pure solutions, crystals are formed *de novo* in a process termed "homogeneous nucleation." *In vivo*, homogeneous nucleation occurs only under special conditions because it requires very high SS levels. In urine, crystal nucleation and growth occurs predominantly by heterogeneous nucleation, which occurs at lower SS levels. *In vivo*, nuclei commonly form on the surface of a dissimilar but complementary crystal or on another surface such as an epithelial lining, cell debris, or urinary casts.<sup>12,25</sup> Crystals can grow by the precipitation of additional salt. However, because the transit time of urine from the collecting duct to the bladder is only 10 minutes, there would appear to be insufficient time for any crystal that forms to grow to the size necessary to cause symptoms. Therefore, many, if not most, renal stones form in association with a fixed point (i.e., nidus) in the collecting system or a papilla.<sup>26</sup> Proposed mechanisms of crystal fixation include epithelial cell internalization of adherent crystals, which are then transported from the luminal to the basement membrane side of the cell. The crystals aggregate and eventually cause cellular damage and erosion through the papillary surface, thus providing an exposed nidus for stone growth.<sup>27,28</sup> Another possible mechanism for crystal deposition in the papilla is that an increased concentration of oxalate, calcium, or phosphate in the papillary interstitium leads to the formation *de novo* of calcium oxalate or hydroxyapatite crystals.<sup>29</sup> These mechanisms are considered elsewhere in this issue.

It is important to remember that any urine abnormality involving SS, urine inhibitors, or both may be the result of a systemic disease. For example, calcium urolithiasis may be the result of primary hyperparathyroidism, sarcoidosis, vitamin D excess, hyperthyroidism, immobilization, enteric hyperoxaluria, primary hyperoxaluria, or dehydrating bowel disease. Low citrate is another example and may result from conditions such as distal renal tubular acidosis (RTA) or chronic diarrhea syndrome.

## ESSENTIAL EVALUATION

The end result of a metabolic evaluation may commit the patient to a treatment regimen, including dietary modifications and medications, for the rest of his or her life. Yet some patients will never form a stone again.<sup>30</sup> Therefore, it is essential to adjust the extent of the metabolic evaluation to the patient's

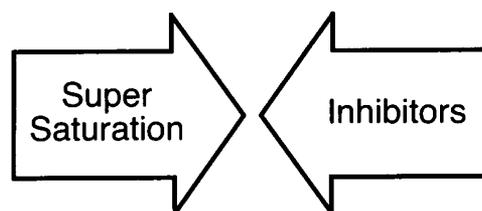


FIG. 1. Opposing factors in stone formation.

TABLE 2. EFFECTS OF INCREASING SOLUTE CONCENTRATION

Zone (SS values)	Effects
Unstable (CaOx >8, brushite >2.5, uric acid >2)	Nuclei form, grow, aggregate
Metastable: upper limit (formation product)	First solid-phase formation
Metastable (CaOx <8, brushite <2.5, uric acid <2)	No spontaneous nucleation; crystal growth can occur; inhibitors can impede or prevent crystallization
Equilibrium point (solubility product); SS = 1	Crystals neither grow nor dissolve
Undersaturation zone (SS < 1)	Nuclei may dissolve (uric acid)

individual circumstances or, in other words, “the punishment must fit the crime.”

All stone-forming patients should have a basic evaluation as suggested in Table 4. *History and physical examination* remain an integral part of the evaluation. Previous episodes of urinary tract infection and stone or gravel passage should be documented. Any stone analysis should be noted. The family history should include specific questions about gout, cystinuria, and RTA or calcium urolithiasis. Some medications can increase the risk of stone formation. For example, carbonic anhydrase inhibitors can induce nephrocalcinosis and nephrolithiasis.<sup>31</sup> Premature infants may develop nephrocalcinosis or nephrolithiasis or both while receiving long-term furosemide therapy.<sup>32</sup> Systemic diseases such as hyperparathyroidism, hyperthyroidism, sarcoidosis, distal RTA, and myeloproliferative disorders should be recognized. Enteric hyperoxaluria can occur in Crohn’s disease and other malabsorptive conditions, as well as after ileocecal resection and jejunoileal bypass.<sup>33</sup> Total colectomy is associated with an increased risk of uric acid stones secondary to loss of water and bicarbonate in the stool.<sup>34,35</sup> Environmental risk factors such as occupation and climate need to be considered. Dietary history should include questions concerning fluid intake, use of dietary supplements, and dietary indiscretion with regard to foods high in calcium, oxalate, and purines.

*Radiologic examination* of the kidney, ureter, and bladder (KUB) and intravenous urography or noncontrast CT scanning should be performed in every patient unless contraindicated. Comparison of any available previous films with new ones is useful. Spiral CT may also be advantageous in determining the chemical composition of the stone.<sup>36,37</sup>

*Stone analysis* is a major first step in the evaluation of all patients. Every effort should be made to collect stone material

from all patients, including those treated with shockwave lithotripsy (SWL). On discharge, we provide such patients with collecting devices in order to preserve any passed gravel for analysis.

*Laboratory examinations* include urinalysis and urine culture and serum calcium, phosphorus, uric acid, electrolytes, and creatinine concentrations. Patients should undergo parathyroid hormone assay only if hypercalcemia or a high-normal serum calcium concentration is found. If the stone composition is unknown, a qualitative cystine screen should be obtained.

### THE SINGLE STONE FORMER

Patients who present after the spontaneous passage of a single stone or more than one stone with very long periods between the episodes are encountered frequently. Some authors recommend an extensive metabolic evaluation for such patients because of the relatively high recurrence rate and the possibility that the initial stone event may be a harbinger of an underlying multisystem disorder.<sup>38,39</sup> Others have suggested consideration of different risk factors in order to identify patients who need further evaluation<sup>3,39,40</sup> (Table 5). Children, patients with stones composed of cystine or uric acid, patients who required surgical removal of the stone, patients with multiple stones or nephrocalcinosis, patients with a solitary kidney, or patients with a positive family history probably should be evaluated. Pa-

TABLE 3. URINARY INHIBITORS OF STONE FORMATION

Inorganic
Pyrophosphate
Magnesium
Organic
Citrate
Tamm-Horsfall protein
Uropontin
Nephrocalcin
Prothrombin F1 peptide
Uronic acid-rich protein
Glycosaminoglycans

Data from references 15–23.

TABLE 4. ESSENTIAL EVALUATION FOR ALL STONE PATIENTS

History and physical examination
Medical risk factors (inflammatory bowel disease, bowel surgery, immobilization, medications)
Urinary tract infections
Previous stone events and stone analysis
Family history
Fluid intake and diet
Environmental risk factors
Occupation
Climate
Laboratory evaluation
Urinalysis and culture
Blood chemistry (calcium, <sup>a</sup> phosphorus, electrolytes, creatinine, uric acid)
Stone analysis
Radiologic studies
Plain film
Intravenous urogram or noncontrast CT scan

<sup>a</sup>If value is high, serum parathormone assay is indicated.

TABLE 5. INDICATORS OF HIGH-RISK STONE FORMERS

Stones in childhood
Cystine, uric acid, or mixed struvite stones
Multiple stones
Nephrocalcinosis
Solitary kidney
Stone requiring surgical removal

tients with pure struvite stones are not likely to have a secondary metabolic abnormality contributing to their stone formation and may not need an extensive evaluation.<sup>41</sup>

By exclusion, only single stone formers with an uneventful clinical course and without any risk factor need the essential evaluation. The issue of further evaluation and its implications (i.e., dietary measures, long-term medication) should be discussed with the patient. Those who choose to undergo metabolic evaluation should do so, even if they presented as a first-time uncomplicated stone former. However, metabolic evaluation is not helpful in predicting which patients will develop recurrence, as patients who present after the first stone have the same pattern of metabolic disorders as patients with multiple stones.<sup>42</sup>

## METABOLIC EVALUATION

Modern stone preventive measures can reduce the recurrence rates significantly. Medical treatment is not appropriate without a metabolic evaluation directing the treatment choice and the patient's follow-up. With an extensive metabolic evaluation, a metabolic or environmental etiology of nephrolithiasis can be identified in as many as 97% of the patients.<sup>43</sup>

The cornerstone of the metabolic evaluation is collection of the patient's urine for a period of time. A number of protocols have been described for the metabolic evaluation of patients with recurrent stone disease or high-risk patients. The protocols differ in the period of urine collection (part of the day or 24 hours), the number of collections, and the provocative tests applied that identify classifications of hypercalciuria by oral calcium deprivation and loading or acid-loading tests for the diagnosis of RTA.

An ambulatory 24-hour urine collection is as effective as an inpatient evaluation in detecting metabolic abnormalities and has been studied extensively.<sup>2</sup> Urine is collected while the patient is eating his/her normal diet and taking his/her usual medication for indications other than stone disease. Drugs prescribed for stone disease, as well as vitamin supplements, should be stopped 5 days before urine collection. It is advisable to postpone the complete diagnostic evaluation for at least 1 month after the resolution of ureteral obstruction or infection or after stone removal procedures.<sup>39</sup> Urine is collected for determination of volume, pH, calcium, phosphate, sodium, potassium, uric acid, magnesium, oxalate, citrate, and creatinine (Table 6). Urinary creatinine excretion is measured to assess the adequacy of urine collection. The SS values for specific salts are calculated using computer programs such as Equil.<sup>44</sup> A 24-hour urine collection is most commonly used, although other periods of time have been described, such as a 16-hour daytime collection reported by Tiselius.<sup>45</sup>

As expected, repeated urine collections may yield higher diagnostic accuracy than a single collection. For example, Yagisawa et al.<sup>46</sup> were able to identify hypercalciuria in 47% v 35% of patients with two 24-hour urine collections rather than one ( $p < 0.001$ ). Our policy is to acquire a minimum of two random 24-hour urine collections in order to correct for any measurement or collection errors in one of the samples.

To further differentiate hypercalciuria into different subtypes, Pak and colleagues have described a method in which two 24-hour urine specimens with patients on a random diet are collected initially. Another 24-hour urine specimen is collected after a week of adherence to a diet restricted in calcium (400 mg per day) and sodium (100 mEq per day) followed by an oral calcium load test. The rationale behind the protocol is differentiation of various mechanisms causing hypercalciuria. The issue is controversial and is reviewed further below.

Two broad concepts exist about the pathogenesis of hypercalciuria. In 1974, Pak and associates<sup>47</sup> suggested that hypercalciuria was heterogeneous and that three types exist: absorptive, renal, and resorptive. Absorptive hypercalciuria was further divided into type I, in which urine calcium concentrations  $>200$  mg per day during both low and high dietary calcium intake, and type II, in which hypercalciuria occurs only during high calcium intake. Coe and associates maintain that such a distinction has no clinical relevance and, further, that the classification represents a spectrum of patients with the same pathogenesis (i.e., a marked increase in the fraction of dietary calcium absorbed and lost in the urine). Excessive urinary calcium losses are offset by increased intestinal calcium absorption but not always completely, and thus, calcium balance is negative in more than half the patients. Negative calcium balance can lead to reduced bone density in some patients, which can be exacerbated by a low-calcium diet.<sup>11,13,48</sup> According to Pak and associates, selective medical treatment adjusted to the

TABLE 6. METABOLIC EVALUATION OF HIGH-RISK AND RECURRENT STONE FORMERS<sup>a</sup>

<i>Study</i>	<i>Reference Values in 24-hour Urine Sample</i>
Volume	$>2000$ mL
pH	$>6.5$ suggests RTA; $<5.5$ in uric acid stones
Creatinine	15–20 mg/kg (women) 20–25 mg/kg (men)
Calcium	$<250$ mg (women) $<300$ mg (men) $<4$ mg/kg (both sexes) $<140$ mg/g of creatinine
Phosphate	500–1100 mEq
Potassium	25–125 mEq
Sodium	$<200$ mEq
Uric acid	$<750$ mg (women) $<800$ mg (men)
Oxalate	$<45$ mg
Citrate	$>320$ mg
Magnesium	$>50$ mg

<sup>a</sup>These studies should be performed in addition to the standard evaluation. Testing should be repeated annually or whenever diet or medication is changed.

different subclassifications of hypercalciuria is preferred. However, there is lack of conclusive experimental verification of this hypothesis,<sup>49</sup> and there are some practical limitations for the protocol that are reviewed below. The unified approach of Coe and associates is based on the view that calcium load studies provide no additional clinically relevant data.

The importance of repeated 24-hour urine collections during follow-up cannot be overemphasized, as such studies are the major tool that allows assessment of the effect of the medical treatment advised, as well as patient compliance. The 24-hour urine collection should be repeated annually and with any change in diet or medication.

## MEDICAL TREATMENT

Medical treatment for stone disease is intended mostly to prevent recurrence and sometimes to dissolve a formed stone. Some of the measures are nonspecific and are recommended for all stone-forming patients regardless of the underlying etiology. Specific treatments are directed by the stone etiology.

### *Nonspecific Measures*

*Increased fluid intake* increases the urine output, lowering the concentration of the solutes involved in stone formation. Historical data strongly suggest that hydration is effective in preventing stone formation.<sup>1</sup> A prospective study in which settlers in one desert town were systematically educated on their arrival about the need for a high fluid intake while those arriving in a similar town were given no specific advice showed that those given advice on fluid intake had only 10% the incidence of urolithiasis of subjects who did not receive the advice.<sup>50</sup> Coe's group identified failure to increase urinary output as the most important factor that predicts stone recurrence.<sup>42</sup> A low urine volume must be considered as a real risk factor, both for the onset of stone disease and for stone relapse.<sup>51</sup> Beverages other than water have been shown to have a protective effect as well. In the study by Curhan and associates,<sup>53</sup> a positive effect of coffee, tea, and wine was noted.<sup>52</sup> Wabner and Pak have reported on the beneficial effects of orange juice consumption. In contrast, grapefruit juice has an adverse effect.<sup>54</sup> There is a consensus that an oral fluid intake that will produce at least 2000 mL of urine per day is adequate hydration for stone patients.<sup>1</sup>

*Dietary treatment* may have a role. Abnormally efficient intestinal absorption of dietary calcium is well known in idiopathic hypercalciuria.<sup>13</sup> Dietary calcium restriction can decrease urinary calcium excretion, especially in patients with hypercalciuria, and thus, low-calcium diets have long enjoyed popularity. However, a low-calcium diet may increase the intestinal absorption of oxalate, reducing the effectiveness of this therapy.<sup>55</sup> Further, bone mineral is found to be abnormally labile in patients with idiopathic hypercalciuria. Bone mineral density tends to be below normal in the majority of stone-forming patients, and some hypercalciuric patients lose bone mineral when placed on a low-calcium diet.<sup>56,57</sup> Finally, in the work by Curhan and associates,<sup>52</sup> a prospective study of the relation between dietary calcium intake and the risk of symptomatic kidney stones in a cohort of 45,629 men, an inverse relation was

found between the intake of calcium and the risk of kidney stones. The incidence of symptomatic kidney stones was lower by almost 50% in men with the highest calcium intake. Leonti et al<sup>58</sup> recently reported similar results, supporting the study by Curhan and associates, showing that a group of stone formers had a significantly lower daily intake of calcium than healthy controls (794 mg v 943 mg/day). Therefore, dietary calcium restriction is not advisable and may even be harmful. Daily intake of 800 to 1000 mg of calcium (two servings of dairy products) is considered adequate.

A high sodium intake inhibits tubular reabsorption of calcium, thus increasing calcium excretion. A significant reduction in urinary calcium has been demonstrated in hypercalciuric patients after dietary sodium restriction.<sup>59</sup> It is reasonable, although not proven efficacious in a prospective study, to advise calcium stone patients to avoid high salt intake. In hypercalciuric patients, a high salt intake decreases the effectiveness of thiazides and increases calcium excretion.<sup>60</sup> Sodium excretion in the urine equals dietary consumption and should be checked with each 24-hour urine study, especially if thiazides have been prescribed. Oral intake should be limited to 100 mEq (2300 mg in the diet) daily.

A small increase in urinary oxalate excretion affects calcium oxalate SS to a much larger extent than a similar increase in calcium excretion. Although most of the oxalate excreted in the urine is endogenously produced as an end product of metabolism, mild degrees of hyperoxaluria are common in stone formers secondary to increased oxalate absorption from the gastrointestinal tract.<sup>13</sup> Therefore, patients with mild hyperoxaluria may benefit from a low-oxalate diet, avoiding foods such as spinach, rhubarb, beets, nuts, chocolate, tea, wheat bran, and strawberries.<sup>61</sup>

Epidemiologic studies showing a correlation between affluence and nephrolithiasis implicated a diet rich in *animal protein* as a risk factor for calcium nephrolithiasis and uric acid stones.<sup>62</sup> High dietary protein intake is associated with increased calcium excretion in healthy subjects as well as in patients with kidney stones. Further, the mild metabolic acidosis resulting from excessive protein intake might stimulate bone resorption, with a secondary increase in calcium excretion and hypocitraturia. Oxaluria and uricosuria are also associated with a high-protein diet.<sup>63</sup> Although studies of low-protein diets are not consistent in showing a beneficial effect, a decrease in dietary protein is advised for all stone patients.

In summary, for most stone-forming patients, conservative measures that include an increase in fluid intake and the elimination of dietary excesses of calcium, sodium, oxalate, and protein is advisable (Table 7). A common initial approach is to try to alter these factors before resorting to specific treatment pro-

TABLE 7. NONSPECIFIC TREATMENT RECOMMENDATIONS

Drink enough liquids to maintain urine output of 2 L per 24 hours
Restrict calcium intake to 800–1000 mg (two servings of dairy products) per day
Restrict salt intake to <100 mEq per day (no salting of food, no consumption of "fast food")
Limit protein consumption (<12 oz of beef/poultry/fish per day)

toloc.<sup>64</sup> The effects of such measures have been referred to as the "stone clinic effect." In a study by Hosking et al,<sup>65</sup> 58% of patients (including single and recurrent stone formers) who were treated conservatively showed no evidence of new stone formation during a mean follow-up of >5 years. Finally, patients should be made aware that abrupt changes in fluid and sodium intake may be associated with side effects such as bloating or salt craving, respectively. These effects resolve spontaneously with time.

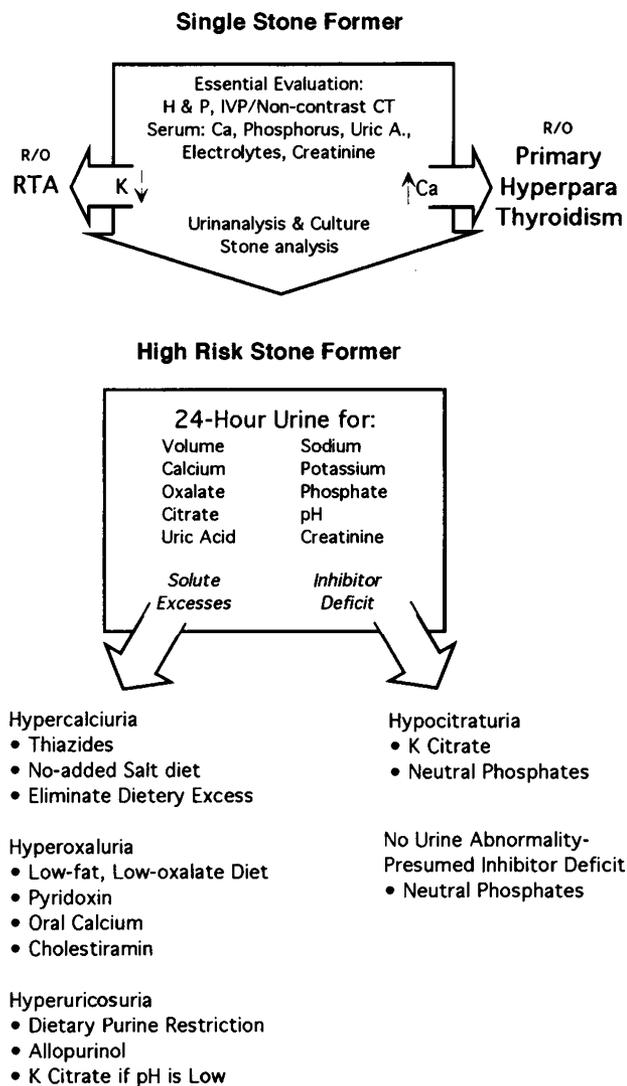
### Specific Treatment

Patients often have more than one metabolic risk factor. For example, Levy et al.<sup>2</sup> reported that among 1270 patients with recurrent nephrolithiasis, 41.3% were found to have a single abnormality, whereas 58.7% had multiple diagnoses. All identified abnormalities should be corrected. However, for simplicity of description, we discuss the major metabolic abnormalities separately. A general outline of the recommended evaluation and treatment of these abnormalities is presented in Figure 2 and will be detailed below. Treatment options for uric acid, cystine, and struvite stones are not within the scope of this article but are discussed elsewhere in this issue.

**Idiopathic Hypercalciuria.** More than half of all patients with calcium oxalate stones have idiopathic hypercalciuria (IH), which affects both sexes equally and occurs in successive generations. There is evidence to support a complex genetic origin for this disorder.<sup>48</sup> Hypercalciuria is defined by excretion of >300 mg/24 hours (man), >250 mg/24 hours (woman), 4 mg/kg of body weight per 24 hours (either sex), or 140 mg/g of creatinine. Patients with IH have by definition a normal concentration of serum calcium and lack a definable disorder that would cause the observed elevation of urine calcium such as RTA, sarcoidosis, hyperthyroidism, or immobilization. These disorders, as well as hyperparathyroidism, account for <10% of all calcium oxalate renal stones and will not be discussed here.

The pathogenesis hypothesis of IH can affect the choice of treatment. Dividing hypercalciuric patients into subgroups by suggesting different etiologic mechanisms would be appropriate only if such distinctions would influence treatment. Thus, if the primary mechanism was believed to be intestinal over-absorption, then a low-calcium diet or drugs that reduce calcium absorption, such as cellulose phosphate, would be appropriate for this subgroup. However, a low-calcium diet has been associated with reduced bone mineral levels and negative calcium balance,<sup>48,56,57</sup> and the benefits of cellulose phosphate are doubtful.<sup>7</sup> Therefore, thiazide therapy is the best currently available treatment for this group of patients. For patients subclassified as having renal hypercalciuria, thiazides, which increase tubular reabsorption of calcium, are the treatment of choice.<sup>49</sup> So in actuality, most hypercalciuric patients, regardless of their subgroup, will benefit from thiazide therapy.

Another problem with the structured specific approach for subgroups of hypercalciuria is that patients with this condition cannot easily be characterized into specific diagnostic groups. Recently, even Pak, who was the proponent of the selective approach, has stated that "strict adherence to the selective approach seems impractical except at a larger stone center" and suggested that "non-complicated" calcium stone formers with



**FIG. 2.** Evaluation and specific treatment options for calcium stone formers.

hypercalciuria should be treated with a combination of thiazides and potassium citrate,<sup>66</sup> which helps prevent hypokalemia and hypocitraturia secondary to thiazide therapy. Therefore, thiazides have emerged as the main contemporary therapy for most IH patients.<sup>11</sup>

Thiazides act directly on the kidney to reduce urinary calcium excretion. In addition, thiazides may cause shunting of absorbed dietary calcium into bone and reduce fractures by promoting a positive calcium balance.<sup>56</sup> Thiazide therapy is also the best-studied intervention for hypercalciuric stone formers. Although double-blind prospective studies with a follow-up of 1 or 2 years failed to show effectiveness, three studies conducted over 3 years showed a significantly lower relapse rate in thiazide-treated patients by the third year.<sup>5,9,67</sup> (See also article by Pearle and associates in this issue.) Therefore, treatment of patients with thiazides probably should be planned for at least 3 years in order to achieve significant results. Optional treatment regimens that have been studied include:

Chlorthalidone (Hygroton) 12.5–25 mg qd to a maximum of 100 mg qd;  
Hydrochlorothiazide (HCTZ; Esidrex, HydroDIURIL, Oretic, Microzide) 25–50 mg bid;  
Hydrochlorothiazide 50 mg with amiloride 5 mg (Moduretic); 1/2 tablet bid;  
Indapamide (Lozol) 2.5 mg qd.

Patients should be advised about the possible value of a low salt (<100 mEq/day) diet because of the negative effect of high salt intake on thiazide efficacy. Side effects are generally mild but may occur in 30% to 50% of the patients. Patients should be monitored for hypokalemia, which can be corrected with potassium citrate or a potassium-sparing diuretic such as amilorid (Midamor); 5 mg qd to tid. Side effects that are more common include lassitude and sleepiness. In addition, decreased libido, hypercholesterolemia, and hyperuricosemia may occur.

Cellulose phosphate (Calcibind) is an oral calcium-binding resin that is taken with meals. It is effective in reducing gastrointestinal absorption of calcium. However, it has not been shown effective in reducing stone formation in a controlled study, perhaps because it can produce secondary hyperoxaluria by making more oxalate available for absorption.<sup>68</sup> Some authors have used cellulose sodium phosphate in cases of documented Type I absorptive hypercalciuria.<sup>25,49</sup> Side effects may include nausea and diarrhea. In addition, when used in patients with normal calcium absorption, it may cause a negative calcium balance, raising the possibility of future bone disease. The resin may also cause hypomagnesemia by binding magnesium in the gut.<sup>13,48</sup> In our view, cellulose phosphate is rarely if ever indicated in the management of patients with IH.

Orthophosphates are salts of sodium or potassium phosphate that act by decreasing urinary excretion of calcium, binding calcium in the intestinal tract, and increasing urinary inhibitor activity, probably through stimulated renal excretion of pyrophosphate and citrate.<sup>60</sup> In one study, when given at an oral dose of 1500 mg per day in three or four doses, orthophosphates were as effective as thiazide diuretics.<sup>69</sup> However, in the only placebo-controlled trial reported, no effect of potassium acid phosphate therapy on stone recurrence was found.<sup>70</sup> The study was criticized for using an acidic salt, whereas neutral phosphates reduce urinary calcium excretion more effectively. Current indications for the use of orthophosphates include failure of more specific types of therapy or inability to tolerate the thiazides. In addition, calcium oxalate stone formers whose metabolic evaluation has failed to reveal any abnormality and who thus may have low urine inhibitor activity may also benefit from orthophosphate treatment. Available preparations are Neutra-Phos (one capsule or packet qid) and K-Phos neutral (250 mg one or two tablets tid/qid). Orthophosphate can cause diarrhea, which usually subsides after the first few weeks of therapy. Rarely, the treatment is associated with soft-tissue calcification in patients with renal insufficiency.

**Hyperuricosuria.** Hyperuricosuria is defined as a urinary daily excretion >800 mg and >750 mg for men and women, respectively. Hyperuricosuria is associated with uric acid stones, but, more interestingly, this condition is found in 10% to 26% of calcium stone formers.<sup>13</sup> Possible mechanisms linking uric acid and calcium oxalate crystallization include heterogeneous nucleation of calcium oxalate by uric acid or its

salts or reduction (by binding) of naturally occurring urinary inhibitors.<sup>71</sup> Most hyperuricosuric calcium oxalate stone formers have normal serum uric acid concentrations and, often, a urinary pH >5.5. Hyperuricosuria generally results from increased dietary purine intake derived from meat, poultry, and fish. Dietary purine restriction seems a logical first step in treatment. However, there are no published data to support its use. Rough guidelines for such a diet have been suggested by Coe: “moderate your diets; keep the total for a day of meat and poultry and of fish at one-half pound, or two-thirds pound (10–12 oz), and make the difference with breads or grains.”<sup>72</sup> If diet fails, medication should be administered.

Allopurinol (Zyloprim, Purinol) has been demonstrated in a placebo-controlled randomized clinical trial in calcium oxalate stone formers with normocalcemia and hyperuricosuria to be effective in reducing stone recurrence.<sup>73</sup> The preferred dose is 100 mg once or twice daily. Adverse effects of allopurinol include gastrointestinal disturbances, rash, and elevations of liver enzymes.

**Hyperoxaluria.** Hyperoxaluria is defined by a urinary oxalate excretion >45 mg/day for either sex. Although oxalate occurs in a majority of kidney stones, most stone formers have normal oxalate excretion rates, between 20 and 40 mg/24 hours.<sup>48</sup> Excessive urinary oxalate originates either from enhanced intestinal absorption (“enteric hyperoxaluria”) or from enhanced endogenous production (which usually accounts for most urinary oxalate).

Endogenous oxalate overproduction is rare and results from a congenital condition termed “primary hyperoxaluria.” There are two types of hereditary autosomal recessive hyperoxaluria. In the most common Type I (1:120,000 live births), reduced activity of hepatic peroxisomal alanine-glyoxylate aminotransferase (AGT) increases the availability of glyoxylate, which is converted to oxalic acid. In Type II, excretion of L-glycemic acid is increased. Recently, a third type (non-Type-1, non-Type-2) of hyperoxaluria has been described. Urine oxalate concentrations in the hereditary forms are typically very high, between 135 and 270 mg/day. Patients with congenital hyperoxaluria begin stone formation in early childhood and later develop nephrocalcinosis, accumulation of insoluble oxalate through the body (oxalosis), and tubulointerstitial nephropathy; and about half will manifest end-stage renal disease by the age of 15.<sup>74</sup>

Pyridoxin at daily dosages of 2 to 15 mg/kg reduces oxalate excretion to normal levels in about 20%, and reduces oxalate levels somewhat in about a third, of patients with Type I disease.<sup>75</sup> Other treatment modalities include high fluid intake supported by calcium oxalate crystallization inhibitors, that is, potassium citrate 150 mg/kg per day, or orthophosphate 30 mg/kg per day. Thiazide therapy may be given as well.<sup>75</sup>

Enteric hyperoxaluria can occur in patients with intestinal fat malabsorption from any cause. Examples include inflammatory bowel disease, celiac sprue, pancreatic insufficiency, and jejunoleal bypass. Long-chain fatty acids and bile acids increase colonic permeability to oxalate and bind calcium, thus freeing oxalate for absorption.<sup>76</sup> Because calcium absorption is severely decreased, these patients typically have very low urinary calcium excretion (i.e., <100 mg/day). Oxalate absorption occurs in the large intestine, so an intact colon is necessary for enteric hyperoxaluria to occur.<sup>77</sup> Treatment strategies include conservative dietary measures (low-fat, low-oxalate) combined with

or followed by medications that reduce oxalate absorption. Oral calcium supplements such as Tums can bind free oxalate and limit absorption. One to two grams with each meal is the recommended dose.<sup>78</sup> Cholestyramine (Questran), 4 g one to six times/day with meals, is a nonabsorbable resin that binds fatty acids, bile acids, and oxalate, thus reducing available oxalate. It is a useful drug because it helps to reduce diarrhea, a significant problem for many patients with malabsorption syndromes. Cholestyramine can cause vitamin K depletion; therefore, prothrombin time should be measured every 6 months. Some patients with malabsorptive syndromes exhibit hypomagnesiuria, which can be corrected with oral magnesium supplements.

**Hypocitraturia.** Low urinary citrate can raise the risk of stones because citrate is a strong calcium-binding molecule, forming a soluble salt, and may also act as an inhibitor of crystallization. Hypocitraturia is defined as a 24-hour excretion of <320 mg and is found in 15% to 60% of stone formers, often in combination with other metabolic abnormalities.

The most important regulator of citrate reabsorption is systemic acid-base status. Acidosis decreases renal citrate excretion, whereas alkalosis has the opposite effect. Hypokalemia, a diet high in animal protein, and urinary tract infection can also lower urinary citrate levels. Hypocitraturia is invariably found in patients with distal RTA (who typically have profoundly low citrate levels; i.e., <50 mg/day) and is also associated with chronic diarrhea states and diuretic-induced hypokalemia. However, in most cases, no underlying cause is found.<sup>13,48,60</sup>

Correcting remediable causes of hypocitraturia is the first treatment step. Administering a base such as potassium bicarbonate or potassium citrate will increase citrate excretion. Sodium bases may increase urinary calcium excretion and thus offset the benefits of increased urinary citrate. Potassium citrate has been shown in randomized clinical trials to significantly decrease stone recurrence.<sup>79</sup> A new drug (K-Mag), which is a combination of potassium citrate and magnesium, has been shown in a placebo-controlled randomized trial to be effective in inhibiting calcium stone formation.<sup>66</sup> Potassium citrate preparations are available in tablets (UroCit K) or solution (PolyCitra-K syrup, PolyCitra-K crystals, K Lyte). The initial dose should be 20 to 30 mEq bid.

## CONCLUSIONS

Surgical treatment of stone disease has advanced considerably in recent decades. Techniques such as SWL, percutaneous nephrolithotomy, and ureteroscopy combined with advances in laser technology have revolutionized the treatment of symptomatic stone disease. Although innovations in the surgical area will occur, further progress in minimally invasive techniques will likely be incremental. On the other hand, we can hope that new areas of research into the pathogenesis of stone formation (e.g., Randall's plaques, inhibitors) will set the stage in the new millennium for equally dramatic advances in the prevention of calcium urolithiasis. Urologists should always recall that the stone they are called on to remove is only the symptomatic expression of a more basic disease, that is, the formation of crystalline material in the upper urinary tract.

## ACKNOWLEDGMENTS

The study was funded in part by the Institute for Kidney Stone Disease, Methodist Hospital of Indiana, and by United States Public Health Service grant PZ1-DK43881.

## REFERENCES

1. Consensus conference. Prevention and treatment of kidney stones. *JAMA* 1988;260:977.
2. Levy FL, Adams-Huet, Pak CYC. Ambulatory evaluation of nephrolithiasis: An update of a 1980 protocol. *Am J Med* 1995;98:51.
3. Marangella M, Vitale C, Bagnis C, Bruno M, Ramello A. Idiopathic calcium nephrolithiasis. *Nephron* 1999;81(suppl 1):38.
4. Clark JY, Thompson IM, Optenberg SA. Economic impact of urolithiasis in the United States. *J Urol* 1995;154:2020.
5. Parks JH, Coe FL. Pathogenesis and treatment of calcium stones. *Semin Nephrol* 1996;16:398.
6. Parks JH, Coe FL. The financial effects of kidney stone prevention. *Kidney Int* 1996;50:1706.
7. Tomson CRV. Prevention of recurrent claim stones: A rational approach. *Br J Urol* 1995;76:419.
8. Williams RE. Long-term survey of 538 patients with upper urinary tract stone. *Br J Urol* 1963;35:416.
9. Borghi L, Meschi T, Guerra A, Noverini A. Randomized prospective study of a non thiazide diuretic, indapamide, in preventing calcium stone recurrences. *J Cardiovasc Pharmacol* 1993;22(suppl 6):S78.
10. Lingeman JE. Nephrolithiasis: A controllable disease. *Indiana Med* 1983;17:313.
11. Coe FL, Parks JH. New insights into the pathophysiology and treatment of nephrolithiasis: New research venues. *J Bone Min Res* 1977;12:522.
12. Balaji KC, Menon M. Mechanism of stone formation. *Urol Clin North Am* 1997;24:1.
13. Asplin JR, Favus MJ, Coe FL. Nephrolithiasis. In: Brenner and Rector's *The Kidney*, ed 5. Philadelphia: WB Saunders, 1996, pp 1893-1935.
14. Parks JH, Coward M, Coe FL. Correspondence between stone composition and urine supersaturation in nephrolithiasis. *Kidney Int* 1997;51:894.
15. Fleisch H. Inhibitors and promoters of stone formation. *Kidney Int* 1978;13:361.
16. Melnic I, Landes RR, Hoffman AA, Burch JF. Magnesium therapy for recurring calcium oxalate urinary calculi. *J Urol* 1971;105:119.
17. Pak CYC, Sakhaee K, Fuller CJ. Physiological and physiochemical prevention of calcium-stone formation by potassium citrate therapy. *Trans Assoc Am Physicians* 1983;96:294.
18. Hess B, Nakagawa Y, Parks JH, Coe FL. Molecular abnormality of Tamm-Horsfall glycoprotein in calcium oxalate nephrolithiasis. *Am J Physiol* 1991;260:F569.
19. Asplin JR, Arsenault D, Parks JH, Coe FL, Hoyer JR. Contribution of human uropontin to inhibition of calcium oxalate crystallization. *Kidney Int* 1998;53:194.
20. Asplin J, Deganello S, Nakagawa YN, Coe FL. Evidence that nephrocalcin inhibits nucleation of calcium oxalate monohydrate crystals. *Am J Physiol* 1991;261:F824.
21. Doyle IR, Marshall VR, Dawson CJ, Ryall RL. Calcium oxalate crystal matrix extract: The most potent macromolecular inhibitor of crystal growth and aggregation yet tested in undiluted human urine in vitro. *Urol Res* 1995;23:53.
22. Atmani F, Khan SR. Characterization of uronic-acid-rich inhibitor

- of calcium oxalate crystallization isolated from rat urine. *Urol Res* 1995;23:95.
23. Cao LC, Boeve ER, de Bruijn WC, Kok DJ, de Water R, Deng G, Schroder FH. Glycosaminoglycans and semisynthetic sulfated polysaccharides: An overview of their potential application in treatment of patients with urolithiasis. *Urology* 1997;50:173.
  24. Pillay S, Asplin JR, Coe FL. Evidence that calgranulin is produced by kidney cells and is an inhibitor of calcium oxalate crystallization. *Am J Physiol* 1998;275:F255.
  25. McDonald MW, Stoller M. Urinary stone disease: A practical guide to metabolic evaluation. *Geriatrics* 1997;52:39.
  26. Finlayson B, Reid F. The expectation of free and fixed particles in urinary stone disease. *Invest Urol* 1978;15:442.
  27. Khan SR. Calcium oxalate crystal interaction with renal tubular epithelium: Mechanism of crystal adhesion and its impact on stone development. *Urol Res* 1995;23:71.
  28. Lieske JC, Norris R, Swift H, Tobak FG. Adhesion, internalization and metabolism of calcium oxalate monohydrate crystals by renal epithelial cells. *Kidney Int* 1977;52:1291.
  29. Hautman R, Lehman A, Komor S. Intrarenal distribution of oxalic acid, calcium, sodium, and potassium in man. *Eur J Clin Invest* 1980;10:173.
  30. Tiselius HG. Investigation of single and recurrent stone formers. *Min Electrol Metab* 1994;20:321.
  31. Prafitt AM. Acetazolamide and sodium bicarbonate induced nephrocalcinosis and nephrolithiasis. *Arch Intern Med* 1969;124:736.
  32. Cohen TD, Ehreth J, King LR, Preminger GM. Pediatric urolithiasis: Medical and surgical management. *Urology* 1996;47:292.
  33. Cryer PE, Garber AJ, Joffsten P. Renal failure after small intestinal bypass for obesity. *Arch Intern Med* 1975;135:1610.
  34. Gigax JH, Leach JR. Uric acid calculi associated with ileostomy for ulcerative colitis. *J Urol* 1971;105:777.
  35. Dobbins JW, Binder HJ. Effect of bile salts and fatty acids on the colonic absorption of oxalate. *Gastroenterology* 1976;70:1096.
  36. Mostafavi MR, Ernst RD, Saltzman B. Accurate determination of chemical composition of urinary calculi by spiral computerized tomography. *J Urol* 1998;159:673.
  37. Saw KC, McAteer JA, Monga AG, Chua GT, Lingeman JE, Williams JC Jr. Characterization of urinary calculi by spiral computerized tomography (CT): Effects of stone composition, stone size and scan collimation. *J Urol* 1999;161:1520 (abstract).
  38. Pak CYC. Should patients with single renal stone occurrence undergo diagnostic evaluation? *J Urol* 1982;127:855.
  39. Preminger GM. The metabolic evaluation of patients with recurrent nephrolithiasis: A review of comprehensive and simplified approaches. *J Urol* 1989;141:760.
  40. Tiselius HG. Investigation of single and recurrent stone formers. *Min Electrol Metab* 1994;20:321.
  41. Lingeman JE, Segel YI, Steele B. Metabolic evaluation of infected renal lithiasis: Clinical relevance. *J Endourol* 1995;9:51.
  42. Strauss AL, Coe FL, Parks JH. Formation of a single calcium stone of renal origin: Clinical and laboratory characteristics of patients. *Arch Intern Med* 1982;142:504.
  43. Preminger GM. Medical management of urinary calculus disease 1: Pathogenesis and evaluation. *AUA Update Ser* 1995;14:38.
  44. Werness PG, Brown CM, Smith LH, Finlayson B. Equil2: A basic computer program for the calculation of urinary saturation. *J Urol* 1985;134:1242.
  45. Tiselius HG. Metabolic evaluation of patients with stone disease. *Urol Int* 1997;59:131.
  46. 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.
  47. Pak CYC, Ohata M, Lawrence EC, Snyder W. The hypercalciurias: Courses, parathyroid functions and idiopathic criteria. *J Clin Invest* 1974;54:387.
  48. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. *N Engl J Med* 1992;327:1141.
  49. Preminger GM. Medical management of urinary calculus disease II: Classification of metabolic disorders and selective medical treatment. *AUA Update Ser* 1995;14:38.
  50. Frank M, de Vries A, Tikva P. Prevention of urolithiasis. *Arch Environ Health* 1966;13:625.
  51. Borghi L, Meschi T, Schianchi T, Briganti A, Guerra A, Allegri F, Novarini A. Urine volume: stone risk factor and preventive measure. *Nephron* 1999;81(suppl 1):31.
  52. Curhan GC, Willett 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* 1993;12:833.
  53. Wabner CL, Pak CYC. Effect of orange juice consumption on urinary stone risk factors. *J Urol* 1993;149:1405.
  54. Goldfarb DS, Coe FL. Beverages, diet and prevention of kidney stones. *Am J Kidney Dis* 1999;33:398.
  55. Bataille P, Pruna A, Gregoire I. Critical role of oxalate restriction in association with calcium restriction to decrease the probability of being a stone former: Insufficient effect in idiopathic hypercalciuria. *Proc Eur Dial Transplant Assoc* 1983;20:401.
  56. Coe FL, Parks JH, Favus MJ. Diet and calcium: The end of an era? *Ann Intern Med* 1997;126:553.
  57. 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.
  58. Leonetti F, Dussol B, Berthezene P, Thirion X, Berland Y. Dietary and urinary risk factors for stones in idiopathic calcium stone formers compared with healthy subjects. *Nephrol Dial Transplant* 1998;13:617.
  59. Silver J, Rubinger D, Friedlaender MM, Popovtzer MM. Sodium-dependent idiopathic hypercalciuria in renal stone formers. *Lancet* 1983;2:484.
  60. Ruml LA, Pearle MS, Pak CYC. Medical therapy of calcium oxalate urolithiasis. *Urol Clin North Am* 1997;24:117.
  61. Massey LK, Sutton RA. Modification of dietary oxalate and calcium reduces urinary oxalate in hyperoxaluric patients with kidney stones. *J Am Diet Assoc* 1993;93:1305.
  62. Parivar F, Low RK, Stoller ML. The influence of diet on urinary stone disease. *J Urol* 1996;155:432.
  63. Breslau NA, Brinkley L, Hill K, Pak CYC. Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism. *J Clin Endocrin Metab* 1988;66:140.
  64. Wilson DM. Clinical and laboratory approaches for evaluation of nephrolithiasis. *J Urol* 1989;141:770.
  65. Hosking DH, Erickson SB, Van den Berg CJ, Wilson DM, Smith LH. The stone clinic effect in patients with idiopathic calcium urolithiasis. *J Urol* 1983;130:1115.
  66. Pak CYC. Southwestern internal medicine conference: Medical management of nephrolithiasis—A new, simplified approach for general practice. *Am J Med Sci* 1997;313:215.
  67. Ettinger B, Citron JT, Livermore B, Dolman LI. Chlorthalidone reduces calcium oxalate calculus recurrence but magnesium hydroxide does not. *J Urol* 1988;139:679.
  68. Backman U, Danielson BG, Johansson G, Ljughall S, Wikstrom B. Treatment of recurrent calcium stone formation with cellulose phosphate. *J Urol* 1980;123:9.
  69. Hosogina KL, Ellison AS, Burtis WJ, Sartori L, Lang RL, Broadus AE. Trichloromethiazide and oral phosphate in patients with absorptive hypercalciuria. *J Urol* 1989;141:269.
  70. Ettinger B. Recurrent nephrolithiasis: Natural history and effect of phosphate therapy. *Am J Med* 1976;61:200.

71. Seftel A, Resnick MI. Metabolic evaluation of urolithiasis. *Urol Clin North Am* 1990;17:159.
72. Coe FL. Commentary: Allopurinol treatment of uric-acid disorders in calcium-stone formers. *J Lithotrip Stone Dis* 1991;3:272.
73. Ettinger B, Tang A, Citron JT, et al. Randomized trial of allopurinol in the prevention of calcium oxalate calculi. *N Engl J Med* 1986;315:1386.
74. Cochat P. Primary hyperoxaluria type 1. *Kidney Int* 1999;55:2533.
75. Toussaint C. Pyridoxine-responsive PH1: Treatment. *J Nephrol* 1998;11(suppl 1):49.
76. Bushinski DA. Nephrolithiasis. *J Am Soc Nephrol* 1998;9:917.
77. Dobbins JW, Binder HJ. Importance of colon in enteric hyperoxaluria. *N Engl J Med* 1977;296:298.
78. Smith LH. Hyperoxaluric states. In: Coe FL, Favus MJ (eds). *Disorders of Bone and Mineral Metabolism*. New York: Raven Press, 1999, pp 707-728.
79. Barcelo P, Wuhl O, Servitge E, Rousaud A, Pak CYC. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J Urol* 1993;150:1761.

Address reprint requests to:

*James E. Lingeman, M.D.*

*1801 North Senate Blvd., Suite 700*

*Indianapolis, IN 46202*

*E-mail: jlingeman@clarian.com*

**This article has been cited by:**

1. Seung Young Oh , Jong Kyou Kwon , Seo Yeon Lee , Moon Soo Ha , Yong Wook Kwon , Young Tae Moon . 2011. A Comparative Study of Experimental Rat Models of Renal Calcium Oxalate Stone FormationA Comparative Study of Experimental Rat Models of Renal Calcium Oxalate Stone Formation. *Journal of Endourology* 25:6, 1057-1061. [[Abstract](#)] [[Full Text](#)] [[PDF](#)] [[PDF Plus](#)]
2. Yong-June Kim, Moon Seon Park, Won-Tae Kim, Seok-Joong Yun, Wun-Jae Kim, Sang-Cheol Lee. 2010. Hypertension Influences Recurrent Stone Formation in Nonobese Stone Formers. *Urology* . [[CrossRef](#)]
3. Scott M. Castle, Matthew R. Cooperberg, Natalia Sadetsky, Brian H. Eisner, Marshall L. Stoller. 2010. Adequacy of a Single 24-Hour Urine Collection for Metabolic Evaluation of Recurrent Nephrolithiasis. *The Journal of Urology* 184:2, 579-583. [[CrossRef](#)]
4. Yun-Sok Ha, Dong-Un Tchey, Ho Won Kang, Yong-June Kim, Seok-Joong Yun, Sang-Cheol Lee, Wun-Jae Kim. 2010. Phosphaturia as a Promising Predictor of Recurrent Stone Formation in Patients with Urolithiasis. *Korean Journal of Urology* 51:1, 54. [[CrossRef](#)]
5. Cheol Park, Yun-Sok Ha, Yong-June Kim, Seok-Joong Yun, Sang-Cheol Lee, Wun-Jae Kim. 2010. Comparison of Metabolic Risk Factors in Urolithiasis Patients according to Family History. *Korean Journal of Urology* 51:1, 50. [[CrossRef](#)]
6. Yong-June Kim, Tae-Hwan Kim, Seok-Joong Yun, Min Eui Kim, Wun-Jae Kim, Sang-Cheol Lee. 2009. Renal Phosphate Control as a Reliable Predictive Factor of Stone Recurrence. *The Journal of Urology* 181:6, 2566-2572. [[CrossRef](#)]
7. Young-Won Kim, Yun-Sok Ha, Yong-June Kim, Seok-Joong Yun, Sang-Cheol Lee, Wun-Jae Kim. 2009. Comparison of Clinico-Metabolic Characteristics between Calcium Oxalate and Uric Acid Stone Formers. *Korean Journal of Urology* 50:9, 897. [[CrossRef](#)]
8. S LEE, Y KIM, T KIM, S YUN, N LEE, W KIM. 2008. Impact of Obesity in Patients With Urolithiasis and its Prognostic Usefulness in Stone Recurrence. *The Journal of Urology* 179:2, 570-574. [[CrossRef](#)]
9. In-Chang Cho, Yong-June Kim, Sang-Cheol Lee. 2007. Metabolic Abnormalities and the Risk for Recurrence in Obese Patients with Urolithiasis. *Korean Journal of Urology* 48:7, 718. [[CrossRef](#)]
10. B MATLAGA, S KIM, S WATKINS, R KUO, L MUNCH, J LINGEMAN. 2006. Changing Composition of Renal Calculi in Patients With Neurogenic Bladder. *The Journal of Urology* 175:5, 1716-1719. [[CrossRef](#)]
11. BIJAN SHEKARRIZ, HSUEH-FU LU, MARSHALL L. STOLLER. 2001. CORRELATION OF UNILATERAL UROLITHIASIS WITH SLEEP POSTURE. *The Journal of Urology* 1085-1087. [[CrossRef](#)]
12. B SHEKARRIZ, H LU, M STOLLER. 2001. CORRELATION OF UNILATERAL UROLITHIASIS WITH SLEEP POSTURE. *The Journal of Urology* 165:4, 1085-1087. [[CrossRef](#)]
13. Hans-G??ran Tiselius. 2000. Metabolic evaluation and therapy. *Current Opinion in Urology* 10:6, 545-549. [[CrossRef](#)]