THE PATHOGENESIS AND TREATMENT OF KIDNEY STONES

Fredric L. Coe, M.D., Joan H. Parks, M.B.A., and John R. Asplin, M.D.

About three fourths of all kidney stones are composed of calcium oxalate; most calcium oxalate stones also contain a small amount of hydroxyapatite, and 10 to 12 percent contain some uric acid. 

Five percent of stones are pure uric acid, 6 percent contain more than 50 percent hydroxyapatite or calcium monohydrogen phosphate (brushite), and less than 1 percent are composed of cystine. Whereas most calcium oxalate stones are less than 2 cm in diameter, struvite, uric acid, and cystine stones may fill the renal collecting system (staghorn calculus). Tiny flecks of calcium salts that encrust calyces can make kidney radiographs seem like pictures of the night sky (nephrocalcinosis). Calcium oxalate, uric acid, or cystine crystals can scour the urinary tract, cause pain and bleeding, and then disperse — a process commonly described as “passing gravel” and more formally termed “crystalluria.”

The composition of every stone should be analyzed. Polarization microscopy is an inexpensive guide to differentiation; infrared and x-ray diffraction techniques surpass microscopy in precision and sensitivity, but we have not found their use essential. Calcium oxalate and calcium phosphate stones are black, gray, or white; on x-ray films they are small (<1 cm in diameter), dense, opaque, and sharply circumscribed. Uric acid stones are white or orange, and uric acid gravel is orange but nearly transparent radiographically unless mixed with calcium crystals or struvite. Uric acid stones are typically seen as filling defects on intravenous pyelograms. CT scanning can distinguish them from kidney tissue or blood clots and reveal their sizes and shapes. Struvite stones seem garned and laminated on radiographs; they look like ginger root. Cystine stones are greenish yellow and flecked with shiny crystallites, like mica. On x-ray films, they look like homogeneous pieces of sculpted wax or soap. Urinalysis can reveal the presence of crystals and provide clues to the type of stone; some of the common types are shown in Figure 1.

Physical Chemistry of Stone Formation

Think about a beaker of water with calcium oxalate crystals in it; the concentration of calcium oxalate salt in the water is just high enough to prevent the crystals from dissolving and not high enough to allow them to grow. That exact concentration is the solubility of calcium oxalate; concentrations above it are called supersaturated, below it undersaturated. In normal urine the concentration of calcium oxalate salt is four times higher than its solubility. High rates of calcium and oxalate excretion and low urinary volumes increase calcium oxalate supersaturation. Because citrate forms a solvate complex with calcium, low urinary citrate excretion increases calcium oxalate supersaturation. A urinary pH above 6.5 increases the proportion of divalent and trivalent phosphate ions, and therefore increases calcium phosphate supersaturation.

When calcium oxalate supersaturation is 7 to 11 times its solubility, the dissolved calcium oxalate can form nuclei of its solid phase (nucleation). Nuclei usually form on existing surfaces (heterogeneous nucleation); possible surfaces in the kidney include epithelial linings, cell debris, urinary casts, and other crystals. Nuclei rarely form in free solution (homogeneous nucleation), and only under special conditions. Theoretically, any factor that increases the number of heterogeneous nuclei in tubular fluid or urine, such as epithelial injury, could lower the upper metastable limit, the supersaturation at which crystals first form. Hyperuricosuria, which promotes the formation of calcium oxalate stones, and lowers the metastable limit of calcium oxalate, may act by producing urate or uric acid seeds that function as heterogeneous nuclei. Both hypercalciuria and hyperuricosuria promote hematuria, probably from crystalluria.

Microscopic nuclei can form objects as large as stones only by growing or aggregating into large clumps. They must also anchor themselves somehow or else be swept away in the urine. Nuclei cannot grow large enough to anchor and occlude renal tubular lumens within the five to seven minutes it takes them to pass through nephrons, but they can aggregate to such a size within a minute. Urate and calcium oxalate crystals anchor to surfaces of cultured renal epithelial cells, and may adhere in vivo to tubular cells or urothelium, and grow at leisure to the size of a stone.

Kidney proteins inhibit all phases of crystallization. Nephrocalcinolytic, an acidic glycoprotein of renal origin that contains the unusual amino acid γ-carboxyglutamic acid, inhibits calcium oxalate nucleation, growth, and aggregation. Tamm-Horsfall mucoprotein, made in renal thick ascending limbs, inhibits aggregation alone. Uropontin, produced by the
Figure 1. Urinary Crystals Commonly Seen in Nephrolithiasis. Calcium oxalate dihydrate crystals are shown in Panel A. Dumbbell-shaped calcium oxalate monohydrate crystals, which are the size of erythrocytes, are shown to the left of the pyramidal dihydrate crystals in Panel B. Elongate, lath-shaped brushite crystals can be seen in Panel C, rhomboidal uric acid crystals in Panel D, uric acid microcrystallites in Panel E, coffin-lid-shaped struvite crystals in Panel F, and cystine crystals in Panel G.
kidney, inhibits the growth of calcium oxalate crystals; its other effects are unknown.

**General Clinical Considerations**

**Clinical Presentation of Stones**

Renal colic begins suddenly and intensifies over a period of 15 to 30 minutes into a steady, unbearable pain that causes nausea and vomiting.22 The pain, like the stone, often passes downward from the flank along a path that curves anteriorly toward the groin. Urinary frequency and dysuria can occur as the stone reaches the ureterovesical junction. When the stone passes into the bladder or moves in the ureter to decompress the urinary system, the pain vanishes so abruptly that we have seen patients glance over their shoulders as if they were looking to see where it could have gone.

Stones may cause obstructive uropathy, especially if they are painless and therefore remain undetected for long periods. Though common and disturbing for patients, bleeding has little importance of its own. Among patients who have kidney stones, cystoscopy is performed at a rate of 13 per 100 patient-years in men and 28 per 100 patient-years in women, with rates of infection of 3 and 20 per 100 patient-years, respectively.23

**Management of Stones**

A recent National Institutes of Health Consensus Conference on nephrolithiasis proposed general guidelines for managing stones in the kidneys and urinary tract (Table 1).24 Most ureteral stones that are less than 5 mm in diameter pass spontaneously, whereas stones that are 7 mm or more in diameter have a poor chance of passing. Stones that lodge in the distal ureter — the portion of the ureter that is below the pelvic brim (the lower margin of the sacrum) and that stop progressing downward are best removed ureteroscopically with a stone basket or disrupted in situ with extracorporeal shock-wave lithotripsy (Table 1).25-27

Stones that are lodged in the proximal ureter (above the pelvic brim) and that stop progressing downward are best pushed upward into the renal pelvis and disrupted by extracorporeal shock-wave lithotripsy.26,27 Pushing a stone backward requires cystoscopy and the passage of a catheter up the ureter. The use of a double-J stent (a ureteral catheter shaped like a "J" at both ends) passed into the renal pelvis may improve the likelihood of completely removing the stone.27 If the stone cannot be pushed back, it can be bypassed with a stent catheter to provide drainage and disrupted in situ with extracorporeal shock-wave lithotripsy.28 In either case, percutaneous nephrolithotomy is needed if lithotripsy fails. Surgical ureterolithotomy should be used only after all other procedures have failed.

Stones that are less than 2 cm but more than 5 mm in diameter in the kidney can best be treated with extracorporeal shock-wave lithotripsy alone; stones that exceed 2 cm, or those that exceed 1 cm and are in the lower renal poles, may best be treated with percutaneous nephrolithotomy.26-28 Because the use of lithotripsy alone leaves residual stones in 35 to 54 percent of cases, whereas percutaneous nephrolithotomy succeeds in most cases. Double-J stents can be placed to

---

**Table 1. Treatments for Stones in Kidney and Urinary Tract**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>Efficacy</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ureteroscopic removal of stone</td>
<td>Stone lodged in distal ureter and not progressing downward</td>
<td>98%†</td>
<td>Need for anesthesia, ureteral injury</td>
</tr>
<tr>
<td>Pushing back the stone with ESWL In situ ESWL</td>
<td>Stone lodged in proximal ureter and not progressing downward</td>
<td>96-100%†</td>
<td>PCNL also required in 1-2% of cases; ureteral tear; ESWL complications†</td>
</tr>
<tr>
<td></td>
<td>Stone lodged in distal ureter and not progressing downward</td>
<td>78% success with no stent; 89% success with stent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kidney stones 0.5 to &lt;2 cm in diameter</td>
<td>77-80% stone-free†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kidney stones &gt;2 cm or &gt;1 cm and in lower pole</td>
<td>35-40% stone-free if stone is &gt;2 cm; 54% stone-free if stone is &gt;1 cm and in lower pole</td>
<td></td>
</tr>
<tr>
<td>PCNL</td>
<td>Stone lodged in proximal ureter and not progressing downward; failure of push-back procedure and ESWL (1-2% of cases)</td>
<td>90% success</td>
<td>4-5 days of hospitalization; need for anesthesia†</td>
</tr>
<tr>
<td></td>
<td>Kidney stones not better treated with ESWL alone</td>
<td>80-85% stone-free‡</td>
<td></td>
</tr>
<tr>
<td>Dissolution with oral or parenteral agents**</td>
<td>Uric acid stones</td>
<td>Varies; poor if stone is coated with calcium oxalate or struvite</td>
<td>Fragments may obstruct the ureter</td>
</tr>
<tr>
<td></td>
<td>Cystine stones</td>
<td>Varies; poor if stone is coated with calcium oxalate or struvite</td>
<td>See text</td>
</tr>
</tbody>
</table>

†Data of Beane et al.22
‡Data of Ljunggren.27
**The complications of ESWL include pain, hematuria (filling of ureter with fragments of stone), bruising of the skin, periureteric hematoma, percutaneous (rare), ureteral, and sometimes, increased blood pressure.

††Data of Ljunggren et al.26 **Data of Segura.28 **Dissolution by local irrigation through nephrostomy or other types of access is not covered in this review.
facilitate the drainage of fragments, particularly in the case of larger stones. Asymptomatic kidney stones of less than 5 mm in diameter should be left untreated. The guidelines for extracorporeal shock-wave lithotripsy and percutaneous nephrolithotomy hold for struvite and uric acid stones; because lithotripsy disrupts cystine stones only with great difficulty, they may require percutaneous lithotomy.

Prevention of Recurrence

Preventing stones from recurring reduces the need for urologic intervention. Because we define new stones as those not visualized on previous radiographs that are passed, removed, disrupted, or seen on x-ray films, we read all renal x-ray films ourselves, correlate the stone counts with the clinical history, and rely heavily on information from hospital, emergency room, and office records. Doctors and patients may call a treatment ineffective and change or stop it if they mistake old stones for new ones.

Prevention requires a diagnosis of the cause of the stone (Table 2), with the use of urine- and blood-chemistry measurements, and stone analysis. We collect three 24-hour urine samples from outpatients following their normal diets, each with a corresponding blood sample drawn between 7 and 9 a.m., 12 hours after the most recent meal. In each urine and blood sample we measure concentrations of calcium, magnesium, phosphorus, uric acid, and creatinine; in one blood sample, sodium and potassium; and in the three urine samples, oxalate, citrate, pH, and volume. We perform cystine screening on all patients.

Although the Consensus Conference recommended collecting at least one blood and urine sample from all patients with recurrent stones, we use three urine samples to estimate variability. We evaluate and treat patients with a first stone, because a majority eventually have a recurrence, if left untreated. The Consensus Conference recommended that only blood measurements be made in patients with a first stone to detect primary hyperparathyroidism and decreased renal function, along with a conventional medical evaluation. The Consensus Conference rejected the idea that extracorporeal shock-wave lithotripsy can supplant medical prevention, since the former has risks and costs and since stones cause pain and time lost from work. Controlled trials that we discuss later in this review document the effectiveness of easily used medical methods of prevention.

Remediable Causes of Calcium Stones

Primary Hyperparathyroidism

Parathyroid hormone increases the synthesis of 1α,25-dihydroxyvitamin D₃ (calcitriol), which increases the intestinal absorption of calcium; parathyroid hormone also raises renal tubular calcium reabsorption as well as the rate of bone turnover. Increased serum parathyroid hormone therefore causes hypercalcemia and hypercalciuria, that increases the supersaturation of calcium oxalate in the urine. High serum levels of the hormone lower the serum phosphorus level, because parathyroid hormone reduces the reabsorption of phosphorus by the renal tubules more than calcitriol raises intestinal phosphorus absorption; low serum phosphorus levels increase calcitriol production.

Diagnosis

Our patients with primary stone-forming hyperparathyroidism usually have serum calcium levels between 10.2 and 10.8 mg per deciliter (2.55 and 2.70 mmol per liter), just above our own upper limit of normal of 10.1 mg per deciliter (2.52 mmol per liter). Others report higher average values. One reason for the occasional reports of "normocalcemic primary hyperparathyroidism" must be the mildness of hypercalcemia as compared to the wide conventional range of normal values (9 to 10.5 mg per deciliter [2.25 to 2.62 mmol per liter]). Some believe that the measurement of ionized calcium levels improves diagnostic accuracy.

The differential diagnosis of hypercalcemia in persons who form stones includes sarcoidosis, a state of calcitriol excess with very low serum parathyroid hormone levels and elevated serum levels of angiotensin II-converting enzyme; familial hypocalciuric hypercalcemia; an autosomal dominant and apparently benign disorder of bone chemistry only, best diagnosed by documenting hypercalcemia in blood relatives and best left untreated; malignant neoplasms; inadvertent use of thiazide diuretics during the evaluation; overuse of vitamin D supplements; treatment with lithium, which can cause a condition very similar to primary hyperparathyroidism; and numerous uncommon causes. We have found that almost all patients with hypercalcemia who form stones have primary hyperparathyroidism; a rare few have sarcoid or incidential familial hypocalciuric hypercalcemia.

Treatment

Among asymptomatic patients, especially postmenopausal women, the question of whether to treat hyperparathyroidism surgically or palliate it medically engenders controversy, but there is agreement about the value of surgical treatment in patients who form stones. For the 85 percent of patients with an adenoma, success rates are high with simple excision. For the 15 percent with enlargement of multiple glands because of hyperplasia, the best treatment probably requires removal of all glands from the neck and transplantation of the patients' own parathyroid gland.

### Table 2. Composition of Stones and Their Causes.

<table>
<thead>
<tr>
<th>Composition of Stone</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium oxalate</td>
<td>Primary hyperparathyroidism</td>
</tr>
<tr>
<td></td>
<td>Idiopathic hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Low urine citrate level</td>
</tr>
<tr>
<td></td>
<td>Hypercalciuria</td>
</tr>
<tr>
<td></td>
<td>Hyperuricosuria</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td>Uric acid</td>
<td>Low urine pH</td>
</tr>
<tr>
<td>Struvite</td>
<td>Urinary tract infection with bacteria that express urease</td>
</tr>
<tr>
<td>Cystine</td>
<td>Cystinuria</td>
</tr>
</tbody>
</table>
tissue into the forearm. Clues to the presence of hyperplasia are familial hyperparathyroidism and evidence of multiple-endocrine-gland neoplasia.\

Idiopathic Hypercalciuria

A syndrome of unexplained hypercalciuria, idiopathic hypercalciuria can be distinguished from primary hyperparathyroidism only by its normal serum calcium levels. Reasonable upper limits for 24-hour urinary calcium excretion in outpatients are 250 mg (6.2 mmol) per day in women, 300 mg (7.5 mmol) per day in men, or 140 mg (3.5 mmol) per gram of creatinine or 4 mg (0.1 mmol) per kilogram of body weight per day in patients of either sex. Because more than half of all patients with calcium oxalate stones have idiopathic hypercalciuria, we shall discuss its pathogenesis and treatment in more detail than those of the other causes of stones.

Cause

Idiopathic hypercalciuria affects both sexes equally and occurs in successive generations and among about half the blood relatives of a given proband, as though inherited as an autosomal dominant trait. In two large families in which many members were affected by idiopathic hypercalciuria, a few had evidence of renal tubular acidosis, as though idiopathic hypercalciuria led to renal tubular acidosis. Erythrocyte calcium ATPase levels may vary directly with the level of urinary calcium excretion in members of families with idiopathic hypercalciuria; both are correlated in parents and their offspring but not between parents, as if the ATPase levels were related to the cause of idiopathic hypercalciuria.

Some members of a Bedouin tribe in which intermarriage is common have hypercalciuria as a result of high serum calcitriol levels caused by renal phosphate wasting. Oral phosphate supplements reverse the hypercalciuria, low serum phosphorus levels, and rickets. In another family, one brother and one sister among seven children of a consanguineous marriage had Fanconi's syndrome, with rickets, elevated serum calcitriol levels, and hypercalciuria. A case report described five members of one family with hypouricemia from renal urate wasting, reduced bone mineral density, normal serum phosphorus levels, and hypercalciuria. Pseudoxanthoma elasticum causes high serum calcitriol levels and hypercalciuria; cystic fibrosis causes hypercalciuria and nephrocalcinosis. Consanguinous breeding of rats with hypercalciuria raises the rates of calcium excretion in succeeding generations. All evidence points to a complex genetic origin of human and murine idiopathic hypercalciuria.

Origin of Hypercalciuria in Idiopathic Hypercalciuria

People with idiopathic hypercalciuria absorb and excrete more calcium in their urine than in that of normal people. A high rate of calcium absorption should suppress the release of parathyroid hormone by raising serum calcium levels after meals, and most patients with idiopathic hypercalciuria have normal or low levels of serum parathyroid hormone and urinary cyclic AMP (cAMP). Fasting should also lower urinary calcium to the levels found in normal subjects who are fasting, but this is true only for some patients.

Pak and colleagues have proposed the existence of two subtypes of absorptive hypercalciuria. By definition, all patients with absorptive hypercalciuria have normal or low levels of serum parathyroid hormone, fasting urinary calcium levels below 0.11 mg per deciliter (the upper limit of normal), and calcium hyperabsorption documented by urinary excretion of more than 0.2 mg of calcium per milligram of creatinine after a 1000-mg oral calcium load given in a synthetic meal. After one week of a diet containing 400 mg of calcium and 100 mg of sodium chloride per day, a daily urinary calcium excretion above 200 mg (5 mmol, the upper limit of normal levels among unaffected subjects following the diet) is indicative of type 1 absorptive idiopathic hypercalciuria. Absorptive hypercalciuria is urinary calcium excretion of less than 200 mg per day is indicative of type 2 renal idiopathic hypercalciuria. Because a diet low in calcium lowers urinary calcium to normal levels in patients with type 2 idiopathic hypercalciuria by definition, subtyping can in principle guide treatment. A third type, which is like type 1 but is associated with serum phosphorus levels of less than 2.9 mg per deciliter (0.9 mmol per liter), appears in some reports; presumably phosphorus supplements can best treat it, as in the Bedouin tribe with a similar syndrome.

A few patients who have high serum parathyroid hormone levels presumably lose calcium into their urine because the renal reabsorption of calcium is reduced (renal leak hypercalciuria), leading to secondary hyperparathyroidism, parathyroid hormone--induced activation of calcitriol production, and calcitriol-mediated overabsorption of calcium by the intestines. Pacifi et al. could differentiate between the renal and absorptive forms of idiopathic hypercalciuria with the use of isotopic-absorption measurements, serum parathyroid hormone levels, and urine cAMP measurements, but not with the use of responses to oral calcium loading alone.

Effects of a Low-Calcium Diet on Calcium Balance in Idiopathic Hypercalciuria

In many calcium-balance studies, all patients with idiopathic hypercalciuria had a negative calcium balance when net calcium absorption fell below 300 mg per day; whereas all normal subjects had a positive calcium balance at net calcium absorptions above 200 mg per day; therefore, idiopathic hypercalciuria causes not only hyperabsorption but also calcium wasting with a low-calcium diet. Nine normal subjects who followed a diet that was very low in calcium (2 mg of calcium per kilogram of body weight per day) excreted less calcium than they ate, whereas 23 of 29 patients with idiopathic hypercalciuria who had low or normal parathyroid hormone levels excreted more calcium than they ate, of these, many had normal serum calcitriol levels. A high rate of calcium absorp-
tion alone cannot account for such calcium wasting. All studies suggest that calcium wasting occurs in most patients with idiopathic hypercalciuria who follow a low-calcium diet, even those with normal serum parathyroid hormone levels.

Bone Mineral Density in Idiopathic Hypercalciuria

Given the calcium wasting that occurs in many patients with idiopathic hypercalciuria in response to a low-calcium diet, one might expect reduced bone mineral density in these patients. One study, reported a reduced mean distal-radius density among patients with renal idiopathic hypercalciuria and a normal density among patients with absorptive idiopathic hypercalciuria. Another study reported reduced distal-radius and radial-shaft bone mineral density among patients with absorptive idiopathic hypercalciuria. Among unselected patients with nephrolithiasis, bone mineral content was reduced by 5.2 percent, whether or not idiopathic hypercalciuria was present. A recent study reported normal vertebral mineral density among patients with type 2 idiopathic hypercalciuria and reduced density among those with type 1 disease. Overall, the evidence supports the increased likelihood of a reduction in bone mineral content in people with stones and idiopathic hypercalciuria.

Effects of Calcitriol Excess in Normal People

Four normal men were given sufficient calcitriol to raise urinary excretion of calcium but not serum levels of calcium. Calculi worsened the negative calcium balance during a low-calcium diet (160 mg per day), from a net loss of 80 mg to one of 290 mg; in other words, calcitriol potentiated the loss of bone mineral. Either high serum calcitriol levels or an abnormally high tissue response to calcitriol because of an increase in the number of receptors could explain both the overabsorption of calcium characteristic of idiopathic hypercalciuria and the mobilization of bone mineral induced by a low-calcium diet. Calcitriol and its analogues can also suppress the secretion of parathyroid hormone, explaining the failure of serum parathyroid hormone levels to rise during a low-calcium diet.

Serum Calcitriol in Idiopathic Hypercalciuria

In groups of patients with idiopathic hypercalciuria that had not been clinically subtyped, the mean blood calcitriol levels were above normal. This finding offers an apparent explanation for the high rates of intestinal calcium absorption and bone mineral loss that occur during a low-calcium diet. In some patients with high serum calcitriol levels, calcium loading initially suppressed serum calcitriol levels to normal; after two weeks the levels rebounded, as though escaping from control. But among 21 patients with idiopathic hypercalciuria who had high rates of calcium absorption, only 7 had high serum calcitriol levels, and we found normal serum calcitriol levels in 4 of 7 patients who had high rates of calcium absorption documented by calculating total metabolic balance. Rates of calcium transport by enterocytes that are high in relation to the effects of calcitriol or, possibly, abnormal levels of the calcitriol receptor that amplify the effects of circulating calcitriol levels could explain the occurrence of calcium hyperabsorption despite the presence of normal calcitriol levels. The pathogenesis of idiopathic hypercalciuria must include more than simple calcium overabsorption in most patients, but the role of calcitriol remains uncertain.

Effects of Thiazide Diuretics on Calcium Balance and Stone Recurrence

Thiazide diuretics lower urinary calcium excretion by increasing fractional calcium reabsorption by the distal nephron and reducing intestinal calcium absorption. Chlorothalidone improves calcium balance in severe idiopathic hypercalciuria by lowering urinary calcium excretion more than it lowers intestinal calcium absorption. In some but not all studies, the use of thiazide diuretics by patients who did not form stones correlates with reductions in the rates of hip fracture and higher bone mineral densities. Thiazide diuretics and related drugs reduce the likelihood of stone formation. In two double-blind trials lasting three years, chlorothalidone or chlorothiazide lower rates of calcium benefits stone disease whatever the base-line rate of calcium excretion. The benefits of thiazide therapy were not apparent until the second year in either study; as expected, two brief, double-blind, placebo-controlled trials lasting 1 year and 18 months, respectively, found no beneficial effects of thiazide treatment. Previous prospective, open trials that had shown excellent results after treatment with thiazide drugs. Per reported recurrence rates of 13 percent among women and 6 percent among men during six years of thiazide treatment, results similar to those of the placebo-controlled trials. Effects of a Low-Calcium Diet on Stone Recurrence

In theory, a low-calcium diet (400-600 mg daily) should be a safe treatment for patients with type 2 idiopathic hypercalciuria, but no studies have confirmed the efficacy of dietary therapy or laid to rest the fear of bone mineral loss; thus, long-term trials are needed. Open studies report rates of recurrence of 29 percent, 9 percent, and 38 percent; none incorporated formal control groups. A low-calcium diet seems less effective than thiazide diuretics and poses a theoretical risk of bone mineral loss.

Sodium Cellulose Phosphate

A calcium-binding resin, sodium cellulose phosphate reduces calcium absorption when taken with meals. Despite encouraging results from uncontrolled studies, a controlled study showed that sodium cellulose phosphate reduced the risk of stone formation no better than did ingestion of fluids and alteration of the diet. Only one study, of two patients with idiopathic hypercalciuria, documents the effects
of sodium cellulose phosphate on calcium balance. Sodium cellulose phosphate has a very limited role in treatment; we have added it to thiazide diuretics to decrease urinary calcium excretion in patients with the rare combination of intractable stone recurrence and idiopathic hypercalciuria. Its efficacy, like that of the low-calcium diet, has not been proved. In addition, sodium cellulose phosphate increases urinary oxalate excretion, presumably by binding calcium in the intestinal lumen. Orthophosphate

In patients with absorptive idiopathic hypercalciuria, an oral dose of 1500 mg of neutral potassium phosphate per day in three to four divided doses lowers urinary calcium excretion as effectively as thiazide diuretics. Two uncontrolled trials reported relapse rates of 25 percent and 9 percent. In the only controlled trial, acid phosphate increased the frequency of stones. Phosphate needs more study of efficacy and systemic side effects.

Low Urinary Citrate

Evidence of Low Urinary Citrate in Nephrolithiasis

We have described low concentrations of urinary citrate as a common trait among patients who form stones, especially women. Urine from normal women contains an average of 59.5 mg of citrate per deciliter (3.10 mmol per liter) and 10.5 mg of calcium per deciliter (2.62 mmol per liter), as compared with 43.2 and 15.7 mg per deciliter (2.25 and 3.92 mmol per liter), respectively, in normal men. The sex-based difference in calcium concentration reflects the higher rate of excretion by men, who are larger than women but produce the same urinary volume. Among patients with kidney stones, the average urinary citrate con-
centration is only 42.3 mg per deciliter (2.2 mmol per liter) in women and 31.9 mg per deciliter (1.66 mmol per liter) in men, whereas calcium concentrations are increased because of the high prevalence of idiopathic hypercalciuria. Two other studies also found this sex-based difference, and others have shown that patients who form stones have low urinary citrate levels, but have not found a sex-based difference in the concentrations.

Effects of Treatment with Citrate

Because citrate lowers calcium oxalate supersaturation by binding calcium, a low citrate concentration can be a risk factor for the formation of stones and treatment with citrate should prevent stones; however, no trials of citrate have included formal controls. In one uncontrolled study, only 12 percent of citrate-treated patients formed calcium oxalate stones over a two-year period. Citrate lowered the rate of stone formation in 10 of 13 patients with idiopathic hypercalciuria who continued to form stones despite treatment with thiazide diuretics. In patients with bowel disease or renal tubular acidosis, who often have low urinary citrate levels because of metabolic acidosis, citrate therapy seems rational, although its efficacy has not been tested. Potassium bicarbonate lowers urinary calcium concentrations and increases calcium balance; sodium bicarbonate does neither, so we prefer potassium alkali salts.

Renal Tubular Acidosis and Calcium Phosphate Stones

If the kidneys lose some or all of their ability to lower urinary pH, the resulting higher pH increases the proportion of phosphate in the divalent and trivalent forms, which combine with calcium to crystallize and raise calcium phosphate supersaturation. If a decrease in renal acid excretion lowers blood pH, acidosis lowers the urinary citrate concentration by raising proximal-tubule citrate reabsorption and also increases urinary calcium loss. Renal tubular acidosis develops in some patients with idiopathic hypercalciuria, perhaps because of papillary calcification, so that mainly calcium phosphate stones are formed. Because the hypercalciuria in these patients arises not from metabolic acidosis but from idiopathic hypercalciuria, it responds to thiazide diuretics but not potassium alkali salts. Other patients inherit renal tubular acidosis; their hypercalciuria arises from metabolic acidosis rather than idiopathic hypercalciuria, and responds to potassium alkali salts.

Although patients who form calcium phosphate stones may acidify their urine normally, the majority have renal tubular acidosis. We measure the blood pH in these patients. If metabolic acidosis is present, along with 24-hour urinary pH values above 6.5 and hypercalciuria, we treat them with a potassium alkali salt (2 meq per kilogram daily in two to three divided doses) and monitor urinary pH, citrate, and calcium. If the hypercalciuria persists, we add a thiazide diuretic to the therapeutic regimen. In the absence of metabolic acidosis, we use thiazide diuretics to treat the hypercalciuria and potassium alkali salts to treat the low urinary citrate level. This is the same regimen we use to treat patients whose urinary calcium excretion does not fall after treatment with potassium alkali salts alone; we find no need to perform ammonium chloride-loading tests to quantify the acidification defects. Rather than measure blood pH, one may look for very low urinary citrate excretion (<100 mg [5.33 mmol] per day) combined with a 24-hour urinary pH above 6.5, a clue we find useful for the diagnosis of renal tubular acidosis.

Hyperoxaluria

Dietary Hyperoxaluria

Normal people excrete 20 to 40 mg (222 to 444 μmol) of oxalate daily; a reasonable upper limit of excretion is about 45 mg (500 μmol) daily in either sex. A simple dietary excess of oxalate, from foods such as spinach, rhubarb, Swiss chard, cocoa, beets, peppers, wheat germ, pecans, peanuts, okra, chocolate, and lime peel, commonly increases urinary oxalate to 50 to 60 mg (556 to 667 μmol) daily. A low-calcium diet and sodium cellulose phosphate increase urinary oxalate excretion. The treatment consists of altering the diet to avoid an excess of oxalate and making follow-up measurements of urine; no trials prove its efficacy.

Enteric Hyperoxaluria

Malabsorption by the small bowel from any cause, including resection, intrinsic disease, jejunoileal bypass, exposes the colonic mucosa to detergents in the form of bile salts and fatty acids, which increase its permeability to charged molecules, including sugars, amino acids, and oxalate. In vitro, colonic epithelium behaves as if it has a nonselective barrier and a size- and charge-selective barrier; ricinoleic and taurocholic acids raise permeability through the former, leaving the latter intact. An ileostomy abolishes enteric hyperoxaluria but, as does alkaline diarrhea of any cause, also lowers urinary pH and citrate concentrations and causes uric acid crystallization, which is best treated with potassium alkali salts. The hyperoxaluria from small-bowel malabsorption often exceeds 100 mg (1 111 μmol) daily and provokes frequent stone formation and even tubulointerstitial renal disease from intrarenal calcifications.

Treatments include reducing dietary oxalate and fat; oral calcium supplements (1 to 4 g of calcium as the carbonate salt in three to four divided doses with meals) that precipitate oxalate in the intestinal lumen; cholestyramine, a nonabsorbable resin that binds fatty acids, bile acids, and oxalate (4 to 16 g daily in four divided doses with meals); oral citrate supplements; and high fluid intake. We prefer to use all treatments, each at a low level, rather than a single one at its maximal level.

Primary Hyperoxaluria

Type 1 primary hyperoxaluria, an autosomal recessive trait, results from molecular abnormalities that
reduce the activity of hepatic peroxisomal alanine-glyoxylate aminotransferase, thereby increasing the availability of glyoxylate, which is irreversibly converted to oxalic acid. Some abnormalities cause the transfer of active alanine-glyoxylate aminotransferase to mitochondria instead of hepatic microsomes (about one third of cases); the rest reduce intrinsic alanine-glyoxylate aminotransferase activity. A rare form of hyperoxaluria results from a deficiency of D-glycerate dehydrogenase or glyoxylate reductase (type 2). Both forms cause a high level of oxalate production and corresponding urinary oxalate excretion above 135 to 270 mg (1.5 to 3 mmol) daily. Stone formation often begins in childhood; tubulointerstitial nephropathy progresses to chronic renal failure. Serum oxalate levels increase in all types of chronic renal failure, exaggerated increases in primary hyperoxaluria cause calcium oxalate deposition in the heart, bones, joints, eye, and other tissues.

Pyridoxine supplements (2 to 200 mg daily) lower oxalate production in some patients. The rest can be treated by increasing urinary volume to 3 liters daily and adding supplemental oral citrate, thiazide diuretics for those with hypercalciuria, and possibly oral phosphate supplements. Renal transplantation requires a special protocol to avoid accelerated renal oxalosis. Liver transplantation restores the missing enzyme; some patients have received this treatment.

Hyperuricosuria

The most compelling evidence that hyperuricosuria (the excretion of more than 800 mg [4.8 mmol] of uric acid per day in men and of more than 750 mg [4.5 mmol] per day in women) contributes to the formation of calcium oxalate stones comes from a prospective trial that showed a reduction of stone formation with allopurinol as compared with placebo. Finlayson et al. found no direct effect of allopurinol on calcium oxalate crystallization. Mechanisms linking uric acid to calcium oxalate crystallization range from heterogeneous nucleation as a result of uric acid crystallization and reduction of naturally occurring urinary inhibitors to salting out of calcium oxalate salt by urate salts. Since an excess of purine in the diet causes hyperuricosuria, normal levels of dietary purine should prevent stones.

Newly Discovered Inhibitor Defects

Some patients who form stones produce Tamm-Horsfall mucoprotein that self-aggregates and therefore becomes unable to inhibit the aggregation of calcium oxalate crystals. Some patients who form stones produce nephrocalcin that is deficient in γ-carboxyglutamic acid and less able to inhibit the growth of calcium oxalate crystals. We and others have described the reduced inhibition of the growth, nucleation, and aggregation of calcium oxalate in the urine of patients who form stones as compared with the urine of normal persons. Inhibitor defects may eventually be found to be the cause of some types of kidney stones.

Uric Acid Stones

The solubility of fully protonated uric acid in urine at a temperature of 37°C is 96 mg per liter. The pK_a (the negative logarithm of the acid ionization constant) for the first proton dissociation approximates 5.35; at that pH, half the uric acid is fully protonated, making supersaturations inevitable at normal excretion rates of 600 to 800 mg (3.6 to 4.8 mmol) per day in 1 to 1.5 liters of urine. We found that the mean (±SE) pH of urine in patients who form uric acid stones was 5.5 ± 0.4, as compared with 6.0 ± 0.4 among patients who form calcium oxalate stones and 5.7 ± 0.4 among patients whose stones contain both materials; the third group makes up approximately 12 percent of our clinic population. The stones are treated by raising urinary pH to 6.5 with potassium alkalies.

Hyperuricosuria in which less than 1200 mg (7.1 mmol) of uric acid is excreted daily need cause little concern if the pH exceeds 6, but above this level treatment with allopurinol may be beneficial. Unlike calcium oxalate stones, uric acid stones readily dissolve once urinary pH rises, unless coated with calcium oxalate.

Struvite Stones

The usual causative bacteria of struvite stones include proteus, klebsiella, pseudomonas species, and enteroccoci; Escherichia coli never cause them. Patients whose clinical symptoms of stone disease are the passage of a stone tend to have idiopathic hypercalciuria and normal renal function and to produce both struvite and calcium oxalate stones. Those who produce only struvite stones present with large stones that cause bleeding, obstruction, or infection, without stone passage; they rarely have idiopathic hypercalciuria and often have reduced renal function. Idiopathic hypercalciuria or other metabolic disorders presumably create calcium stones in the first group that later become infected. Contralateral spread is frequent.

Struvite stones require removal; extracorporeal shock-wave lithotripsy and percutaneous nephrolithotomy (Table 3) can be used to reduce the damage incurred by the growth and spread of these stones. Prolonged use of antibiotics in patients with stones amounts to treatment for an infected foreign body. Once patients are free of stones, they should benefit from antibiotics directed against the predominant urinary organisms, although no controlled studies support this reasonable approach. An inhibitor of the urease enzyme that can reduce stone formation has proved of limited use because of side effects.

Cystine Stones

Because of hereditary defects of amino acid transport, a few persons excrete in their urine excessive amounts of cystine, the disulfide of cysteine, which is soluble in urine to the level of only 24 to 48 mg per deciliter (1 to 2 mmol per liter). The rate of cystine
excretion in these patients ranges from 480 to 3600 mg (2 to 15 mmol) per day, so that a high fluid intake can prevent stones in only some. We measure urinary cystine and estimate the urinary volume needed to dissolve it; if it is within 4 liters daily, we use only high fluid intake, with attempts to avoid overnight dehydration, and increase urinary pH above 7 to increase cystine solubility; this procedure is safe unless idiopathic hypercalciuria also occurs. If increasing urine volume alone is insufficient, we begin treatment with penicillamine (1 to 2 g daily) or tiopronin. Both combine with cysteine to form a soluble salt that reduces through competition the formation of cystine. The ability of acetylcysteine to increase urinary cystine disqualifies it as a treatment, even though it forms a soluble cysteine disulfide. Treatment of stones that are already formed resembles that for struvite stones except that infection is unlikely to occur. The stones are hard to disrupt by extracorporeal shock-wave lithotripsy, and percutaneous nephrolithotomy is often required. Like uric acid stones, they may dissolve with a high fluid intake or appropriate drugs.

REFERENCES


