CHAPTER

20 Nephrolithiasis

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In the United States, the prevalence of kidney stones has risen over the past 30 years.[1] By 70 years of age, 11% of men and 5.6% of women will have a symptomatic stone.[1] Nephrolithiasis is a costly malady to society. Estimates in the 1970s exceeded $5 billion annually in the United States.[2] More current estimates exceed $30 billion. The incidence of nephrolithiasis in the United States is highest in the Southeast,[3,4] with peak incidence occurring in the late summer months. In addition, sedentary, white collar workers are more likely to form stones than are active, blue collar laborers.[5,6] The rising prevalence of renal calculi highlights the importance of environmental factors, such as diet, in their formation. Fructose consumption, which increased since the introduction of high fructose corn syrup, is associated with stone formation.[7] Increased rates of hypertension and obesity are linked to nephrolithiasis.[8] Stones are distinctly less common in African Americans, American Indians, and people of Asian descent. The age and sex distribution of patients referred for evaluation of nephrolithiasis shows a 2:1 ratio of male to female patients and a maximum incidence in the 30- to 50-year-old group (excluding patients with cystinuria and infection stones).

The natural history of stone disease is characterized by recurrence. Although many studies of the natural history and incidence of stones have been biased by referral practices and differences in definition of recurrence, there is clear evidence in the literature of the recurrent nature of stone disease.

A common dilemma faced by the clinician is whether or not to evaluate and treat the first-time stone former. The risk of recurrence after an initial episode has been estimated to be about 50% by 5 years, with almost two thirds of patients having a recurrence by 9 years.[6,9] Even when nephrolithiasis is evaluated and treated appropriately, the incidence of recurrence in first-time stone formers is not significantly different from that in treated patients with a history of multiple stone episodes.[10] In fact, these patients most likely represent recurrent stone formers in the initial stage of their disease. These and other data demonstrating Randall's plaque[11,12] suggest that such patients should be evaluated and treated in the same manner as patients with recurrent nephrolithiasis.

Patients who have undergone shockwave lithotripsy represent another group at risk for stone recurrence. Stone fragmentation often leads to regrowth of stone material, because residual fragments may act as a nidus for ongoing crystal deposition and stone formation. Medical therapy aimed at correcting underlying urinary abnormalities in these patients may prevent or limit stone growth and recurrence.[13]

Despite the almost inevitable risk of nephrolithiasis recurring if it is left untreated, diagnostic evaluation and selective treatment of metabolic abnormalities that decrease the incidence of new stone formation and can induce complete remission are not routinely practiced.[14] Calcium, uric acid, cystine, and struvite stones differ from one another in terms of pathogenesis and treatment. Therefore, each stone type is described separately. The clinical manifestations by which the stones present are not related to the composition of the stone, and this should be kept in mind.

CLINICAL MANIFESTATIONS

The classic presentation of nephrolithiasis is acute renal colic manifesting as colicky flank pain radiating to the groin. As stones descend in the ureter, the pain may localize to the abdominal area overlying the stone and radiate to the gonad. Peritoneal signs are generally absent. Stones at the ureterovesical junction may cause lower quadrant pain that radiates to the urethral tip, urinary urgency, frequency, and dysuria resembling bacterial cystitis. Exam often reveals patients in distress, unable to find a comfortable position, with tenderness in the costovertebral angle or lower quadrant. Gross or microscopic hematuria is present 90% of the time, but the absence of hematuria does not preclude the diagnosis of nephrolithiasis. Owing to the shared splanchnic innervation of the renal capsule and intestines, hydronephrosis and distension of the renal capsule may produce nausea and vomiting. Thus, renal colic may mimic acute abdominal or pelvic conditions.

The best means of confirming the diagnosis of a urinary stone is unenhanced computed tomography (noncontrast helical CT scan) of the abdomen and pelvis. The sensitivity approaches 96% with a specificity of 100%.[15] Positive and

negative predictive values are 100% and 91%, respectively. Negative CT scans often detect other abnormalities including appendicitis, pelvic inflammatory disease, diverticulitis, abdominal aortic aneurysm, and bladder cancer. Plain abdominal radiography assesses whether the stone is radiopaque, which is the case 75% to 90% of the time. Ultrasonography has a high specificity but a much lower sensitivity than CT. Ultrasonography is appropriate as the initial imaging test in pregnancy and in pediatrics and in patients who should avoid radiation. Intravenous pyelography has been replaced by helical CT as the preferred imaging test.[16] Secondary signs of urinary tract obstruction such as ureteral dilatation, hydronephrosis, and perinephric stranding, are variably seen depending on the duration of pain prior to imaging and the sign itself.[17]

Management of acute renal colic involves a decision whether urgent intervention is required or not. The presence of an obstructed infected upper urinary tract, renal deterioration, intractable pain or vomiting, anuria, or obstruction of a solitary or transplanted kidney are all indications for urgent intervention. Intervention is carried out by urology, and is beyond the scope of this chapter. Pain management has traditionally included narcotics, but stimulation of dependency and long-term effects make nonsteroidal anti-inflammatory drugs (NSAIDs) attractive alternatives. When urgent intervention is not selected, the interval between acute colic and elective intervention for failure of stone passage is an important topic. Observation for up to 4 weeks is considered generally reasonable.[18]

CALCIUM STONES

Classification of Calcium Nephrolithiasis by Urinary Chemistries

Biochemical and physical disturbances that contribute to the formation of calcium stones are quite varied, based on two surveys from the mid-1990s.[19,20] Several disturbances have the potential to create the environment conducive to renal stone formation. Several investigators utilize the presence of such disturbances as the basis for diagnostic categorization of nephrolithiasis.[19–21] Earlier studies based on ambulatory evaluations of patients with nephrolithiasis reported 10 metabolic etiologies composing four types of hypercalciuria, hyperuricosuria, hyperoxaluria, renal tubular acidosis (RTA), uric acid stones, and infection stones, and an 11% incidence of finding no metabolic abnormalities.[22] Now more than 15 etiologic categories of nephrolithiasis have been described (Table 20.1). A single diagnosis is found in the minority of patients whereas approximately 60% have more than one diagnosis. The finding of no metabolic abnormality can be reduced to the range of 2% to 4% of patients with care and repeated measures. Hypercalciuric nephrolithiasis accounts for about 60% of the patients. Hyperuricosuria associated with calcium nephrolithiasis can be subdivided into hyperuricosuric calcium nephrolithiasis and patients with gouty diathesis. Hyperoxaluric calcium nephrolithiasis, which occurs in about 8% of patients with recurrent stones, has been subdivided into enteric, primary, and dietary variants. Hypocitraturic calcium nephrolithiasis, which affects about 30% of patients in its idiopathic variant, is also associated with incomplete RTA and the chronic diarrheal syndrome. Hypomagnesiuric calcium nephrolithiasis, infection stones, and cystinuria are uncommon, accounting for 7%, 6%, and 1% of patients, respectively. The acquired problem of low urinary volume, less than 1 L per day according to Levy and colleagues[19] and less than 1.5 L per day according to Seltzer and Hruska,[20] is the single most common abnormality.

The descriptions of clinical subtypes that follow represent the minimal diagnostic criteria used to establish the presence of the entities listed in Table 20.1, according to Hruska and Seltzer.

Absorptive Hypercalciuria Type I

Diagnostic criteria include: calcium nephrolithiasis, normocalcemia, normophosphatemia, hypercalciuria (>200 mg per day) on a calcium-restricted diet, normal fasting urinary calcium (<0.11 mg per dL glomerular filtrate [dL GF]), exaggerated calciuric response to an oral calcium load (>0.20 mg urinary calcium per mg urinary creatinine), and normal to suppressed serum parathyroid hormone (PTH) function.[23–30]

Absorptive Hypercalciuria Type II

Criteria are the same as for type I, except for normal urinary calcium (<200 mg per day) on the restricted diet.[23–29,31]

Absorptive Hypercalciuria Type III (Renal Phosphaturia)

Diagnostic criteria are characterized as similar to type I, except for persistent hypophosphatemia (2.5 mg per dL or less).[32]

Sodium-Linked Phosphate Transporter

Low serum phosphate concentrations due to a decrease in renal phosphate reabsorption occur in some patients with renal calcium stones and/or bone demineralization. Two different heterozygous mutations in the sodium-linked phosphate transport protein encoded by the NPT2a gene have been associated with this disorder.[33] Subsequent studies have shown that although genetic variants of NPT2a are not rare, they do not seem to be associated with clinically significant renal phosphate or calcium handling anomalies in a large cohort of hypercalciuric stone-forming pedigrees.[34]

Renal Hypercalciuria

Diagnostic criteria include: calcium nephrolithiasis, normocalcemia, normophosphatemia, hypercalciuria on the restricted diet, elevated fasting urinary calcium (>0.11 mg per dL GF), and elevated serum parathyroid hormone (PTH).[35]

Primary Hyperparathyroidism (Resorptive Hypercalciuria)

Criteria for diagnosis include: nephrolithiasis, hypercalcemia, hypercalciuria, and high serum PTH with surgical confirmation of abnormal parathyroid tissue.[23–26,28,36,37]

20.1 Urinary Chemistries in Evaluation of Nephrolithiasis[a]

Category	Seltzer and Hruska[80] Jewish Hospital (n = 587)		Levy et al.[79] University of Texas Southwestern (n = 1270)	
	Sole occurrence (%)	Combined occurrence (%)	Sole occurrence (%)	Combined occurrence (%)
Hypercalciuria	14	51	—	—
Male (>250 mg/24 hr)	8	34	—	—
Female (>225 mg/24 hr)	6	17	—	—
Absorptive hypercalciuria	—	37	6.1	23.1
Fasting hypercalciuria	—	14	4.3	13.9
Renal hypercalciuria	—	1	0.3	1.3
Renal phosphaturia	—	2	2.1	7.6
Primary hyperparathyroidism	—	1	0.8	1.3
Hyperuricosuria	8	42	—	—
Male (>0.75 g/24 hr)	6	30	—	—
Female (>0.70 g/24 hr)	2	12	—	—
Hyperuricosuric calcium nephrolithiasis	—	—	8.3	27.6
Gouty diathesis	—	—	3.1	6.9
Hypocitraturia	9	34	—	—
Male (<250 mg/24 hr)	5	18	—	—
Female (<300 mg/24 hr)	4	16	—	—
Complete distal RTA	—	—	0.08	0.16
Incomplete distal RTA	—	—	0.0	1.1
Chronic diarrheal syndrome	—	—	0.2	1.8
Idiopathic	—	—	3.5	24.4
Hyperoxaluria (>40 mg/24 hr)	8	34	—	—
Enteric hyperoxaluria	—	—	0.2	1.4
Primary hyperoxaluria	—	—	0.0	0.4
Dietary hyperoxaluria	—	—	0.4	5.7
Hypomagnesuria (<5 mEq/24 hr)	5	26	0.3	6.5 (<50 mg/24 hr)
Low urinary volumes (<1500 mL/24 hr)	26	61	1.7	13.5 (<1,000 mL/24 hr)
No diagnosis/difficult to classify	—	2	—	4.0

[a]The category definitions in the table refer to Jewish Hospital, Washington University, St. Louis. Criteria for the University of Texas Southwestern data are provided in the text.
RTA, renal tubular acidosis.

Fasting Hypercalciuria and Elevated Fasting Urinary Calcium

Calcium nephrolithiasis and hypercalciuria on a restricted diet can be categorized into a resorptive form because of fasting hypercalciuria. Fasting hypercalciuria is further characterized by normal to suppressed parathyroid function, eliminating renal calciuria, normocalcemia, and normophosphatemia (>2.0 mg per dL).

Hyperuricosuric Calcium Nephrolithiasis

The diagnostic criteria for hyperuricosuric calcium nephrolithiasis (HUCN) include: calcium nephrolithiasis, hyperuricosuria

(>700 mg per day for females; >750 mg per day for males), and frequently a low urinary pH of ≤5.5.[38–40]

Gouty Diathesis

Criteria include uric acid or calcium nephrolithiasis and low urinary pH (<5.5) in the absence of excessive gastrointestinal alkali losses[41–43] or animal protein excess. Hyperuricemia, hypertriglyceridemia, and a history of gouty arthritis may be present.

Hyperoxaluric Calcium Nephrolithiasis

Criteria include calcium nephrolithiasis and hyperoxaluria (>44 mg per day). The three forms of hyperoxaluric calcium nephrolithiasis are:

1. Enteric hyperoxaluria, defined as the presence of ileal disease (Crohn disease, ulcerative colitis, jejunoileal bypass, or intestinal resection), or fat malabsorption with hyperoxaluria on the random and restricted diets.[44–47]
2. Primary hyperoxaluria, consisting of marked hyperoxaluria (>80 mg per day) without evidence of bowel disease, high oxalate diet, low calcium diet, treatment with calcium-binding agents, enhanced oxalate absorption, or high doses of vitamin C.[48]
3. Dietary hyperoxaluria, marked by high oxalate diet, hyperoxaluria on a random diet, and normal urinary oxalate excretion on the restricted diet.[47,49,50]

Enteric hyperoxaluria is typically associated with hypocitraturia due to intestinal loss of HCO_3, low urinary volume, and low normal urinary calcium excretion.

Hypocitraturic Calcium Nephrolithiasis

Diagnostic criteria include calcium nephrolithiasis and hypocitraturia (<320 mg per day),[39] that compose:

1. Distal RTA, which is characterized by systemic metabolic acidosis or defective urinary acidification following an ammonium chloride load and urinary pH above 6.5. The acidosis is a hypokalemic, hyperchloremic nonanion gap metabolic acidosis.[50] In the complete form, metabolic acidosis is present before an ammonium chloride load, whereas in the incomplete form, urinary acidification following an ammonium chloride load is impaired despite normal serum electrolytes before the load.
2. Chronic diarrheal syndrome, which is defined as chronic diarrhea with excessive alkali loss from various gastrointestinal disorders (e.g., gastric resection, ileal disease, Crohn disease, and ulcerative colitis).[51]
3. Idiopathic hypocitraturia of unknown etiology.

Hypomagnesiuric Calcium Nephrolithiasis

Criteria for diagnosis include: nephrolithiasis, hypomagnesuria (<50 mg per day) on the random diet, and absence of a diarrheal disorder.[52]

Infection Stones

Criteria for diagnosis include struvite or carbonate-apatite nephrolithiasis.[53]

Cystinuria

Diagnosis is based on cystine nephrolithiasis and urinary cystine level higher than 200 mg per day.[54]

Low Urine Volume

Diagnosis is based on calcium or uric acid nephrolithiasis and urine volume less than 1 L per day.[55]

No Metabolic Abnormality

This is attributed to calcium nephrolithiasis and a normal biochemical evaluation.[56]

Difficult to Classify

Those that fall into this category are generally nephrolithiasis with recognized stone risk factors.[57] A definitive diagnosis cannot be made due to borderline or inconsistent laboratory values or to the absence of critical data (e.g., stone analysis or roentgenographic visualization).

HYPERCALCIURIC NEPHROLITHIASIS

The majority of patients with calcium nephrolithiasis exhibit hypercalciuria (Table 20.1) and have idiopathic hypercalciuria, which is a term used to describe recurrent nephrolithiasis associated with hypercalciuria, and is probably a distinct entity. However, most of the data suggest that multiple metabolic abnormalities besides excess calcium excretion contribute to nephrolithiasis associated with hypercalciuria. Furthermore, there is a much higher incidence of idiopathic hypercalciuria than nephrolithiasis in the general population.[58] Several estimates place the incidence of idiopathic hypercalciuria at 2% to 4%,[59] whereas the incidence of nephrolithiasis is no more than 0.5% to 1.0%. Between 40% and 50% of calcium stone formers excrete excess calcium in their urine, defined as more than 300 mg per 24 hours (men), 250 mg per 24 hours (women) on ≥1,000 mg calcium intake, or 4 mg per kg body weight per 24 hours (either sex). The term idiopathic hypercalciuria applies if the serum calcium level is normal and sarcoidosis, RTA, hyperthyroidism, malignant tumors, rapidly progressive bone disease, immobilization, Paget disease, Cushing disease (or syndrome), and furosemide administration have been excluded. Virtually all normocalcemic hypercalciuria encountered in patients with nephrolithiasis falls under the umbrella of "idiopathic hypercalciuria."[19]

Among patients with recurrent calcium stones who have served as control subjects in randomized, controlled trials of interventions, new stones formed in 43% to 80% of subjects within 3 years.[14,60–62]

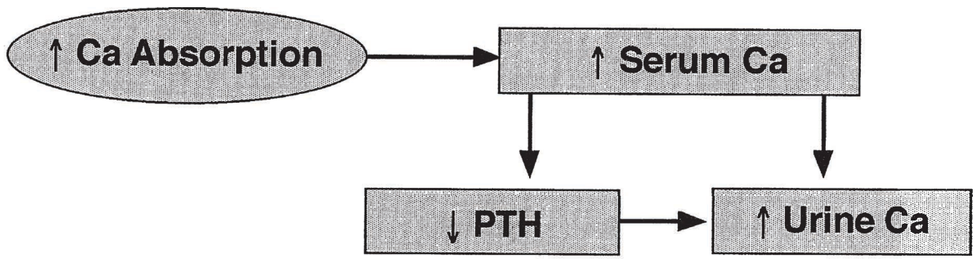

FIGURE 20.1 Pathogenesis of absorptive hypercalciuria. Intestinal hyperabsorption of calcium leads to an increase in serum calcium and a reduction of parathyroid hormone (PTH). The increase in the filtered load of calcium and the reduced calcium reabsorption produced by loss of PTH activity lead to hypercalciuria.

Idiopathic Hypercalciuria

Idiopathic hypercalciuria is an inherited syndrome. Studies of families of patients with hypercalciuric nephrolithiasis reveal a high incidence of hypercalciuria in first-degree relatives.[63] The pattern of inheritance in consecutive generations with high frequency is compatible with an inherited trait with the broad characteristics of autosomal dominant transmission. This pattern of inheritance was demonstrated in large kindred.[64] Hypercalciuria also occurs in children at the same rate as in adults.[65] Spontaneous hypercalciuria similar to that observed in hypercalciuric nephrolithiasis of humans has been demonstrated in the laboratory rat,[66,67] which has become an animal model of the human disorder.

The pathogenesis of idiopathic hypercalciuria involves excessive intestinal calcium absorption and depressed renal tubular calcium reabsorption (Fig. 20.1). The latter is largely due to suppression of PTH[68,69] and can be considered as a major factor in preventing hypercalcemia associated with increased intestinal absorption. When placed on low calcium diets, patients with hypercalciuric nephrolithiasis often demonstrate a negative calcium balance.[70] This could be due to defective renal tubular calcium reabsorption, but renal hypercalciuria should produce secondary hyperparathyroidism, which is rarely observed.[19,20] In addition, considerable evidence indicates that PTH levels are suppressed and that the negative calcium balance stems from excessive skeletal remodeling and bone resorption.[68,69] The question of whether depressed renal tubular calcium reabsorption greater than that expected with PTH suppression contributes to the hypercalciuria of nephrolithiasis remains unanswered. It is supported only by data from a few patients in whom secondary hyperparathyroidism has been documented (see "Renal hypercalciuria" in Table 20.1).

In hypercalciuric calcium oxalate stone formers, the initial site of calcium/phosphate crystal deposition is the basement membrane of the thin limbs of Henle's loop. There is subsequent extension to the vasa section, then the interstitium and, in the most severe cases, to the papillae. Alternatively, in patients with hyperoxaluria secondary to intestinal bypass and idiopathic calcium phosphate stones, the initial crystals were again calcium/phosphate complex, but these arose within the tubule lumens of terminal collecting ducts. Non–stone formers, when subjected to nephrectomy, had neither plaque nor crystals. Thus, there are different sites of crystallization depending on the metabolic abnormalities leading to stone formation.[71,72]

Additionally, in patients with idiopathic hypercalciuria, there was evidence for crystal-induced cell injury in areas of dense crystal deposition, whereas in the bypass patients there was not only cell injury, but also cell death.[11]

The genetically hypercalciuric stone forming rats spontaneously form calcium/phosphate stones unless their diet is augmented with an oxalate precursor.[73]

In the genetic hypercalciuric stone forming rats, calcium oxalate (but not calcium/phosphate) stones induce marked proliferation of the urothelium resulting in sequestration of stones.[67]

Thus, rats and humans appear protected against calcium oxalate stone formation unless a nucleation site, such as the calcium/phosphate crystal, is present.

Absorptive Hypercalciuria

Increased intestinal absorption of calcium is a uniform finding in patients with hypercalciuric nephrolithiasis[20] (Fig. 20.1). At issue is whether increased absorption is the primary defect or caused secondarily in the idiopathic hypercalciuric syndrome (Figs. 20.1 to 20.4). All forms of hypercalciuric nephrolithiasis are associated with increased intestinal calcium absorption. Those associated with intestinal calcium hyperabsorption on a secondary basis—renal hypercalciuria, primary hyperparathyroidism, and renal phosphaturia—are relatively uncommon forms of hypercalciuric nephrolithiasis. Furthermore, fasting hypercalciuria appears to be the expression of increased skeletal remodeling and intestinal calcium hyperabsorption together. All of this indirectly suggests that a specific problem producing intestinal calcium hyperabsorption is a major, if not the basic, underlying defect in idiopathic nephrolithiasis.

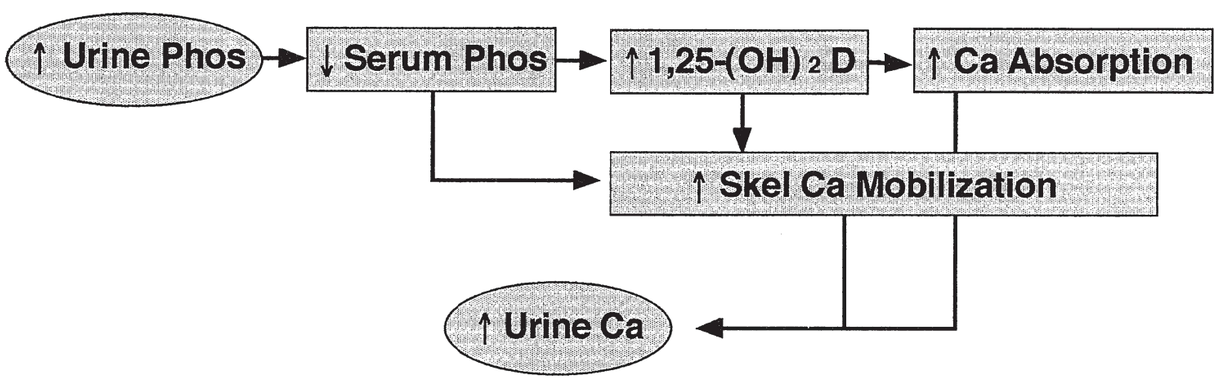

FIGURE 20.2 Renal phosphaturia. Hypophosphatemia leads to increased production of $1,25(OH)_2D_3$, intestinal hyperabsorption of calcium, and increased skeletal calcium mobilization. As a result, hypercalciuria develops.

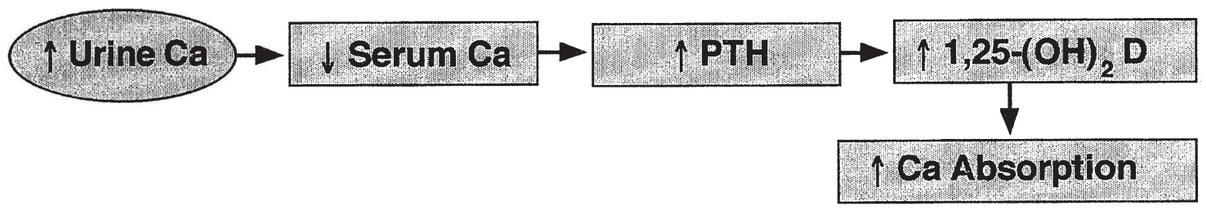

FIGURE 20.3 The pathogenesis of renal hypercalciuria. Defective renal calcium reabsorption leads to hypocalcemia and a stimulation of parathyroid hormone (PTH) secretion. The latter increases the production of $1,25(OH)_2D_3$, stimulating calcium absorption and leading to hypercalciuria. The hypercalciuria in turn compensates for the reduction in serum calcium but compensation never completely restores normal calcium, and elevated PTH values are required in this syndrome.

Intestinal Calcium Absorption

Net calcium absorption is the difference between the mucosal absorptive rate and the secretion of calcium into biliary, duodenal, and pancreatic fluids. Although calcium absorption rates may be measured using oral radiolabeled calcium, only overall balance studies in which fecal losses are measured can quantitate net calcium absorption. The mucosal to serosal absorptive rate is higher in patients with hypercalciuric nephrolithiasis than in healthy individuals[26,36,74–81] (Table 20.2), but overlap is extensive. In six studies, individuals with no signs of hypercalciuric nephrolithiasis absorbed an average of 27% to 52% of an oral dose of radioactive calcium, whereas those with hypercalciuric nephrolithiasis absorbed 22% to 80%. If one chooses only the six studies incorporating normal control subjects, the more efficient calcium absorption by hypercalciuric nephrolithiasis subjects is particularly evident. Increased mucosal-to-blood transport of calcium, but not magnesium, has also been demonstrated directly by in vivo jejunal perfusion in hypercalciuric nephrolithiasis.[29] At normal calcium intakes, <1,500 mg per day, calcium absorption in the duodenum and proximal jejunum is an active process mediated by a mucosal membrane calcium pump (ECaC)[82,83] and efficient cytosolic calcium binding proteins (calbindin),[84] both transcriptionally regulated by calcitriol. At high calcium intakes, passive transport mechanisms in the more distal small bowel and colon may account for most of calcium absorption as the proximal active calcitriol-regulated mechanisms are suppressed.

In normal individuals, urine calcium excretion rises slowly with net absorption[85] (Fig. 20.5), and calcium balance is usually positive when the absorption rate exceeds 200 mg per 24 hours. At all levels of net absorption, urinary calcium excretion was higher in hypercalciuric than in normal subjects, so much so that none of the patient data fell within the 95% confidence band derived from studies of normal individuals (Fig. 20.6). For example, in the range of 200 to 300 mg of net calcium absorption, not one of 38 normal subjects excreted as much as 300 mg of calcium in the urine, whereas 16 hypercalciuric patients did (compare Figs. 20.5 and 20.6). In other words, hypercalciuric nephrolithiasis subjects excreted in the urine an abnormally high percentage of the calcium they absorbed from the intestine. This is compatible with suppression of renal tubular calcium transport rates by low levels of PTH. Net absorption rates exceeded 200 mg per 24 hours in 55 normal subjects (Fig. 20.5). Urine calcium excretion was less than net absorption; that is, calcium balance was positive in 48 subjects. If a generous margin for error (50 mg per 24 hours) is allowed in the balance data, none of the 55 normal individuals were in negative calcium balance. Among 37 hypercalciuric patients with a calcium absorption rate above 200 mg per 24 hours, however, calcium excretion exceeded net absorption in 23 patients by more than 50 mg per 24 hours (Fig. 20.6). In other words, negative calcium balance was frequent in idiopathic hypercalciuria subjects but not in normal individuals. This is compatible with either reduced tubular reabsorption, which should produce elevated levels of PTH, or with excessive bone resorption. The latter appears most likely.

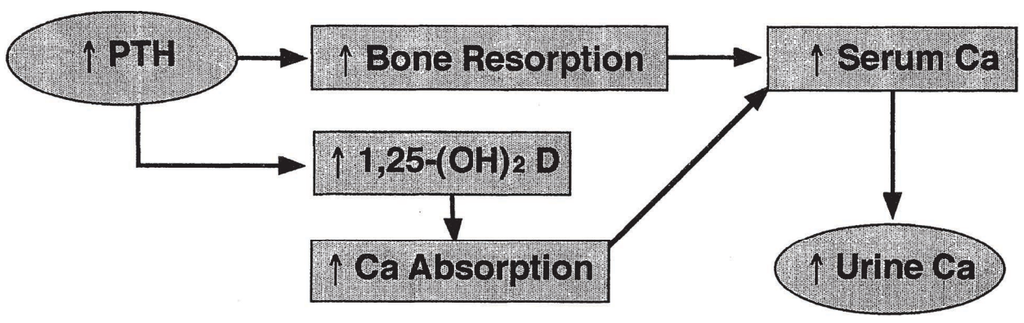

FIGURE 20.4 Pathogenesis of hypercalciuria and primary hyperparathyroidism. Excess secretion of parathyroid hormone (PTH) stimulates bone remodeling and elevations of $1,25(OH)_2D_3$ and calcium absorption. The resultant increase in serum calcium leads to an increase in the filtered load of calcium. The latter overwhelms the stimulation of renal tubular calcium transport by PTH, and hypercalciuria results.

Renal Tubular Calcium Reabsorption

Two systematic studies[86,87] have evaluated overall renal fractional calcium reabsorption (Table 20.3). In both, the filtered load of calcium was calculated from inulin clearance or creatinine clearance and ultrafilterable serum calcium concentration. The fraction of the filtered calcium load excreted was calculated for several clearance periods in normal and hypercalciuric nephrolithiasis subjects. Fractional calcium excretion was clearly high in the hypercalciuric nephrolithiasis subjects. The effects of hydrochlorothiazide and acetazolamide on the renal tubular handling of sodium, magnesium, and calcium suggested to the authors a generalized defect in proximal tubular reabsorption.[86–88] These studies did not examine the role of suppressed or elevated PTH levels in the subjects with hypercalciuric nephrolithiasis. The general finding of a tendency for PTH levels to be

20.2 Intestinal Calcium Absorption in Normal Subjects and Patients with Idiopathic Hypercalciuria

Reference (no.)	Method	Calcium intake (mg/24 hr)	Dietary calcium absorbed (%)[a]	
			Normal subjects	Idiopathic hypercalciuria
Caniggia et al.[124]	Fecal ^{45}Ca	Free diet[b]	None studied	22.0 (1)
Birge et al.[123]	^{47}Ca, PO/IV	800	52.2 ± 13.2 (6)	58.5 ± 8.6 (4)
Wills[125]	^{47}Ca, PO/IV	400	49.0 ± 10.0 (4)	76.0 ± 17.0 (5)
Pak[126]	Fecal ^{47}Ca	400	45.6 ± 9.0 (29)	69.7 ± 7.0 (9) 58.1 ± 13.0 (11)[c]
Pak et al.[86]	Fecal ^{47}Ca	400	50.0 ± 7.0 (20)	71.0 ± 7.0 (22)[d] 50.0 ± 17.0 (2)[e]
Ehrig et al.[126]	$^{47}Ca/^{45}Ca$, PO/IV	462–952	None studied	47.8 ± 11.0 (22)[f] 37.6 ± 11.0 (22)[g]
Kaplan[94]	Fecal ^{47}Ca	400	48.0 ± 8.0 (11)	80.0 ± 9.0 (211)[d] 73.0 ± 7.0 (3)[e]
Shen[128]	$^{47}Ca/^{45}Ca$, PO/IV	Free diet[b]	27.0 ± 9.0 (14)	40.0 ± 9.0 (15)
Barilla[129]	Fecal ^{47}Ca	400	None studied	69.5 ± 6.4 (10)[d] 70.1 ± 10.4 (8)[e]
Zerwekh and Pak[130]	Fecal ^{47}Ca	400	None studied	69.0 ± 7.0 (11)[d] 68.0 ± 9.0 (10)[d]

[a]Values are means ± standard deviations; numbers in parentheses represent numbers of patients studied.
[b]Usual diet but not measured.
[c]Eleven patients listed as having normocalcemic primary hyperparathyroidism may be considered hypercalciuric.
[d]Absorptive idiopathic hypercalciuria.
[e]Renal idiopathic hypercalciuria.
[f]Prior to therapy.
[g]Three to 16 months after administration of hydrochlorothiazide.
Ca, calcium; PO, orally; IV, intravenously.

suppressed and the rarity of secondary hyperparathyroidism call for a reexamination of the issue regarding renal tubular calcium fluxes.

A rare syndrome, X-linked hypercalciuric nephrolithiasis (XLHN), or Dent disease, is characterized by recurrent calcium nephrolithiasis and has been found to be due to mutations in a proximal tubular intracellular vesicle chloride transport protein, CLCN5.[89–93] Two other types of hypercalciuric nephrolithiasis, which map to the same defective gene on the X chromosome (Xp11.22) as Dent disease, X-linked recessive nephrolithiasis and recessive hypophosphatemic rickets, are associated with inactivating mutations in CLCN-5.[89]

The CLCN-5 gene is a member of a family of genes that encode voltage-gated chloride channels.[90] CLCN-5 is found in the kidney tubules and in bone cells. All mutations in the CLCN-5 gene found to date have been functional, with loss of function manifested as a lowered conductance of the mutated channel. CLCN-5 is distributed in the human kidney in the proximal tubule, in the thick ascending limb of the loop of Henle, and in the α-type intercalated cells of the collecting duct.[90] These sites are where calcium is resorbed from the filtrate. CLCN-5 knockout animals are hypercalciuric and proteinuric.[91]

CLCN-5 colocalizes with the vacuolar H+-ATPase in proximal tubular cells and a-type intercalated cells. CLCN-5 mutations are associated with modifications in the polarity and expression of H1-ATPase, but not ultrastructural alterations in proximal tubular cells.[93] The variability in diseases

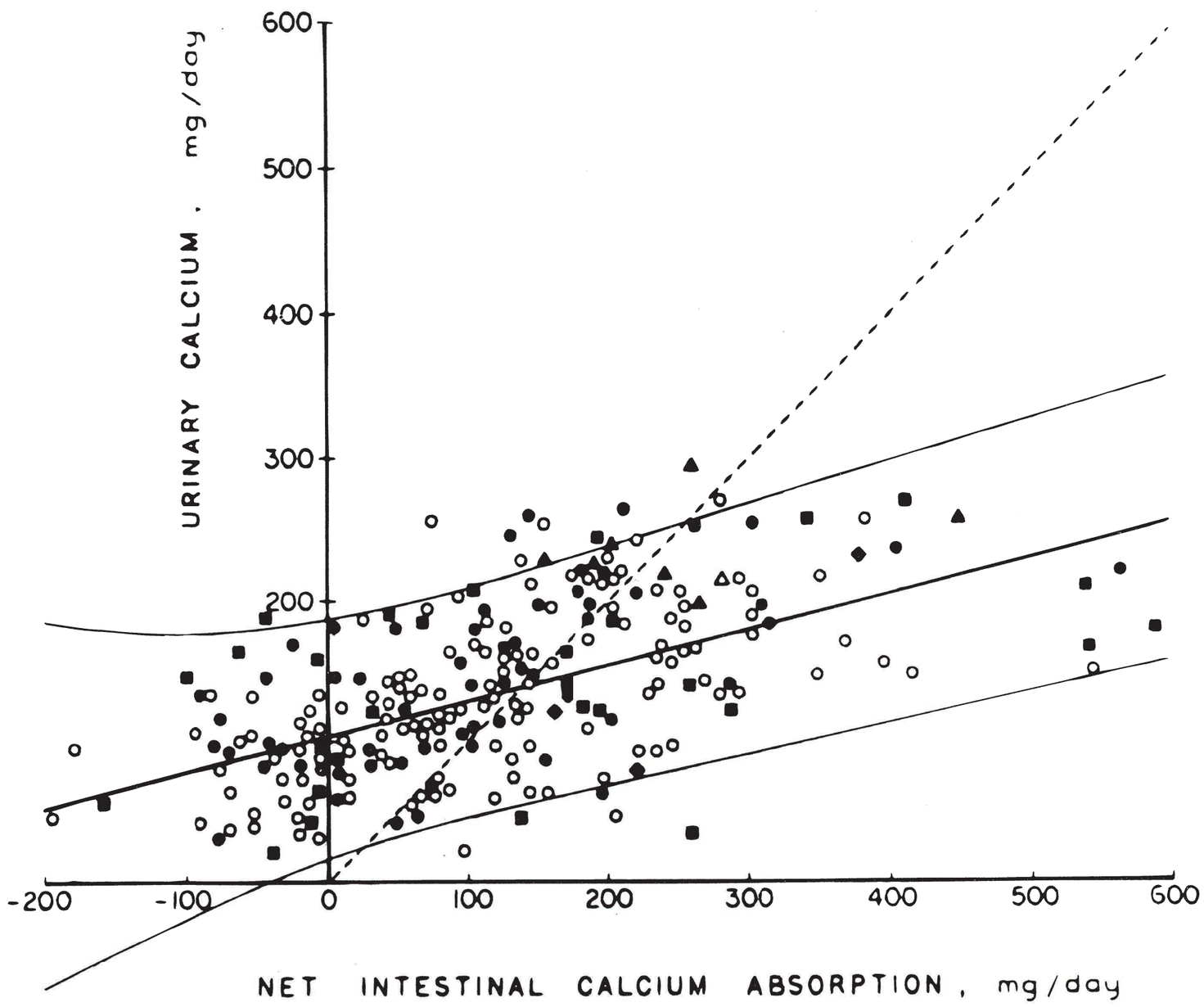

FIGURE 20.5 Urinary calcium excretion as a function of net intestinal calcium absorption. Data are derived from 6-day balance studies on 195 normal adults. Each symbol represents individual subjects from different sources: *circles,* Knapp[238]; *squares,* Lafferty and Pearson[239]; *diamonds,* Liberman et al.[240]; and *triangles,* Edwards and Hodgkinson.[241] *Open figures* represent women, and *solid figures* represent men. *Solid lines* represent mean and 2 standard deviations. The *dotted line* is the line of identity; points above the line reflect negative calcium balance. (From Coe FL, Favus MJ. Nephrolithiasis. In: Brenner BM, Rector FC, eds. *The Kidney,* 2nd ed. Philadelphia: WB Saunders; 1991, with permission.)

with the CLCN-5 mutations involves impaired solute reabsorption by the proximal tubule and range from kaliuresis, glycosuria, phosphaturia, and/or hypouricemia. Constant findings of Dent disease include hematuria and low molecular weight proteinuria. Dent disease progresses to renal failure due to nephrocalcinosis and tubulointerstitial nephritis.

Thiazide diuretics reduce hypercalciuria in patients with CLCN-5 mutations, but thiazides can make these patients become hypokalemic. The beneficial effect must be weighed against the potential side effect profile.[92] Langman finds little reduction in stone formation even when urinary calcium is lowered to normal in such individuals.[94]

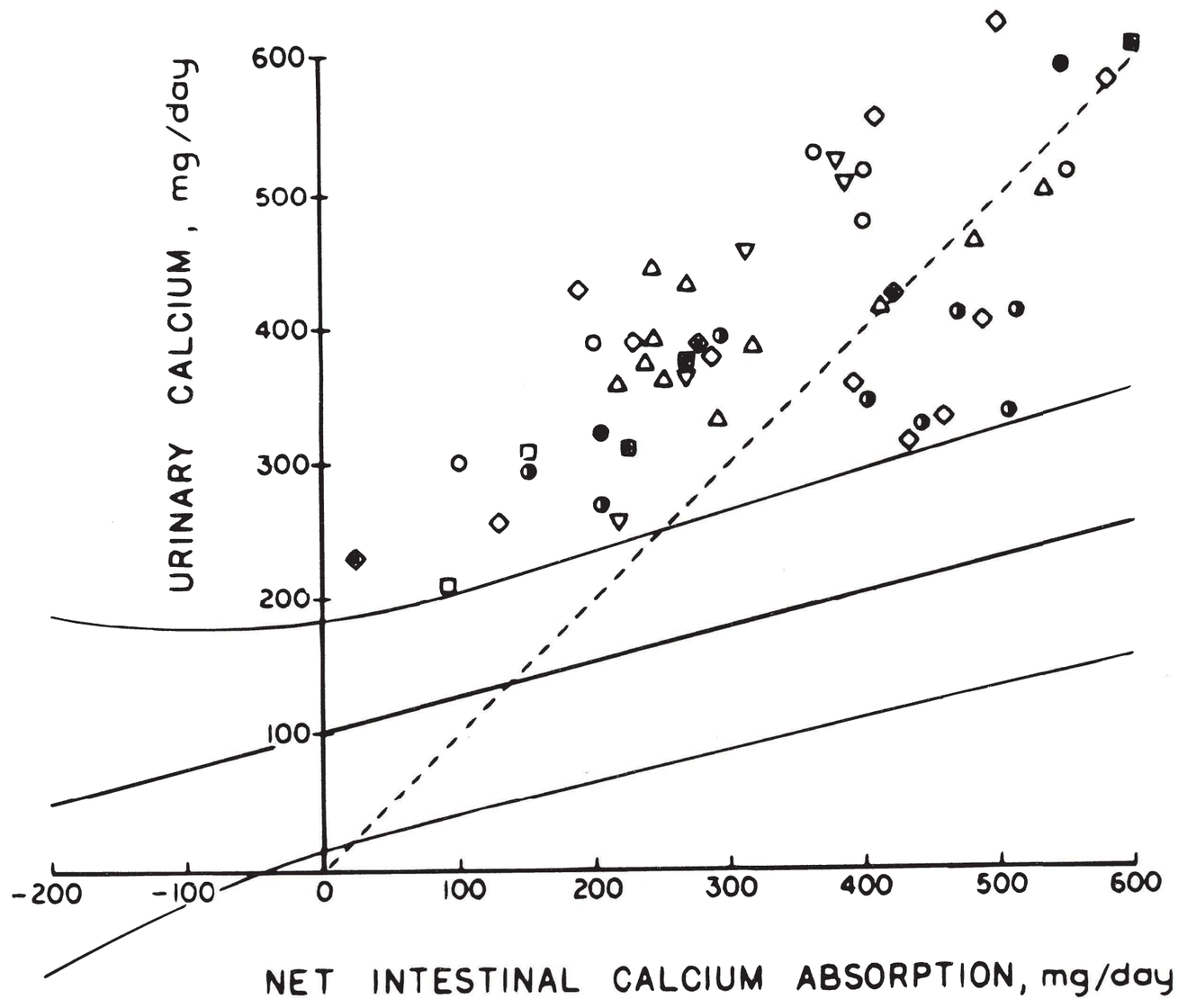

FIGURE 20.6 Urinary calcium excretion as a function of net intestinal calcium absorption from 6-day balance studies performed on 51 patients with idiopathic hypercalciuria reported as follows: *open square,* Henneman et al.[243]; *open squares with dot in center,* Jackson and Lancaster[244]; *open triangles,* Harrison[245]; *open circles with dot in center,* Dent et al.[246]; *open inverted triangles,* Parfitt et al.[247]; *closed diamonds,* Edwards and Hodgkinson[241]; *open diamonds,* Liberman et al.[240]; and *half-darkened circles,* Lemann.[248] *Solid lines* represent mean and 2 standard deviations derived from balance studies from 195 normal adults, shown in Figure 26.10. The *dotted line* is the line of identity, with positive calcium balance below the line. (From Coe FL, Favus MJ. Nephrolithiasis. In: Brenner BM, Rector FC, eds. *The Kidney,* 2nd ed. Philadelphia: WB Saunders; 1991, with permission.)

20.3 Fraction of Filtered Calcium Excreted in the Urine by Normal and Hypercalciuric Subjects[a]

	Normal subjects	Hypercalciuric subjects[b]
Edwards and Hodgkinson[137]	0.94% (7)	2.94% (14), $P < 0.001$
Peacock and Nordin[135]	1.27% (5)	4.25% (9), $P < 0.01$

[a]Number of subjects studied are shown in parentheses next to fractional excretion values.
[b]Urine calcium >300 mg/24 hr (men) or 250 mg/24 hr (women).

Another Voltage-Gated Chloride Channel

Bartter syndrome is a disease arising from one of three possible genes in the thick ascending limb that bear mutations in the Na^+-K^+-2Cl- gene NKCC2, in the K^+ channel ROMK, or in the chloride channel CLCNKB. Each of these mutations produces a phenotype that includes hypercalciuria and kidney stone formation with or without nephrocalcinosis. A missense mutation in the CLCNKB gene leads to disease of intrafamilial heterogeneity of urinary calcium levels. Some family members have Bartter syndrome with frank hypercalciuria, but others have hypocalciuria and a clinical phenotype of Gitelman syndrome.[95]

Hypomagnesemia/Hypercalciuria

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is an autosomal recessive tubular disorder that is frequently associated with progressive renal failure. The primary defect is related to impaired tubular reabsorption of magnesium and calcium in the thick ascending loop of Henle. Mutations in PCLN-1, which encodes the renal tight junction protein paracillin-1, were identified as the underlying genetic defects. Affected patients usually present in childhood or adolescence with symptomatic hypocalcemia.[96–98] Recurrent nephrolithiasis and nephrocalcinosis are also seen and progression to renal insufficiency and an acidification defect are common. The problem with acidification has been attributed to defective ammonia transfer to the deep nephrons and impaired medullary hydrogen ion secretion due to nephrocalcinosis.[99] Treatment with magnesium salts and thiazides seems to have no effect on the progression of the disease.

A second form of primary hypomagnesemia, Gitelman syndrome, is associated with hypocalciuria. It is due to mutations in the gene encoding the thiazide-sensitive sodium-chloride-cotransporter. Because thiazides are used to treat hypercalciuric nephrolithiasis, it is important to know that they can mimic the syndrome of hypomagnesemia including hypokalemia induced by magnesuria.[100]

Skeletal Remodeling

The high frequency of negative calcium balance in patients with idiopathic hypercalciuria on low calcium diets was the first indication that exaggerated bone resorption characterized the syndrome. Additional evidence for elevated skeletal remodeling in hypercalciuric nephrolithiasis has accrued. Several investigators[69,101] have documented reduced vertebral bone density in hypercalciuric nephrolithiasis by both CT and dual energy X-ray absorptiometry. Patients who exhibit fasting hypercalciuria tend to have a greater reduction in trabecular bone density than do other hypercalciuric patients, but there is significant overlap, and patients with absorptive hypercalciuria and normal fasting calcium excretion exhibit a high prevalence of reduced bone mineral density. Increased rates of skeletal remodeling with resorption favored over formation are supported by the findings of increased osteocalcin secretion and increased urinary hydroxyproline levels in patients with fasting hypercalciuria.[69] The pathogenesis of exaggerated bone remodeling rates may be due to elevations in 1α,25-dihydroxycholecalciferol ($1\alpha,25[OH]_2D_3$) levels, or due to elevations in bone cytokine activity such as prostaglandin activity[102] and interleukin-1 activity.[69] The result of this exaggerated skeletal remodeling is an increase in calcium release to the systemic circulation and suppression of PTH secretion.[103] One possibility is that exaggerated skeletal remodeling is a component of the syndrome of idiopathic hypercalciuria. Activation of skeletal remodeling in the hypercalciuric patient results in increased skeletal remodeling, leading to the loss of a quantum of the skeleton before counterregulatory influences decrease remodeling rates, removing the component of fasting hypercalciuria from the hypercalciuric syndrome. Such a scenario is sufficient to explain the clinical picture, as we currently understand it. Greater clarification of the roles of fasting hypercalciuria, and of bone remodeling, and their pathogenesis is required in patients with hypercalciuric nephrolithiasis. The role of skeletal remodeling in nephrolithiasis was further clarified by the recent discovery of a mutation in the type 2a, sodium-dependent phosphate cotransporter gene found in the proximal tubule and osteoclasts.[33]

Fasting Hypercalciuria

Except for negative calcium balance, either primary intestinal calcium absorption or a primary renal calcium leak could produce the findings summarized in Tables 20.2 and 20.3 and in Figures 20.5 and 20.6. Primary intestinal overabsorption increases postprandial serum calcium levels

above normal and increases the filtered load of calcium (Fig. 20.1). PTH secretion is reduced by the hypercalcemia, and suppression of PTH secretion would reduce calcium reabsorption because PTH stimulates renal tubular calcium reabsorption. In contrast, a renal tubular transport defect (Fig. 20.2) leading to hypercalciuria would produce secondary hyperparathyroidism. PTH, in turn, would stimulate the production of $1\alpha,25(OH)_2D_3$ and produce intestinal calcium hyperabsorption. Hyperabsorption would elevate postprandial serum calcium levels, raising the filtered calcium load and decreasing the magnitude of secondary hyperparathyroidism. The only way of distinguishing one mechanism from the other is by testing specific predictions that differ in the two forms of hypercalciuria. Clinically, PTH levels are the most clear-cut basis of distinction. Fasting hypercalciuria is not a means of detecting a renal calcium leak because it can be and is caused by exaggerated bone remodeling.

Absorptive hypercalciuria is associated with low or normal fasting immunoreactive PTH (iPTH) levels. The absorptive hypercalciuria hypothesis predicts a spectrum of fasting PTH values, but it forbids the combination of elevated fasting urinary calcium-creatinine ratio, and normal-to-suppressed iPTH levels. Normal PTH levels are typically observed in patients with fasting hypercalciuria and hypercalciuric nephrolithiasis. The renal model requires elevated fasting urinary calcium-creatinine ratios and a high serum iPTH level. This is seen uncommonly (Table 20.1).

On the other hand, evidence exists for suppressed PTH levels in patients with hypercalciuric nephrolithiasis who exhibit fasting hypercalciuria[103] (Fig. 20.7). When fasting hypercalciuric subjects are treated with sulindac, an NSAID agent, their urinary calcium excretion is decreased but, more importantly, their PTH levels are increased. This suggests that a bone resorptive process is releasing calcium to the circulation and suppressing PTH. Inhibition of bone resorption by sulindac results in an increase in PTH levels, suggesting that the levels are suppressed in patients with fasting hypercalciuria.[103]

Past studies attempting to detect low or normal PTH levels[26,35,79,104,105] suffer from difficulties with the radioimmunoassay for PTH. More recent double-antibody techniques that enable the measurement of intact hormone and the detection of low circulating PTH levels circumvent these problems and support the finding of low or normal PTH levels in patients with hypercalciuric nephrolithiasis.

Pathogenesis of Absorptive Hypercalciuria

A potential explanation for the pathogenetic process identified in absorptive hypercalciuria is abnormally elevated $1,25(OH)_2D_3$ levels. Patients with idiopathic hypercalciuria tend to exhibit elevations in $1,25(OH)_2D_3$ levels.[32,36,70,79,106] The frequency of high $1,25(OH)_2D_3$ levels in idiopathic hypercalciuria is controversial, but it appears to range from 30% to 40%. Kaplan[36] demonstrates that fractional calcium absorption correlates with the serum concentration of $1,25(OH)_2D_3$. Two thirds of the patients in this study did not have elevated $1,25(OH)_2D_3$ levels.

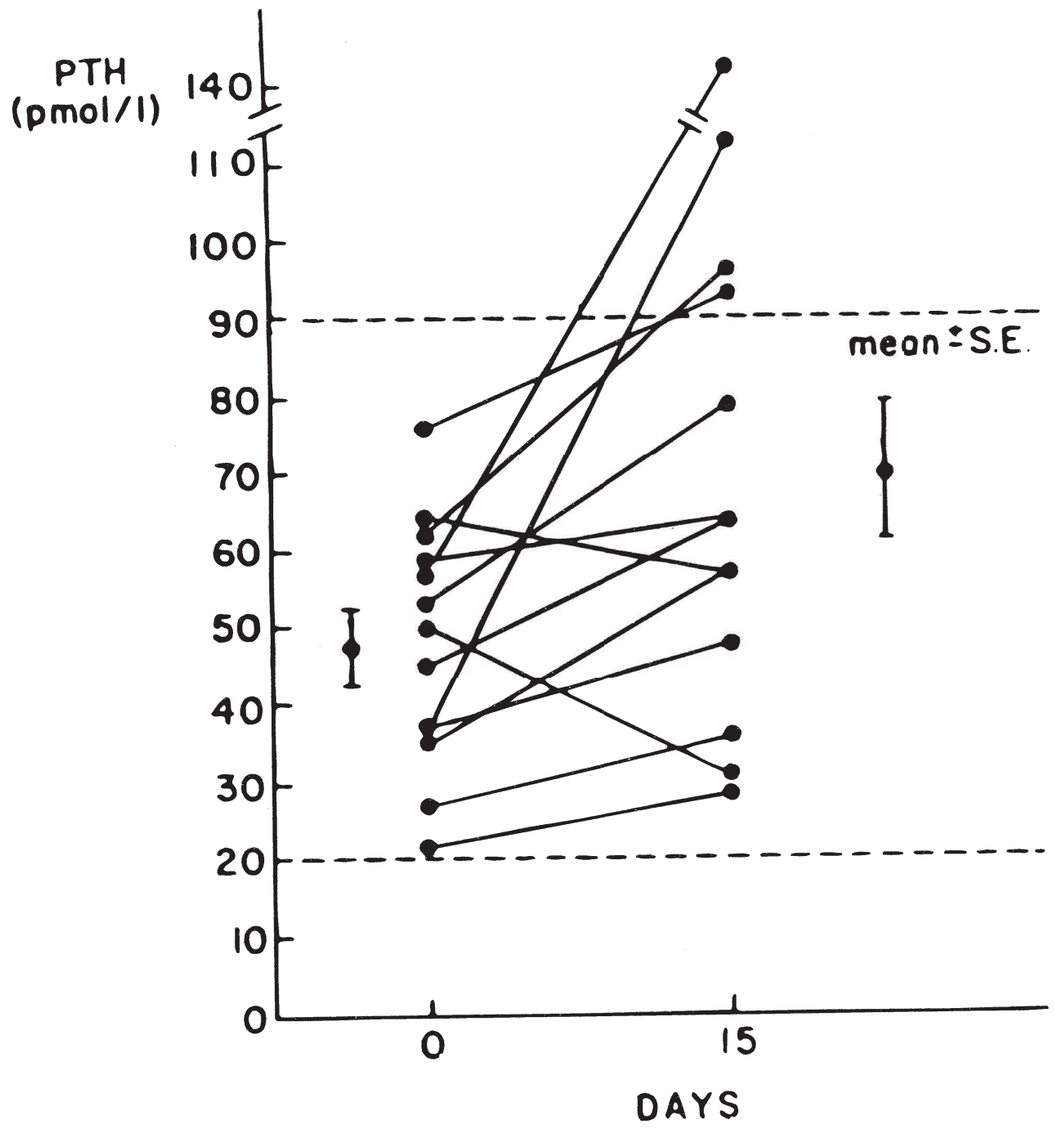

FIGURE 20.7 Changes in serum immunoreactive parathyroid hormone (PTH) in patients with fasting hypercalciuria after 15 days of diclofenac treatment. *Dotted lines* indicate the normal range of PTH. (From Filipponi P, Mannarelli C, Pacifici R, et al. Evidence for a prostaglandin-mediated bone resorption mechanism in subjects with fasting hypercalciuria. *Calcif Tissue Int.* 1988;43:61, with permission.)

On the other hand, evidence exists that shows that increased intestinal absorption of calcium may be primary and independent of vitamin D. Several studies indicated that the hypophosphatemia observed in idiopathic hypercalciuria is not sufficient to stimulate $1,25(OH)_2D_3$ levels.[107,108] Breslau[109] used ketoconazole, an imidazole antimycotic agent[110] capable of reducing serum $1,25(OH)_2D_3$ levels by 40%, in normal subjects and in patients with primary hyperparathyroidism after 1 week of therapy.[111] Ketoconazole was used as a probe to investigate the pathogenetic importance of $1,25(OH)_2D_3$ in patients with absorptive hypercalciuria. Twelve of 19 patients responded to ketoconazole with a reduction in serum $1,25(OH)_2D_3$ levels, intestinal calcium absorption, and 24-hour urinary calcium excretion. In the responding patients, intestinal calcium absorption was directly correlated with serum $1,25(OH)_2D_3$ levels and 24-hour urinary calcium excretion. In seven nonresponders, a reduction in $1,25(OH)_2D_3$ produced no change in intestinal calcium absorption or 24-hour urinary calcium excretion. The authors conclude that absorptive hypercalciuria is a heterogeneous disorder composed of both vitamin D–dependent and vitamin D–independent subsets.[109] The vitamin D–dependent subsets incorporate patients with elevated $1,25(OH)_2D_3$ levels, patients with abnormally responsive vitamin D receptors, and patients with allelic variations

20.4 Types of Renal Stones Formed and Frequency of Occurrence[a]

	CaOx and Cap	CaOx	Cap	Uric acid	Cystine	Struvite	Number of stones
Nordin and Hodgkinson[1]	46.0	14.7	8.0	2.9	3.3	25.1	243
Lagergen[2]	44.2	15.1	7.6	3.6	1.1	28.1	460
Melick and Henneman[3]	30.3	27.1	20.6	12.9	2.6	14.8	155
Prien[4]	34.3	32.7	5.3	5.8	2.9	19.0	1,000
Sutor et al.[5]	35.9	28.5	7.4	2.47	1.61	24.1	810
All series	37.2	26.3	7.4	4.5	2.2	22.3	2,668

[a]Numbers represent the percentage of each stone type in the series. Total numbers of stones surveyed are shown in the last column.
CaOX, calcium oxalate; Cap, calcium phosphate.
From Coe FL, Favus MJ. Nephrolithiasis. In Brenner BM, Rector FC Jr., eds. The Kidney, 2nd ed. Philadelphia: WB Saunders; 1991, with permission.

in the vitamin D receptor that have been incriminated in causing osteoporosis.[112] Animal studies in the genetically hypercalciuric rat support the possibility that an abnormal vitamin D receptor could contribute to the pathogenesis of absorptive hypercalciuria.[113]

Pathogenesis

The crystals that form into renal stones consist of calcium salts, uric acid, cystine, or struvite (magnesium ammonium phosphate). Calcium stones are the predominant variety (Table 20.4) and they are composed of calcium oxalate (CaOx), CaOx and calcium phosphate as apatite, or apatite alone.[12,114–119] Two forms of CaOx crystals—monohydrate and dihydrate—differ in their lattice structure and microscopic appearance[120] and this may be relevant to pathophysiology. The calcium phosphate crystals are most commonly apatite or hydroxyapatite. Calcium carbonate is a crystal form usually found mixed in struvite stones or a high pH environment. Occasionally, brushite (calcium hydrogen phosphate), whitlockite (calcium orthophosphate), and octacalcium phosphate are found.[118] Calcium phosphate crystals are as common in stones as are CaOx crystals (Table 20.4), but the amount of CaOx in mixed stones generally exceeds that of calcium phosphate. Additionally, pure CaOx stones are much more frequent than are pure calcium phosphate stones.

Formation of Renal Stones

The formation of renal stones composed of calcium salts is a complex process that remains poorly understood despite considerable efforts over many centuries. The process consists of a calcium salt precipitating from solution (nucleation) forming a crystal. Subsequent crystal growth and aggregation lead to a stone nidus. When the aggregate adheres to the tubulopelvic uroepithelium, continued epitaxial growth of the crystal aggregate eventually leads to a detectable size, making it a renal stone.

Nucleation

Nucleation describes the process that occurs when the activity of calcium salts reaches the level at which the solid phase begins. If one compares urine to an aqueous solution, it quickly becomes apparent that urine is able to hold much higher levels of calcium salt in solution than is water. If one considers an aqueous solution containing crystals of a calcium salt when the crystal neither grows nor shrinks, the solution is in equilibrium. The product of the free ion concentrations (activity product) at this equilibrium determines the equilibrium solubility product (SP) of the salt (Fig. 20.8). Solutions with concentrations of salt less than the equilibrium SP are undersaturated. A higher free ion activity product will cause the solid phase, the crystals, to grow (epitaxy). However, if the crystals are removed from a

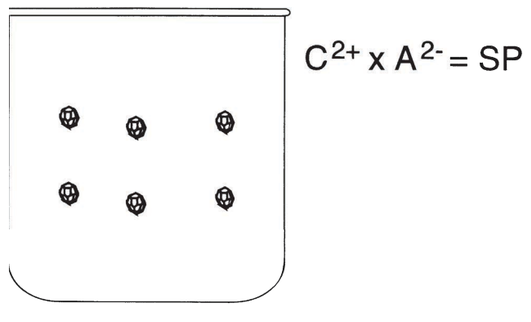

FIGURE 20.8 A solution containing calcium salt (a calcium salt consists of cations, C^{2+}, and anions, A^{2-}) crystals is in equilibrium when the crystals neither grow nor shrink. At this point, the product of the free ion concentration (activity product) is the equilibrium solubility product (SP) of the salt.

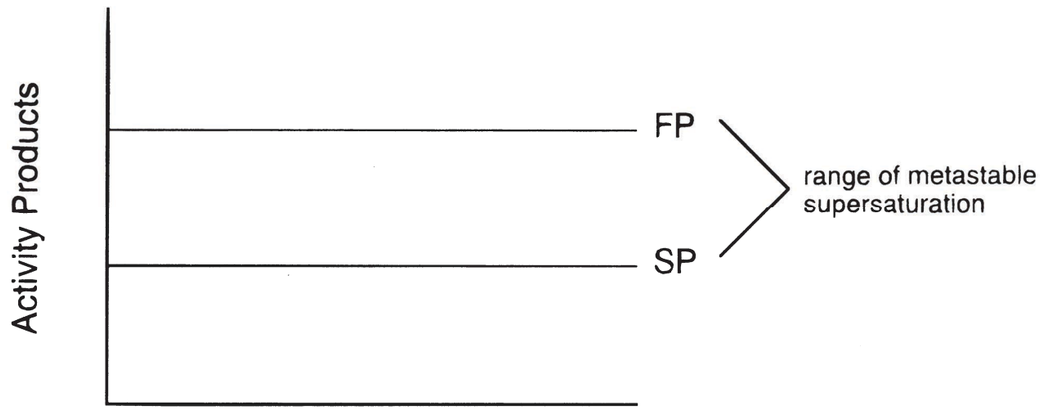

FIGURE 20.9 When calcium salts are added to a solution, precipitation (nucleation) does not occur until free ion activity products well above the solubility product are reached. The activity product at which solid phase begins to form is the formation product.

solution at the level of the equilibrium SP and then the ion activity product is elevated, the activity product that would have caused growth of preformed crystals now results in no appearance of a new solid phase. This solution is called metastably supersaturated (Fig. 20.9). The activity products of calcium salts in urine are almost constantly in the range of metastable supersaturation. In the range of metastable supersaturation, if the activity products are raised sufficiently, new crystals will appear. The activity product at which new crystals form is called the formation product (FP), or the upper limit of metastability (Fig. 20.9). Above the level of the FP, a solution is unstable, creating new crystal nuclei. Urine may be undersaturated, metastably supersaturated, or unstable with respect to CaOx or the stone-forming calcium phosphate crystals (brushite, octacalcium phosphate, hydroxyapatite, and apatite), but most of the time it is metastably supersaturated and, particularly for brushite, close to the FP.

Factors Influencing Urinary Supersaturation

The multiple factors influencing urinary supersaturation in a clinical setting are shown in Table 20.5. The renal excretion of calcium salts that precipitate and take part in stone formation is a primary determinant of urinary supersaturation. Thus, urinary volume, calcium, oxalate, and phosphate ions all participate in the risk of calcium stone formation. In addition, binding of calcium and oxalate to cells, or the solid phase, and urine pH (which influences relative amounts of monohydrogen phosphate and dihydrogen phosphate) drastically alter free ion concentrations and have great importance in regulating saturation—at least equal to the role of the total concentrations of the respective substances. This is the reason why hypercalciuria, oxaluria, unduly alkaline urine, and low urinary volumes are not sufficient to ensure that stones will form in and of themselves. Binding of the components of calcium salts also complicates the measurement of urine saturation, and simple concentration measurements give only small clues to actual free ion activity products.

Alternative substances to calcium salts may be considered as inhibitors of urinary saturation and contribute to the ability of urine to hold salts in solution to a much greater extent than does a simple aqueous solution. The known inhibitors of urinary saturation include the divalent cation magnesium, which forms oxalate, and phosphate salts, which are more soluble compared to those of calcium. In addition, citrate and sulfate are anions with which calcium forms soluble complexes as alternatives to phosphate or oxalate. Urine also contains substances to which calcium binds, thereby reducing the free ion activity. Pyrophosphate, nephrocalcin, and osteopontin are other inorganic and organic crystal inhibitory calcium-binding sites, and are discussed in greater detail later in this chapter. In addition, certain substances to which calcium salts may complex actually promote precipitation. In this category, uric acid and sodium urate are found. These substances are also discussed later in the chapter.

20.5 Factors Affecting Urinary Supersaturation in the Clinic

Renal excretion rates
- Calcium
- Oxalate
- Phosphate
- Protons
- Water

Inhibitors
- Magnesium
- Citrate
- Nephrocalcin
- Osteopontin
- Tamm-Horsfall protein
- Others (pyrophosphate, glycosaminoglycans)

Promoters
- Uric acid, urate
- Altered epithelial calcium oxalate binding

Measurements of Urinary Supersaturation

Because simple concentration measurements give little clue to the activity of specific ions in urine, several strategies have been designed to estimate urinary supersaturation.[61,121,122] These approaches are computer-based calculations of urinary free ion activity for calcium, oxalate, and phosphate derived from their concentrations and their known tendencies to form soluble complexes with each other and with other ligands such as citrate and sulfate. A calculated free ion activity product such as the CaOx ion product, when divided by the corresponding equilibrium SP, yields an activity product ratio (APR), which estimates the degree of saturation (Fig. 20.10). A ratio above one indicates urinary supersaturation. Ratios below one represent undersaturation. The upper limit of metastable supersaturation can be

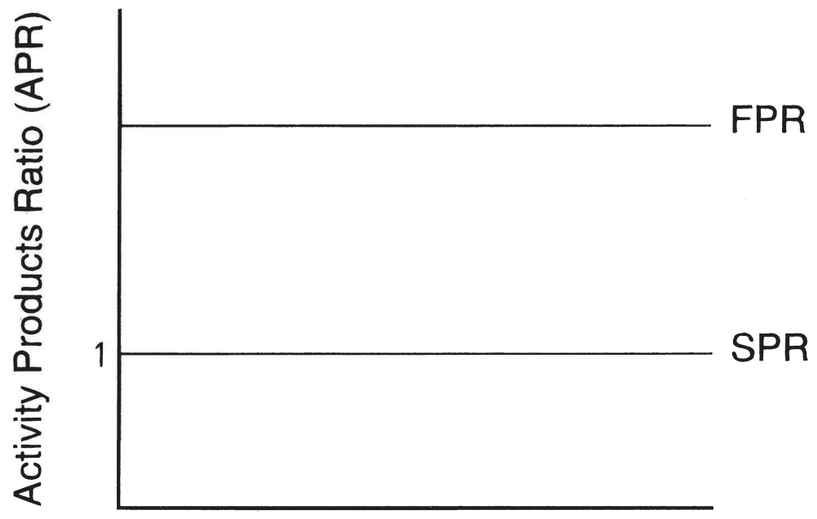

FIGURE 20.10 The calculated activity product of a calcium salt factored by its solubility product (SP) yields a ratio (R) describing undersaturation (<1), saturation (1), metastable supersaturation (>1), and the formation product ratio (FPR) at the point when the solid phase begins to form. The FPR determined for calcium oxalate (CaOx) by Pak and Holt[23] was 11 ± 3.

determined by raising the APRs to the point at which precipitation or solid phase formation begins to appear. The APR at this point is called the formation product ratio (FPR).[61] Pak and Holt[123] modified the approach to measuring urinary supersaturation by adding seed crystals to urine and incubating at 37°C with stirring at constant pH, for 2 days. The ratio of concentration products at the start and end of the incubation must equal the APR, even though the concentration products themselves do not equal the activity products. Pak and Holt[121,123] show that the assumption of stable activity coefficients is valid, so that that the empirical concentration product ratio is a valid estimate of the APR, within limits.

Observations of Urinary Supersaturation

Several investigators[124–128] with varying approaches have accumulated evidence indicating that urine from stone formers is more supersaturated than normal (Table 20.6). Because of differences in methodology, the absolute values of activity products differ among investigators. However, stone formers, whether hypercalciuric or normocalciuric, had higher average values of urine saturation than did those who did not form stones. This held whether saturation was measured with respect to CaOx, brushite, octacalcium phosphate, or hydroxyapatite.

An important observation common to approaches both with and without the use of seed crystals is that activity products of normal urine, on average, are above the equilibrium SP (Fig. 20.9) or oversaturated, except with respect to brushite. In the data from Pak and Holt[123,127] and Weber,[128]

20.6 Urine Calcium Oxalate and Calcium Phosphate Activity Product Ratios in Normal Subjects and in Stone Formers[a]

	Normal subjects	Hypercalciuric stone formers	TCH Normocalciuric TCH stone formers
Calcium oxalate monohydrate			
Robertson[b]	3 ± 1.2 to 10.7 ± 1.3	5.5 ± 1.3 to 18.2 ± 1.3	—
Pak[c]	1.45 ± 0.70	2.8 ± 1.4	2.2 ± 6.1
Weber[d]	1.97 ± 0.90	3.3 ± 2.2	2.2 ± 1.0
Brushite			
Pak[e]	0.35 to 0.26	1.74 ± 0.79	0.9 ± 0.5
Marshall[f]	1.15 ± 0.60	1.35 ± 0.70	4 ± 1.4
Octacalcium phosphate	63	79	200
Hydroxyapatite	4.6×10^5	9.1×10^5	2.9×10^8

[a]All values are means ± standard deviations.
[b]From Robertson et al.[20,24,25] and Marshall et al.[26]; values of APR were calculated from activity products; the equilibrium solubility product (K_{sp}) was taken as 1.7×10^{-9} m^2.
[c]From Pak[27]; values of APR were measured by experiments.
[d]From Weber[28]; values of concentration product ratio (see text) were measured by seeding experiments.
[e]From Pak et al.[23]; K_{sp} of brushite was taken as 9.32×10^{-7} m^2; values of APR were calculated.
[f]From Marshall[26]; K_{sp} of octacalcium was taken as 2.3×10^{-18} m^2 and of hydroxyapatite as 1.1×10^{-56} m^2; values of APR were calculated.
APR, activity product ratio.
Modified from Coe FL, Favus MJ. Nephrolithiasis. In: Brenner BM, Rector FC Jr., eds. The Kidney, 2nd ed. Philadelphia: WB Saunders; 1991, with permission.

this is a visible fact: Added crystals grew in urine from most normal persons. The use of urine measurements to assess supersaturation may be insufficient to reveal the full crystallization potential that exists in the renal tubule. Hautmann and colleagues[129] studied the calcium and oxalate concentrations in tissue from cortex, medulla, and papillae of human kidneys. The CaOx concentration product in the papillae exceeded that of urine and the concentrations in the medulla and cortex. If the high chemical concentration product in the papillae reflects a high free ion product in tubular fluid or interstitium, CaOx crystallization in this region may occur more rapidly than would be predicted from the ion product of the final urine.

Formation Products

The urinary APR at which urine produces new crystals has been measured for CaOx and brushite for those with no signs of stone formation and hypercalciuric, normocalciuric, and hyperparathyroid stone formers. Surprising variability was reported by Pak[127] (Fig. 20.11). However, the APR at the limit of metastability, the FPR, is higher in normal urine than in urine from stone formers. Furthermore, the FPR in urine from patients with hyperparathyroidism may be below the value observed for simple aqueous salt solution. This low of a value of FPR suggests facilitation of crystal formation. This type of data from several investigators yielded several conclusions. The first is that urine is abnormally supersaturated in stone formers. The values of APRs lie close enough to the FPR, at least for CaOx, so that new crystal formation would be expected. Most urine, even from those without stone formations, is metastably supersaturated with respect to CaOx so that growth of crystal nuclei into a significant mass is predictable.

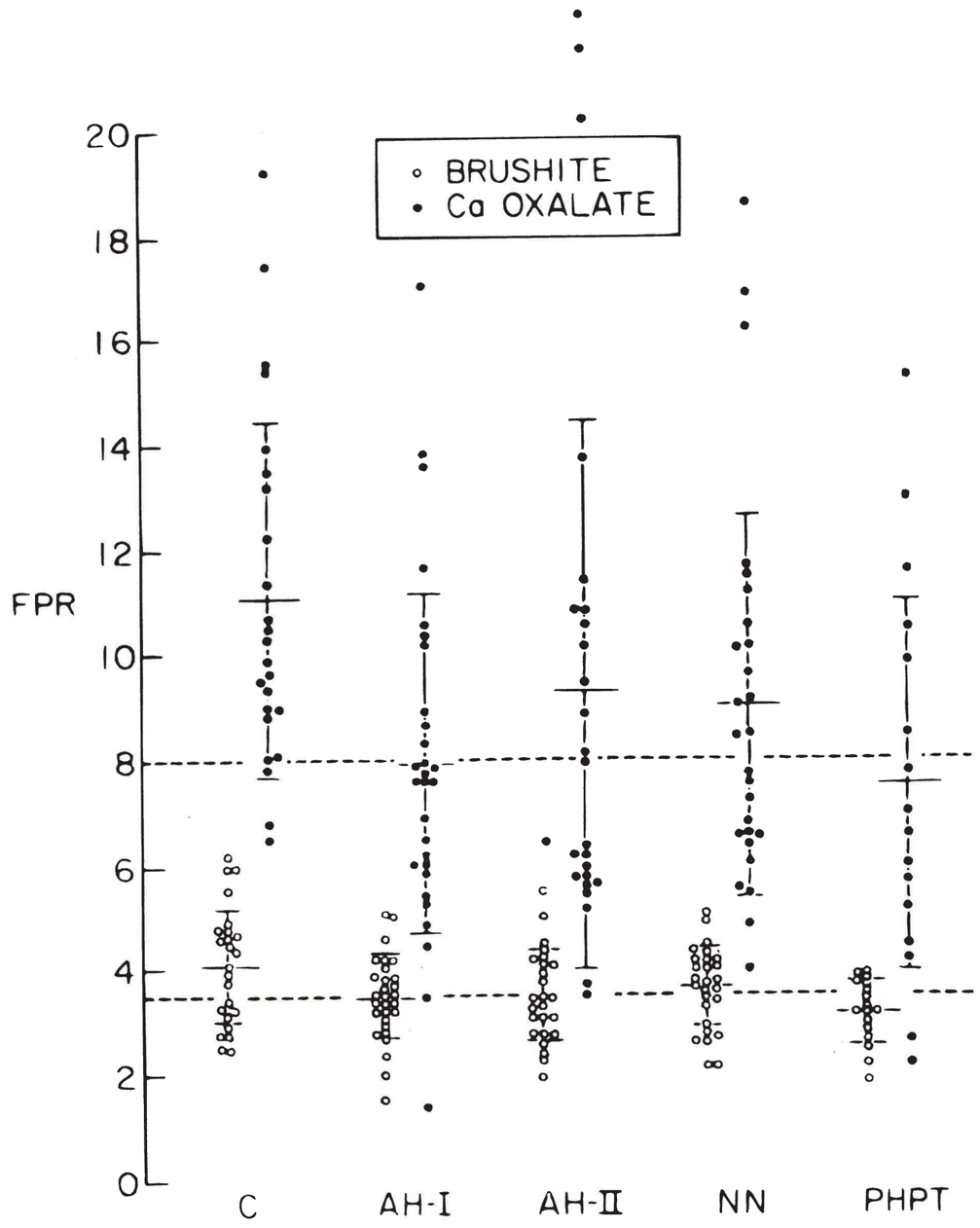

FIGURE 20.11 Formation product ratios (FPRs) for calcium oxalate (CaOx) and brushite of urine from normal subjects and stone formers. Each point shows the value for a single urine sample. For an aqueous solution, the activity product ratios at which spontaneous crystallization of CaOx and brushite occurs, the so-called FPRs, are shown by *dotted lines* at 8 and 3.6, respectively. *C*, control subject; *AH-1* and *AH-2*, severe and mild absorptive hypercalciuria; *NN*, normal calciuric stone formers; *PHPT*, primary hyperparathyroidism. Mean values in standard deviations (SD) are shown by *horizontal lines*. (From Pak CYC, Holt K. Nucleation and growth of brushite and CaOx in urinary stone-formers. *Metabolism*. 1976;25:665, with permission.)

Homogeneous Versus Heterogeneous Nucleation

Nucleation, the initial precipitory event in stone formation, may be homogeneous or heterogeneous. In an unstable solution, crystals form spontaneously by homogeneous nucleation. Much higher levels of supersaturation are required to produce homogeneous nucleation than heterogeneous nucleation.[130] The latter occurs in metastably supersaturated urine as certain macromolecules, or other crystals that can act as nuclei, stimulate precipitation. Because urine contains a number of macromolecular and cellular degradation products, crystallization is most often heterogeneous.[130,131]

The efficiency of heterogeneous nucleation depends on the similarity between the spacing of charged sites on the preformed surface and the spacing in the lattice of the crystal that is to grow on that surface. This matching is referred to as epitaxis, and its extent is usually referred to as a good or poor epitaxial relationship.[132] A number of urine crystals have good epitaxial matching and behave toward one another as heterogeneous nuclei. Monosodium urate and uric acid are excellent heterogeneous nuclei for CaOx,[133,134] so uric acid or urate could, by crystallization, lower the FPR for CaOx. Heterogeneous nucleation is thought to play a role in linking hyperuricosuria to CaOx stones,[38,135–138] a matter discussed later in this chapter. Epitaxial overgrowth of CaOx on a surface of uric acid has been experimentally documented.[139] At a pH above 6.9, brushite may transform to hydroxyapatite, which can serve as a nucleus for CaOx.[140] Based on observations that calcium phosphate is the most common crystal in human urine,[141] is ubiquitous in human urinary stones, and is often seen at the center of mixed CaOx/calcium phosphate urinary stones,[142] nucleation of CaOx crystals is proposed to be induced by calcium phosphate.[11,12] In addition, both apatite and brushite crystals induce crystallization of CaOx in vitro from metastable solutions of CaOx.[143,144] The other possible epitaxial relationships have not yet been linked explicitly to particular varieties of stone disease.[145] However, the low FPRs in primary hyperparathyroidism suggest that heterogeneous nucleation may be occurring.

Crystal Growth

Once present, crystal nuclei grow if suspended in urine with an APR above one (Fig. 20.12). Crystal growth is critical to stone disease, because microscopic nuclei are too small to cause obstruction. Crystals are regular lattices, composed of repeating subunits, and they grow by incorporation of calcium and oxalate, or phosphate, into new subunits on their surfaces. In metastable solutions at 37°C, growth rates of CaOx and the stone-forming calcium phosphate crystals are rapid. Appreciable changes in macroscopic dimensions occur over hours to days. Growth rate increases with the extent of oversaturation and tends to be most rapid in urine having the highest APR.

Factors Influencing Crystal Growth

In urine, the upper limit of metastability is higher and crystal growth rates are lower than in a salt solution with the same APR. The nature of the materials that confer crystal growth rate inhibition on urine is incompletely known. Crystal growth inhibitors for calcium phosphate crystals may not be the same as the substances that affect CaOx crystal growth.

Inorganic pyrophosphate increases the FPs of calcium phosphate and CaOx in salt solutions and, by absorbing their surfaces, retards the growth of hydroxyapatite[138] and CaOx crystals.[140] Urinary pyrophosphate concentrations range from 20 to 40 μM in adults. This concentration is sufficient to inhibit crystal growth.[146] Fleisch and Bisaz[137] suggest that urine raises the FP for calcium phosphate above the level expected from the pyrophosphate it contains. They suggest that other inhibitors accounted for approximately 50% of the total inhibition of calcium phosphate crystal growth. Smith and colleagues[147] have produced similar estimates. Bisaz[148] suggests that pyrophosphate, citrate, and magnesium ions contribute about 77% of the total calcium phosphate crystal inhibition capacity of urine. However, several investigators[140,149] concluded that urine pyrophosphate contributes insignificantly to CaOx crystal growth inhibition.

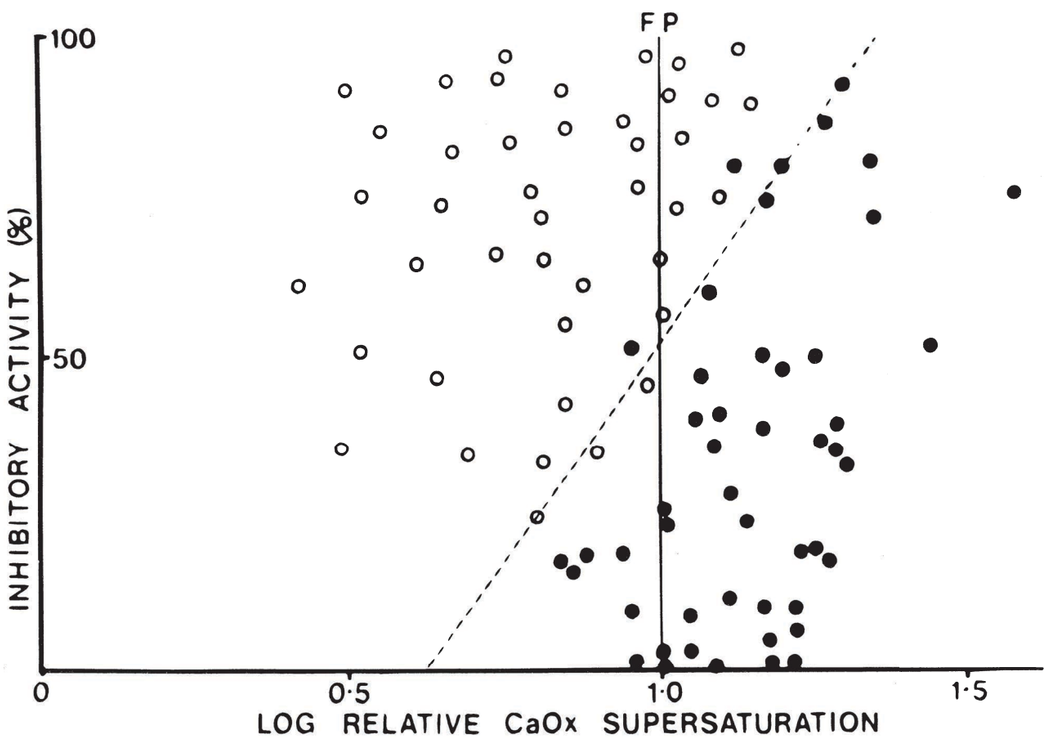

FIGURE 20.12 Saturation-inhibition index of urine from stone formers in normal subjects. The ability of dilute urine to prevent crystal aggregation in an in vitro system (inhibitory activity) is shown as a function of relative supersaturation with respect to calcium oxalate (CaOx) (*x* axis). A value of 1.0 represents the saturation at the level of the formation product (FP); a value of 0.1 would be near the solubility product. Stone formers (*solid circles*) and normal subjects (*open circles*) fall into separate zones; the *dotted line*, obtained by statistical analysis, is the best plane of separation. (From Robertson WG, Peacock M, Marshall RW, et al. Saturation inhibition index as a measure of the risk of calcium oxalate stone formation in the urinary tract. *N Engl J Med*. 1976;294:249, with permission.)

Inhibitors of Calcium Oxalate Crystal Growth

Some progress has been made describing the urinary inhibitors of CaOx crystal growth. The studies of Robertson and associates[150,151] suggesting that a urinary proteoglycan may significantly contribute to CaOx crystal growth inhibition have not been further supported. Strongly acidic peptides such as nephrocalcin and osteopontin have been described as important inhibitors of CaOx crystal growth.[59,146,152–155] Strongly acidic peptides such as poly-L-aspartate and poly-L-glutamic acids inhibit CaOx crystal growth, and urine appears to contain several glycopeptides unusually rich in these two amino acids. Two of the best known of these are nephrocalcin and osteopontin.[155] Treatment of urine with nonselective proteases diminishes the inhibition of CaOx crystal growth,[146] which may be related to urinary glycoproteins. Nephrocalcin contains γ-carboxyglutamic acid (Gla), and is an amphiphilic molecule with a molecular mass of about 15 kd. It tends to self-aggregate into a series of higher molecular mass polymers.[59,152]

Nephrocalcin from stone formers lacks the Gla residues, which is associated with a loss of ability to form stable film at an air-water interface, perhaps reflecting decreased amphiphilicity. The nature of the molecular abnormality leading to decreased inhibition of CaOx crystal growth is unknown. A separate abnormality in nephrocalcin has been identified from the urine of patients with X-linked recessive nephrolithiasis.[156] Nephrocalcin from affected males and carrier females with X-linked recessive nephrolithiasis is poorly phosphorylated, with decreased ability to inhibit crystal growth.

Osteopontin (OPN) is a more recently isolated CaOx crystal growth inhibitor.[153] Expression of OPN under basal conditions is limited to bone matrix, kidney, inner ear, decidual glands, and smooth muscle.[157] OPN is found in breast milk and serum.[158,159] It is expressed in response to various mitogens and growth factors, including phorbol esters and transforming growth factor-beta (TGF-β)[160,161] and is also expressed by cells in response to injury. Kleinman[162] finds that renal tubular OPN expression increases markedly after ischemic injury. However, OPN excretion is not decreased in renal stone formers. It appears that the level of phosphorylation is the critical issue in regard to the function of OPN as a urinary crystal inhibitor.[155] The full OPN protein is not required for functional activity. Small domains of the OPN primary sequence were able to independently inhibit

calcium oxalate monohydrate (COM) crystal growth. The phosphorylated OPN peptides are potent inhibitors of COM crystal growth, but not COM crystal aggregation.[155] The extent of phosphorylation of OPN is responsive to hormonal influences such as those of vitamin D.[163] The role of OPN in the kidney is not fully understood, although it is protective against CaOx monohydrate crystal aggregation and retention in the kidney as demonstrated by studies in OPN null mice, genetic hypercalciuric stone-forming rats, and humans.[67,164]

The role of OPN in biology is complex.[165] It is an osteoclast autocrine regulating motility and bone resorption.[166] OPN is a ligand for the cell surface receptors of $\alpha_v\beta_3$ and CD44, and it stimulates osteoclast signal transduction upon binding.[166,167] In the kidney $\alpha_v\beta_3$ is found largely on the basolateral surface of the distal nephron[168] and CD44 localization is unknown, whereas OPN is secreted mainly by the thick ascending limb into the tubular fluid at the luminal surface of the epithelial cell. OPN is structurally related to proteins found in other mineralized tissues, notably mollusk shells, which have contrasting effects on crystallization depending on whether they are in solution or immobilized on a surface. When in solution, these proteins inhibit calcite, CaOx, and apatite crystal growth.[169] However, if these proteins are immobilized on a support before incubation with a supersaturated solution of the mineral phase, they are able to initiate crystal nucleation in specific orientations.[170] It is believed that OPN serves as a modulator of crystallization and is important for ordered crystal structure of the bone.[171] In its phosphorylated state, it inhibits and thereby regulates apatite formation.[172] OPN is also found in association with the pathologic calcification of stone matrix[173] and atherosclerotic plaques.[160,174] Phosphorylation of OPN renders it inhibitory to vascular calcification[175] and skeletal mineralization.[171]

Tamm-Horsfall protein (THP) is the major urinary glycoprotein of normal urine. THP from stone formers is abnormal, with a higher tendency to aggregate under conditions of increased ionic strength and low pH.[176] Normal THP is an inhibitor of crystal aggregation, but THP from stone formers is less active in preventing aggregation and, under some conditions, THP from stone formers may promote the formation of crystal aggregates, especially in the presence of high concentrations of calcium. The structural abnormalities responsible for impaired inhibitory activity are not completely understood.[177] One study demonstrated that Tamm-Horsfall glycoprotein and citrate concentrations are linearly related to CaOx monohydrate agglomeration inhibition.[178] The effects of the two substances are synergistic. Tamm-Horsfall glycoprotein removal from the urine dramatically reduced CaOx agglomeration.[178]

Hallson and Rose[179] suggested that certain materials in urine, which they refer to as uromucoids, might promote calcium phosphate crystallization and aggregation. The significance of these findings is unclear. Of greater interest, urate anions in urine appear to bind and adsorb inhibitor substances, suggesting that hyperuricosuria could promote CaOx stones by reducing levels of urine crystal growth inhibitors.[150] When incubated in vitro, monosodium urate is able to bind heparin, a potent proteoglycan inhibitor of CaOx crystallization.[180] This demonstrates that at least one specific polyanion inhibitor could be adsorbed by a solid phase of uric acid.

Relationship of Oversaturation and Crystal Growth Inhibition to Clinical Nephrolithiasis

The force that drives calcium salts out of solution, into the solid phase, is oversaturation. Compared to homogeneous nucleation, heterogeneous nucleation facilitates stone formation by decreasing the degree of oversaturation required for nucleation. Inhibitors such as magnesium, pyrophosphate, osteopontin, and nephrocalcin suppress nucleation; increase the supersaturation needed to produce the solid phase; and retard the growth of nuclei already formed. In the most important stone-forming conditions, oversaturation, heterogeneous nucleation, and reduced inhibitors have documented, or at least postulated, roles that vary from one disease to another (Table 20.7). Treatment is often successful in reversing stone formation by eliminating the disturbances that enhance the risk of stones or, in some cases, by introducing secondary biochemical changes that compensate for the underlying defect.

Oversaturation occurs in idiopathic hypercalciuria, primary hyperparathyroidism, and hyperoxaluria because of overexcretion (Table 20.7). Both hypercalciuria and phosphaturia occur in RTA. Oversaturation with respect to calcium phosphate salts, which make up most of the stones in RTA, is also increased by alkaline urine and by low levels of urinary citrate, an important calcium-binding agent.

The finding of urine formation products below those of simple salt solutions provides evidence for heterogeneous nucleation in hyperparathyroidism. The basis for this finding is unknown. Hyperuricosuria is thought to engender urine crystals of uric acid or sodium hydrogen urate, which are efficient heterogeneous nuclei for CaOx.[38,133,134] It is uncertain whether these crystals are in a gel state.[150]

Low levels of urine inhibitors have been demonstrated in some hypercalciuric and normocalciuric stone formers.[125] Robertson[125] reports lower inhibitor levels in hyperuricosuric stone formers. In general, the levels of crystallization inhibitors in the urine of stone formers differ from those in non–stone formers and, consequently, their urine samples can be distinguished from samples of normal people more reliably when inhibitor content is measured than by the use of supersaturation measurements alone (Fig. 20.13). This fact highlights the presence of low inhibitor levels in stone-forming patients and suggests that inhibitors are very important in preventing stones.

More recent measurements of urinary inhibitors of CaOx monohydrate crystal growth show that the lowest inhibitor levels occur in patients with hypercalciuria, but not hyperuricosuria,[180] and that samples from normal subjects can be distinguished from those of stone formers no more

20.7 Pathogenetic Mechanisms in Some Established Forms of Calcium Nephrolithiasis

	Mechanisms		
	Overexcretion	**Heterogeneous nucleation**	**Reduced inhibition of stone formation**
Idiopathic hypercalciuria	+	−	Unknown
Primary hyperparathyroidism	+	+	−
Hyperuricosuria	−	+	−
Renal tubular acidosis	+	Unknown	−
Hyperoxaluria	+	−	−
No detectable metabolic abnormality	−	−	−

reliably by a combination of inhibitor and supersaturation measurements than by measurements of inhibition alone. Nephrocalcin from urine of stone-forming patients[181] or CaOx stones[182] seems abnormal; it lacks Gla and forms weak air-water films. The difference between these results and those of Robertson[125] is probably related to differences in methodology. Hallson and Rose[179] present additional evidence that inhibitors of crystallization are functionally important and differ in stone formers from those in normal subjects.

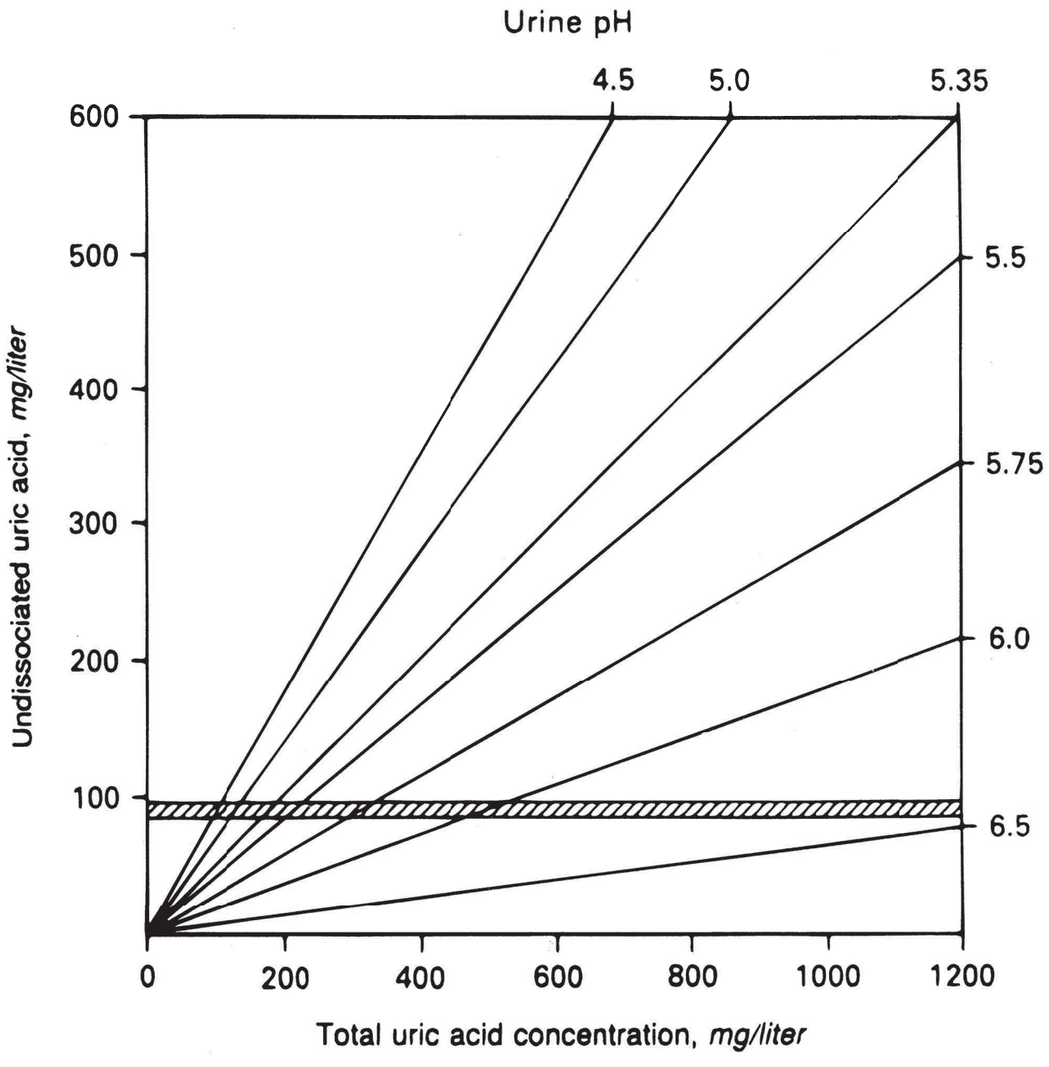

FIGURE 20.13 Nomograms showing undissociated uric acid concentration at values of urine pH and total uric acid concentration. The solubility limit for uric acid is shown by crossed hatched bars (96 ± 2 mg per L). (From Coe FL. Uric acid and calcium oxalate nephrolithiasis. *Kidney Int.* 1983;24:392, with permission.)

Medical Management of Hypercalciuric Nephrolithiasis

The conservative recommendations made for all patients, regardless of the underlying etiology of stone disease, are affected somewhat by the diagnosis of hypercalciuria. Measures undertaken to increase urinary output to more than 2 L per day, to avoid high oxalate and sodium intake, and to restrict animal proteins with extremely high purine levels are generally recommended in any patient with recurrent nephrolithiasis. With these conservative measures alone, a significant number of patients are able to normalize urinary risk factors for stone formation and reduce the incidence of recurrence. After 3 to 4 months of conservative therapy, the patient needs reevaluation. If the patient's metabolic or environmental abnormalities have been corrected, the conservative approach to therapy should be considered and the patient followed every 6 months with repeat 24-hour urine testing. Follow-up is essential, not only to monitor the efficiency of treatment but also to encourage patient compliance. However, if a metabolic defect persists despite conservative treatment, medical therapy may be instituted. For example, if significant sodium-dependent hypercalciuria persists despite dietary recommendations of restricting salt intake, medical therapy with thiazides or citrate may be instituted.

The issue of dietary calcium in patients with hypercalciuric nephrolithiasis has become an important one. It is clear that adequate calcium intake is needed to maintain skeletal homeostasis during adulthood and old age. However,

high calcium intakes are not tolerable in patients with hypercalciuric nephrolithiasis and absorptive hypercalciuria. Nevertheless, a low-calcium diet promotes oxalate absorption by decreasing CaOx salt formation in the intestine. In the absence of calcium, increased free oxalate anion is available for absorption. The impact of low-calcium diets favoring hyperoxaluria has been tested in a large population study from Framingham, Massachusetts.[183] Curhan and coworkers[183] show that dietary calcium intake is inversely associated with the risk of kidney stones in patients who did not have a prior history of kidney stones. Thus, low-calcium diets increased the risk of the development of a kidney stone. It is important to realize that this study specifically excluded most patients with idiopathic hypercalciuria who had already had a renal stone. It is a mistake to recommend high-calcium diets in patients with hypercalciuric nephrolithiasis, especially those who have absorptive hypercalciuria.

Despite improved elucidation of pathophysiology and formulation of diagnostic criteria for nephrolithiasis of different causes, selective medical treatment programs for nephrolithiasis have not been widely implemented. Confusion and controversy regarding the pathogenesis of hypercalciuria, and the absence of an ideal therapeutic approach to absorptive hypercalciuria, have contributed to this situation. Thiazide diuretic therapy remains the mainstay of the medical approach to hypercalciuria. Treatment with a thiazide is ideal, pathophysiologically, for renal hypercalciuria. Thiazides directly stimulate renal tubular calcium transport and suppress the secondary hyperparathyroidism associated with the condition. However, renal hypercalciuria, as previously discussed, is an uncommon form of hypercalciuria associated with nephrolithiasis. Because idiopathic hypercalciuria is largely an intestinal overabsorption problem, an ideal treatment would be one that directly and specifically inhibits calcium absorption. Such a pharmacologic agent is not available.

Sodium Cellulose Phosphate

Sodium cellulose phosphate reduces urinary calcium excretion, especially in patients with intestinal hyperabsorption. However, sodium cellulose phosphate induces a reciprocal increase in oxalate excretion due to the binding of intestinal calcium. The resultant hyperoxaluria offsets the beneficial effects of the hypocalciuria induced. In one study, the oxalate excretion rate rose from 30 to 60 mg per 24 hours[184] and the mean APR for CaOx fell only 20%, from 2.75 to 2.19. Other investigators[185] described the clinical response of recurrent CaOx stone disease to cellulose phosphate. The therapy reduced stone recurrence in patients who received cellulose phosphate to the same degree accomplished by just reducing dietary calcium intake. The latter is known to be ineffective as a single therapeutic approach. Thus, cellulose phosphate is not a treatment for the typical calcium stone former. Although the rationale for its use might seem reasonable, it is flawed by the reciprocal hyperoxaluria. In addition, the high frequency of negative calcium balance in patients with idiopathic hypercalciuria must also be of concern with use of this type of agent.

Thiazides

Thiazides have been extensively used for the treatment of hypercalciuric nephrolithiasis.[186–188] Hydrochlorothiazide is most effective in patients with renal hypercalciuria because, by reducing the high PTH levels, hydrochlorothiazide inhibits its $1\alpha,25(OH)_2D_3$ production and reduces intestinal calcium absorption. Thiazides exert significant hypocalciuric action in patients with intestinal hyperabsorption without reducing intestinal calcium absorption.[30] Nonetheless, thiazides may show long-term effectiveness in absorptive hypercalciuria. Despite the hypocalciuric action of thiazides and the resultant increase in serum calcium, intestinal calcium absorption remains persistently elevated. These studies suggest that retained calcium is added to the skeleton at least during the first few years of therapy. Bone density, determined in the distal third of the radius by photon absorptiometry, increases significantly during thiazide treatment and absorptive hypercalciuria, with an annual increment of 1.34%.[189] With continued therapy, however, the increase in bone density stabilizes and the hypocalciuric effect of thiazide becomes attenuated. These results suggest that thiazide treatment causes low turnover of bone, which interferes with the continued calcium accretion in the skeleton. The resulting hypocalciuric effect of thiazide is blunted by an increase in the serum calcium level and the resultant increase in filtered calcium load.[189]

In addition to the aforementioned studies, several controlled and uncontrolled studies documented the effectiveness of thiazide therapy in hypercalciuric nephrolithiasis.[119] Thiazides directly inhibit the sodium chloride cotransport protein for apical sodium entry in the diluting segment of the cortical thick ascending limb and the early distal nephron. This transport protein is also expressed in the osteoblast, which may further contribute to the positive actions of thiazides in patients with absorptive hypercalciuria leading to increased skeletal calcium accretion. Additional studies will be required to delineate the role of this potential mechanism in the therapeutic benefits resulting from thiazides.

Orthophosphate

Orthophosphate (neutral or alkaline salt of sodium/potassium phosphate given in doses of 0.5 g of phosphorus three to four times per day) reduces $1,25(OH)_2D_3$ synthesis. However, no convincing evidence exists that this treatment restores normal intestinal calcium absorption. Orthophosphate reduces urinary calcium by directly impairing the renal tubular reabsorption of calcium and by binding calcium in the intestinal tract. Urinary phosphorus is markedly increased during therapy—a finding reflecting the absorbability of soluble phosphate. Physicochemically, orthophosphate reduces the urinary saturation of CaOx, but increases that of brushite. Moreover, the urinary inhibitor activity is increased, probably owing to the stimulated renal excretion of pyrophosphate and citrate. The results of studies on the efficacy of orthophosphate are mixed.[189–191] Although reports to the

contrary have appeared, orthophosphate therapy can cause soft tissue calcification and PTH stimulation.[192] Furthermore, orthophosphate therapy is contraindicated in patients with nephrolithiasis complicated by urinary tract infection and in patients with renal insufficiency.

PRIMARY HYPERPARATHYROIDISM

In the past, primary hyperparathyroidism was a major cause of hypercalciuric nephrolithiasis. The advent of routine screening of serum chemistries in hypercalcemic patients led to early detection of primary hyperparathyroidism. Consequently, most patients with primary hyperparathyroidism are detected in an asymptomatic phase before nephrolithiasis becomes a problem. Currently, primary hyperparathyroidism accounts for less than 1% of hypercalciuric nephrolithiasis[19,20,193] (Table 20.1).

The pathogenesis of nephrolithiasis in primary hyperparathyroidism is a direct response to the presence of excessive PTH levels in the circulation. PTH is the primary regulator of renal tubular calcium transport and one of the primary mechanisms regulating bone remodeling. PTH regulates intestinal calcium absorption secondarily through $1,25(OH)_2D_3$. PTH acts on the proximal nephron by decreasing phosphate reabsorption increasing the production of $1,25(OH)_2D_3$ (see Chapter 72). In the thick ascending limb and the distal nephron, PTH directly stimulates tubular calcium reabsorption by regulating both transcriptional and posttranslational modifications of transport proteins both at the entry step in the luminal membrane and the exit step, the calcium ATPase, on the basolateral membrane. Measurement of tubular calcium reabsorption in hypercalcemic patients is technically difficult, but perhaps of a diagnostic value.[194] Enhanced tubule reabsorption of calcium is responsible for normal urinary calcium excretion rates in some hyperparathyroid patients,[195,196] and for the observation that for any given level of serum calcium, urinary calcium excretion is lower in hyperparathyroidism than in other nonparathyroid types of hypercalcemia (i.e., sarcoidosis and multiple myeloma).

Although PTH stimulates tubule calcium reabsorption, urinary calcium excretion is greatly elevated in primary hyperparathyroidism due to the increase in filtered calcium load.[197] The elevation of circulating $1,25(OH)_2D_3$ contributes to the hypercalcemia and. as a result, adds to the hypercalciuria seen in patients with primary hyperparathyroidism.

A major component of hypercalcemia stems from PTH stimulation of bone remodeling. PTH affects both bone formation and bone resorption through its direct actions on marrow cells at varying stages of osteoblast differentiation. Stimulation of osteoprotegerin ligand in the osteoblast and marrow stromal cells stimulates osteoclast differentiation.

Renal stones observed in patients with primary hyperparathyroidism are usually composed of hydroxyapatite and CaOx. Stones often recur and become bilateral if the diagnosis is not made early in the course of the disease. Nephrocalcinosis may be the only renal manifestation of hyperparathyroidism. PTH increases the APRs for CaOx and brushite mainly due to hypercalciuria. Phosphate overexcretion may be observed, but it also may be absent because chronic phosphaturia tends to cause a negative phosphorus balance. The urine pH is not abnormally alkaline in primary hyperparathyroidism and the magnitude of the acidosis is negligible when glomerular function is normal. This suggests that altered acid-base metabolism in hyperparathyroidism does not contribute significantly to stone formation.[120] Pak and Holt[123] demonstrate an unexplained reduction of the FPR for CaOx and brushite in primary hyperparathyroidism (Fig. 20.11). The diagnosis of primary hyperparathyroidism rests with repeated determination of the serum calcium and iPTH levels. The assays for circulating PTH levels using double-antibody techniques enable the detection and measurement of the intact hormone.[198,199] More recently, the "intact" hormone assays have been recognized as also detecting PTH inhibitory peptides lacking the first few amino acids from the NH_2-terminus.[200] Assays that specifically recognize PTH and its first amino acid have been developed and are referred to as "bioactive" PTH assays.[200,201] In the diagnosis of primary hyperparathyroidism, detection of familial hypocalciuric hypercalcemia is critical. This inherited disease is produced by a mutation in the PTH gland calcium sensor such that PTH secretion is not adequately sensitive to the serum calcium levels. Affected patients may exhibit mild hypercalcemia and mild hyperparathyroidism but do not have complications related to the hyperparathyroid state. Thus, detection of patients with the familial disease is crucial so that they are not exposed to surgical therapy for primary hyperparathyroidism. The very low urinary clearance of calcium factored by creatinine excretion is currently the most sensitive means of separating primary hyperparathyroidism from familial hypocalciuric hypercalcemia.[202]

Surgical removal of adenomas or excess parathyroid tissue is indicated in patients with primary hyperparathyroidism who have sustained complications of the disease. Nephrolithiasis is one of the main complications of primary hyperparathyroidism, and any patient who has had a renal stone should undergo surgical correction of the disease state.

HYPERURICOSURIA

Hyperuricosuria can be a significant factor in the formation of calcium stones. Reduction in calcium stone formation in hyperuricosuric patients treated with allopurinol establishes hyperuricosuria as a contributory agent.[135,186,203] Hyperuricosuria is defined as a urinary excretion rate of uric acid that exceeds 700 mg per 24 hours in women or 750 mg per 24 hours in men.

Hyperuricosuria is not the cardinal risk for the development of uric acid stones. Instead, the overriding pathophysiologic process is the unduly acidic urine.[204] Epidemiologic data from converging sources have featured obesity, type II diabetes mellitus, and the metabolic syndrome as strong

associations with low pH.[205–208] With the obesity epidemic in the United States, the incidence of nephrolithiasis has grown in parallel.[209,210] Increased calcium excretion in the obese covaries with intake of animal protein and sodium. No relationship was found between body mass index (BMI) and urinary supersaturation of calcium oxalate. These results suggest that the augmented incidence of nephrolithiasis in the obese is secondary to uric acid stones.[205]

Either of two theories may explain the mechanism by which uric acid promotes calcium stone formation. The prevailing hypothesis states that through epitaxy,[211] the growth of one crystal on the substance of another, uric acid can serve as a seed for precipitation of a calcium salt. Studies have demonstrated that sodium urate accelerates precipitation of CaOx or calcium phosphate in vitro.[133,134] This has been attributed to physiologically relevant urinary concentrations of monosodium urate (0.1 mg per mL).[133] An alternative hypothesis states that urate can complex with and thus neutralizes endogenous urinary acid mucopolysaccharides, which normally retard the crystallization of CaOx.[212]

Urinary uric acid depends on both the renal filtered load of uric acid and its subsequent tubular transport. Hyperuricosuria is usually due to a high filtered load. The source of this uric acid is purines, which come from the dietary intake of purine-rich foods, endogenous synthesis of purines from nonpurine precursors, and salvage of purine bases from tissue catabolism.[213] Coe and colleagues[214] have studied the contribution of dietary purine overconsumption to hyperuricosuria in CaOx stone formers. They find that hyperuricosuric patients consume more purine than control subjects eating isocaloric diets. Overall, a very close correlation exists between urine uric acid and dietary purine intake. Coe and colleagues[214] also find that excessive purine intake does not fully account for the hyperuricosuria, as some patients excrete more urate than normal subjects consuming equivalent amounts of purine. A purine-rich diet is also rich in protein. Gutman[215] hypothesizes that, in some instances, a high-protein diet causes overproduction of uric acid, as the increase in urinary uric acid during a high-protein diet is only partially accounted for by the purine content. It is possible that abnormal tubular handling of urate resulting in hyperuricosuria and normal or low serum urate levels also occurs. Patients with such a defect and stones have been described.[213] Similarly, the Dalmatian dog, which has been well studied, can have hyperuricosuria due to enhanced tubular secretion of urate.[216] Although purine load is the most common mechanism for hyperuricosuria, other factors are contributory.

The treatment of hyperuricosuric calcium stone formers focuses on decreasing the hyperuricosuria. All of these patients should be administered a low-purine diet, which will decrease urinary uric acid excretion,[39,214,217] although in some patients the effectiveness in stone prevention is unproven. A low-purine diet involves avoiding meat, fish, and poultry. Hyperuricosuric calcium stone formers may also be treated with allopurinol, which blocks xanthine oxidase, the last enzymatic step in the purine degradative pathway before uric acid is produced. Very good evidence shows that allopurinol decreases stone formation in this group of patients,[135,186] including the results of a prospective controlled study by Ettinger and colleagues.[203] The usual starting dose of allopurinol is 300 mg per day. A follow-up measurement of 24-hour urinary uric acid excretion after institution of allopurinol will determine the adequacy of the dose. Potassium citrate may be an alternative to allopurinol in patients with mild hyperuricosuria (600 to 1,000 mg per day) in whom hypocitraturia is present, as citrate will inhibit CaOx precipitation.[218]

Uric acid transporters are localized to both the apical and basolateral membranes of the PCT epithelial cells and are coupled to sodium and organic ion transport. The inhibition of the apical membrane URAT1 transporter by probenecid, NSAIDs, salicylates, and losartan can worsen hyperuricosuria.[219]

RENAL TUBULAR ACIDOSIS

RTA is a known risk factor for both nephrocalcinosis and calcium stones. The patients may have severe disease, as in one study by Caruana and Buckalew[220] in which the patients had a mean of 51 ± 14 stone episodes. Only the hypokalemic form of distal RTA (type I RTA) is associated with kidney stones, but the cause of the RTA may be idiopathic or secondary to systemic diseases.[220] Most patients present with nephrolithiasis, a normal serum bicarbonate level but abnormal urinary acidification in response to an ammonium chloride challenge. These patients are believed to have incomplete RTA.[221] The complete form of RTA is often accompanied by nephrocalcinosis. An early description by Albright[222] was of a 13-year-old girl severely affected by RTA with renal calculi, but also with rickets combined with dwarfism. The calculi may be CaOx, calcium phosphate, or a mixture of both, but the presence of calcium phosphate makes RTA a likely etiology.[220,223,224] When both nephrocalcinosis and RTA appear in concert, it may be difficult to define the primary event because nephrocalcinosis can both cause RTA or occur as a result of it. For example, when medullary sponge kidney is associated with kidney stones, nephrocalcinosis, and RTA, it is unclear which is the primary problem.[225]

RTA results in hypercalciuria and hypocitraturia, both of which predispose to nephrolithiasis. Induction of metabolic acidosis with ammonium chloride results in hypercalciuria,[226] which is associated with a net systemic positive acid balance with a stable serum bicarbonate level, suggesting that the acid load is buffered. Because gastrointestinal absorption of calcium does not increase with metabolic acidosis, bone is the likely source of both the urinary calcium and the buffering capacity. This is most likely the link between distal RTA and rickets.[222] Furthermore, as expected, alkali therapy corrects the acidosis and the osteomalacia.[227] Citrate excretion, a known inhibitor of calcium precipitation, is low in patients with RTA due to increased reabsorption.[220]

Simpson[228] demonstrated in vitro inhibition of citrate oxidation by renal cortical slices incubated in medium with a high pH. Furthermore, hypokalemia, a frequent accompaniment of distal RTA, also results in hypocitraturia due to increased reabsorption.

Distal RTA often presents as a familial disease. Primary distal RTA is inherited as either an autosomal dominant or autosomal recessive trait (OMIM179800, 276300, and 602722). Autosomal recessive distal RTA often presents in infancy, whereas autosomal dominant distal RTA may not present until adolescence or young adulthood.[229] Patients with autosomal dominant and recessive distal RTA have been shown to harbor mutations in the gene encoding the chloride-bicarbonate exchanger AE1 (SLC4A1).[229–235] Mutations in ATP6N1B, encoding a kidney vacuolar proton pump protein 116kD subunit, cause recessive distal RTA with preserved hearing.[229,236] On the other hand, mutations in the gene encoding B1 subunit of the proton pump (ATP6V1B1) and (ATP6V0A4) cause renal tubular acidosis with sensory neurodeafness.[229,237,238] Mutations in the genes encoding carbonic anhydrase (CA) II,[239–241] kidney anion exchanger 1 (K AE1),[231,234–236,242] and subunits of the H+-ATPase[229,238,243] have also been identified in patients with distal RTA.[229] In the familial forms of RTA, renal deposition of calcium salts (nephrocalcinosis) and renal stone formation commonly occur. Replacement of alkali corrects the systemic metabolic defects and improves the nephrocalcinosis and nephrolithiasis. Such treatment does not affect the hearing loss of the patients with recessive distal RTA.

Pseudohypoaldosteronism type II is a genetic disorder that produces a clinical phenotype that includes hypertension, hyperkalemia, and metabolic acidosis. It has been linked to mutations in the gene encoding WNK-1 or -4 and is localized to the distal nephron.[244] A recent study demonstrated that in an affected family with a mutation in the WNK4 gene, there was marked hypercalciuria and osteopenia. Thiazide diuretics completely reversed both the urine and bone abnormalities.[244] Distal RTA is possible only if fasting urine pH is above 5.3. If so, an ammonium chloride challenge is necessary to prove the diagnosis. A urine pH above 5.3 after ammonium chloride–induced (100 mg per kg) acidification indicates the presence of RTA.

The treatment of RTA-associated nephrolithiasis consists of alkali therapy. Coe and Parks[245] and Wilansky and Schneiderman[246] document dramatic decreases in stone disease when patients with RTA are treated with alkali. This treatment may also result in an associated decrease in nephrocalcinosis. The dose of alkali is 1 mEq per kg (approximately 80 mEq per day) in four divided doses orally, but the dose should be adjusted to normalize 24-hour urinary citrate excretion. The alkali is usually given in the form of citrate, which both normalizes urinary citrate[247] and decreases urinary calcium.[227,246,247] Potassium citrate is preferable over sodium citrate, because potassium citrate causes a greater decrease in calcium excretion.[247] By replacing buffer capacity with oral alkali, potassium citrate causes calcium excretion to fall as less bone buffers are mobilized. It is likely that sodium citrate does not decrease hypercalciuria as much as the potassium salt, because the extra sodium may have a calciuric effect. Potassium citrate is contraindicated in severe renal insufficiency, and care should be taken to avoid hyperkalemia in the presence of mild or moderate renal insufficiency.

HYPEROXALURIA

Excessive urinary oxalate excretion (>40 to 45 mg per day) contributes to stone formation by increasing the saturation of urine with respect to CaOx. Signifying the importance of hyperoxaluria, increased urinary concentration of oxalate has a greater impact than does urinary calcium on the saturation of CaOx.[248] Hyperoxaluria is a relatively frequent finding in patients with kidney stones and was detected in 34% of 587 consecutive patients evaluated for recurrent nephrolithiasis at the Jewish Hospital of St. Louis Kidney Stone Center from 1987 to 1993. In 8% of these patients, hyperoxaluria was the only identifiable defect (Table 20.1).[249]

Oxalate is an end product of metabolism excreted primarily by the kidneys. Under normal conditions, oxalate is poorly absorbed from the gastrointestinal tract and only about 10% of urinary oxalate can be accounted for by dietary intake.[250] Urinary oxalate excretion varies among patients and is determined by intrinsic oxalate production and metabolism and gastrointestinal oxalate absorption.

Oxalate Production and Metabolism

Oxalate production occurs through a number of metabolic pathways, some of which remain incompletely characterized (Fig. 20.14). The oxidative metabolism of glyoxylate is a major contributor to oxalate production; in addition, ascorbic acid and tryptophan are converted directly to oxalate. Pyridoxine (vitamin B_6) is required as a cofactor for the transamination of glyoxylate to glycine. Moreover, deficiency of vitamin B_6

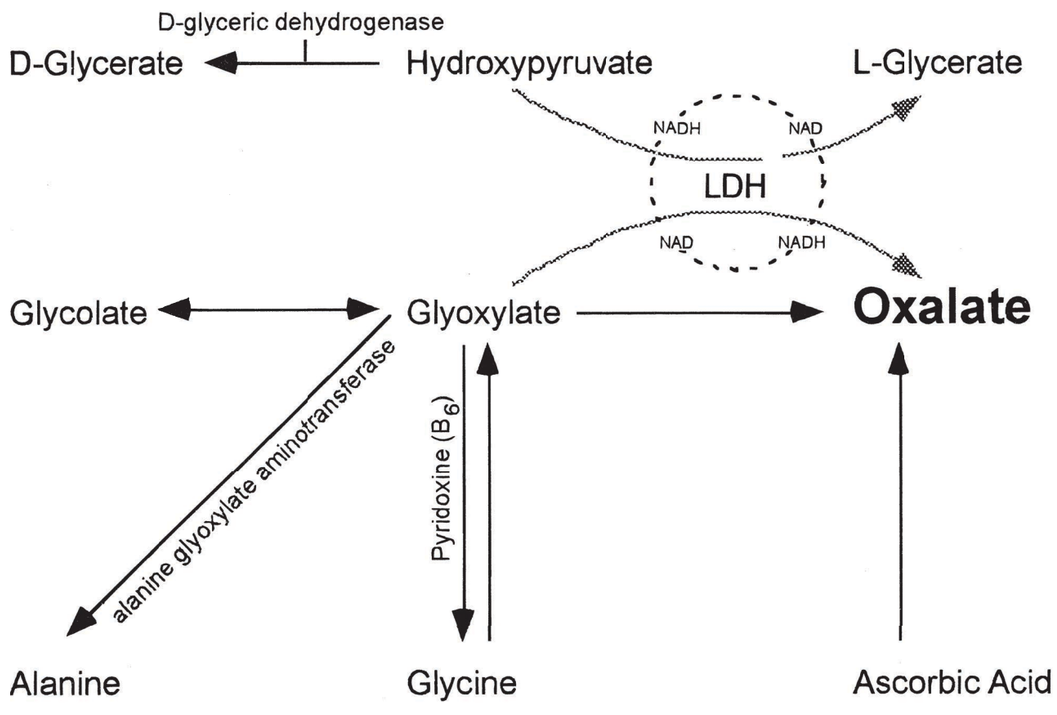

FIGURE 20.14 Metabolic pathways of oxalate production. Oxidative metabolism of glyoxylate is the major endogenous source of oxalate. Ascorbic acid (vitamin C) is also directly converted to oxalate.

may result in accumulation of glyoxylate, increased production of oxalate, and hyperoxaluria.[251] Disordered red cell oxalate exchange and defective oxalate transport may occur as an inherited trait and has been proposed to be a factor in hyperoxaluria within certain families.[252]

Increased availability of substrate for oxalate production can occur clinically in patients taking large doses of ascorbic acid (vitamin C) and in those who ingest ethylene glycol. Metabolism of ethylene glycol results in increased production of glycolate, increased glyoxylate, oxalate formation, and hyperoxaluria. Ascorbic acid, when taken in large doses (4 to 8 g per day), may lead to marked increases in urinary oxalate[253]; however, in some patients, hyperoxaluria may develop with doses as small as 500 mg per day.

Primary hyperoxaluria (PHO) is a rare metabolic disorder with autosomal recessive inheritance. PHO is induced by one of two enzymatic defects, both of which result in markedly enhanced conversion of glyoxylate to poorly soluble oxalate which is then excreted in the urine. Glyoxylate is normally metabolized in three ways. Glyoxylate is converted to glycine by the hepatic peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT). AGT is abnormal in type I PHO.[254] Pyridoxine (vitamin B_6) is a coenzyme of AGT. Glyoxylate is converted to glycolate by the cytosolic enzyme glyoxylate reductase/D-glycerate dehydrogenase (GRHPR). GRHPR is deficient in type II PHO.[255] Patients with this disorder excrete increased amounts of L-glyceric acid as well as oxalate. Glyoxylate is also converted to oxalate by lactate dehydrogenase.

A small number of patients fit the diagnostic criteria for having primary hyperoxaluria (PH), but when studied in vitro, they demonstrate full function of the two now enzymatic defects. This group constitutes about 7% of the 95 patients reported in the Mayo Clinics International Registry and such patients are classified as type III.[256–259]

Type I PHO is much more common than type II. The defect in AGT, which normally converts glyoxylate to glycine, results in an increase in the glyoxylate pool available for conversion to oxalate. The AGT gene maps to chromosome 2q36–37 and encodes for a 43 kDa protein. A number of different mutations have been identified in the coding region of the AGT gene in type I PHO. These defects lead to absent AGT protein, and/or absent AGT catalytic activity.[254] The GRHPR gene has been mapped to chromosome 9 and contains nine exons, spanning 9 kilobases.[260]

In most patients with type I PHO, glycolate excretion is increased. Practically all patients with type II disease have increased excretion of L-glyceric acid. In general, hyperoxaluria plus increased urinary excretion of glycolate or L-glyceric acid is strongly suggestive, but not absolutely diagnostic, of either type I or II PHO. In addition, hyperoxaluria alone, without increased glycolate or L-glyceric acid excretion, does not exclude the diagnosis of PHO.[48]

The presence of AGT deficiency can be confirmed by liver biopsy. Evaluation of the hepatic tissue includes quantification of enzymatic activity, an immunoblot to analyze the protein, and an immunoelectronic examination to demonstrate the virtual absence of AGT in the peroxisomes. AGT activity is less than 2% of normal in one-third of cases and ranges from 2% to 48% of normal in the remaining patients.[255] The relative ease in modern laboratory medicine with performing sequence analysis, and the delineation of the molecular basis of many of the mutations behind PHO type I and PHO type II, has led to the proposal of molecular diagnostic algorithms that may obviate the need for invasive biopsy procedures.[261,262]

Phenotypically, type I PHO is heterogeneous, ranging from severe infantile oxalosis and death to milder forms with renal stone disease in later life. Type II PHO has a less severe clinical course, but there may be a decline in renal function associated with the presence of nephrocalcinosis. Children with nephrolithiasis secondary to hyperoxaluria should have urinary glycerate measured to exclude type II PHO.[10]

Gastrointestinal Oxalate Absorption

Increased absorption of oxalate occurs with excess dietary oxalate intake, diminished binding of oxalate by dietary calcium and magnesium, or enhanced permeability of the colon to oxalate. Foods with relatively high oxalate content include spinach, beets, rhubarb, asparagus, cranberries, wheat germ, colas, teas, chocolates, nuts, beans, and various green leafy vegetables. Once ingested, oxalate forms insoluble salts with available calcium (and magnesium) in the intestinal lumen and is poorly absorbed; any free unbound oxalate is available for absorption distally in the colon.

Disorders characterized by absent or dysfunctional small bowel, as well as any causes of fat or bile acid malabsorption, can lead to hyperoxaluria.[263] Fat malabsorption allows luminal calcium and magnesium to saponify, leaving inadequate free calcium (and magnesium) to bind oxalate. Bile acid malabsorption causes increased permeability of the colon to oxalate.[264] Thus patients with inflammatory bowel disease, those who have had ileal bypass surgery or resection, and those with disorders associated with malabsorption develop hyperoxaluria due to an increase in unbound oxalate and enhanced colonic absorption.

Patients following a low-calcium diet and those taking sodium cellulose phosphate for the treatment of absorptive hypercalciuria may also manifest hyperoxaluria as a result of such therapy. Diminished oral calcium intake (with a low-calcium diet) and binding of calcium and magnesium in the gut by sodium cellulose phosphate allow increased amounts of unbound oxalate to be presented distally in the colon where it is readily absorbed.[265,266]

Therapy

Treatment of primary hyperoxaluria is difficult. Reducing sodium intake to 2 to 3 gm per day and limiting or avoiding high-oxalate foods is recommended. Supplemental citrate, magnesium, and phosphorus may help decrease urinary oxalate crystallization. Calcium intake should not be restricted

because this can increase intestinal calcium absorption. Approximately 10% to 40% of patients respond to pyridoxine supplementation, but vitamin C and D supplements should be avoided. Dialysis does not remove oxalate adequately. Hepatic transplantation remains the only therapy capable of correcting the underlying abnormalities in these patients.[267]

Treatment of patients with enteric hyperoxaluria should include a low-fat diet with restriction of oxalate-rich foods, appropriate therapy of any underlying gastrointestinal disorders, and avoidance of a low calcium intake. Some patients may benefit from the addition of oral calcium and magnesium supplements taken with meals, which act to bind dietary oxalate in the intestinal lumen, making it unavailable for absorption. Cholestyramine may also be of some benefit in those patients with significant fat and bile acid malabsorption as it acts as a nonabsorbable resin to bind fats and bile acids. Pyridoxine supplements may be effective in patients with moderate to severe hyperoxaluria.[268]

Patients with chronic diarrhea frequently have hypomagnesemia, hypokalemia, metabolic acidosis, hypocitraturia, and low urinary volumes. For these reasons, they also are prone to the development of uric acid stones. Therapy involves increased fluid intake, correction of hypokalemia and hypomagnesemia, and oral citrate supplements. Attention must also be paid to treatment of the underlying intestinal disorder and diarrhea.

Uric Acid Stones

Uric acid stones are radiolucent stones responsible for approximately 5% of kidney stones in the United States. Other populations may have a higher relative incidence of uric acid stones as a cause of urolithiasis. Due to the difficulty in visualizing these stones on an abdominal radiograph, an intravenous pyelogram is often necessary to make the diagnosis. Stones containing some calcium may be visualized on the radiograph, which may have important therapeutic implications.

Pathogenesis

Uric acid is the normal breakdown product of purine metabolism and is a natural urinary constituent. Precipitation of uric acid to form a stone can be demonstrated best by the relationships demonstrated in Figure 20.8.[42] The solubility limit of undissociated uric acid is 96 ± 2 mg per L at 37°C. In a given sample of urine, undissociated uric acid is dependent on the total uric acid concentration and urinary pH. The clinical laboratory routinely measures total uric acid excretion, but the undissociated uric acid can be inferred from both the total uric acid concentration and the urinary pH.

The total urinary uric acid concentration is a function of both uric acid excretion and urinary volume. Hyperuricosuria is defined as a urinary excretion rate of uric acid that exceeds 700 mg per 24 hours in women or 750 mg per 24 hours in men. When patients with gout were assessed for risk factors for stone disease, it was found that the incidence of stones increases with increasing degrees of hyperuricosuria.[269] A urinary excretion rate of uric acid of more than 1 g per 24 hours is associated with a 50% incidence of stones.[269] Urinary uric acid excretion depends on both the renal filtered load of uric acid and its subsequent tubular transport. Hyperuricosuria is usually due to a high filtered load. As stated earlier, the source of this uric acid is mostly purines,[213] usually from meat, fish, and poultry. A purine-rich diet is also rich in protein and, as Gutman[215] hypothesizes, in some instances a high-protein diet also causes overproduction of uric acid as the increase in urinary uric acid during a high-protein diet is only partially accounted for by the purine content. The overriding risk for uric acid nephrolithiasis is acidic urine.[270] Low urine pH leads to stone precipitation with relatively modest amounts of uric acid excretion whereas urine pH above 6.0 requires large amounts of urinary uric acid for lithogenesis. In two large cohorts of uric acid stone formers, there was a strong negative correlation between BMI and urine pH.[208] Each component of the metabolic syndrome appears to confer a risk for more acidic urine.[206] The dysfunction is impaired ammoniagenesis and, therefore, insufficient buffering of urinary protons. Low ammonium production leaves free protons to be buffered by titratable acids (i.e., phosphates and sulfates) thereby lowering urine pH. Reabsorption of filtered citrate is stimulated in the proximal tubule in states of acidosis/acid loads and hypocitraturia results.

The link between metabolic syndrome and impaired ammoniagenesis is thought to be mediated by insulin resistance.[207,271,272] Impaired ammoniagenesis is not the only pathogenic feature of patients with abnormally low urine pH. Increased net acid excretion and titratable acidity has been observed in uric acid stone formers even on fixed diets.[272–274] The biochemical origin of these findings is unclear, but may be related to post-prandial alkaline tide.[275,276]

Diseases Associated with Uric Acid Lithiasis

Among patients with uric acid lithiasis, a family history of gout or kidney stones often exists, predominantly in men. Most cases of uric acid lithiasis are idiopathic, but some disease associations should be considered when treating a patient with uric acid stones.

Primary Gout

Twenty-two percent of patients with primary gout have uric acid stones.[269] Eighty-three percent of these stones are pure uric acid, whereas 4% are mixed stones and the rest are calcium stones. Often, the uric acid stone disease antedates the diagnosis of gout. Conversely, the stones may only appear after administration of uricosuric drugs for gout. As discussed previously, uricosuric agents may treat the gout but cause uric acid stones.

Secondary Gout

Underlying diseases that cause gout confer a higher risk for kidney stones than does primary gout (42% versus 22%).

These diseases are associated with excess generation of uric acid due to nucleotide turnover (e.g., myeloproliferative disease, polycythemia due to congenital heart disease, and chronic granulocytic leukemia).

Chronic Diarrhea

Because intestinal fluid losses may result in urinary concentration of excreted urate, chronic diarrhea can result in uric acid stones. Likewise, fecal bicarbonate loss causes renal regeneration of bicarbonate with subsequent urinary acidification and more undissociated urate.

Familial Disease

Hereditary disorders associated with overproduction of uric acid include inborn errors of metabolism such as Lesch-Nyhan syndrome and type I glycogen storage disease. Lesch-Nyhan is caused by hypoxanthine-guanine phosphoribosyl transferase (HGPRT) deficiency and Kelley-Seegmiller syndrome is a partial enzymatic defect.[277] Type I glycogen storage disease is secondary to glucose-6-phosphatase deficiency. A single gene that is located distally on the long-arm of the X chromosomes codes for HGPRT. Purification of mutant HGPRT genes in patients with partial or complete deficiency of HGPRT has led to the identification of single amino acid substitutions in five known variants of HGPRT.[278] The lack of feedback control by the purine salvage pathway leads to massive overproduction of uric acid and may lead to repeated episodes of urolithiasis and renal failure. Several families with inherited predispositions to uric acid stones have been described,[279] although the underlying cause is unknown. A candidate gene for uric acid nephrolithiasis has been identified on 10g21-g22 from a local Sardinian population with known susceptibility to uric acid kidney stone disease.[280]

Treatment

The fact that urinary uric acid concentration and urine pH can influence urate precipitation underlies the following treatment modalities.

Existing stones can be dissolved with alkali (to keep the urine pH at 6.5 or above) and a large amount of fluids to keep the urine output at more than 2 L per day. Allopurinol should also be given to reduce hyperuricosuria. Uric acid stones that contain calcium may be refractory to dissolution. Furthermore, the presence of obstruction or refractory pain may necessitate more rapid therapies such as lithotripsy or invasive urologic techniques.

Stone prevention necessitates dietary counseling and alkali therapy. Dietary modification entails keeping urine output at more than 2 L per day and reducing dietary purine intake (i.e., meat, fish, and poultry). Furthermore, patients should also reduce their protein intake to decrease both urine uric acid and the acid load. Likewise, alcohol intake should be limited because it may increase uric acid production. Alkali treatment should be given, aiming for a urine pH of 6.5. Approximately 1 mEq per kg of potassium citrate given in three divided doses is effective.[215] Sodium bicarbonate may be a less desirable form of alkali because the sodium load may aggravate hypercalciuria, which may aggravate nephrolithiasis.

Allopurinol can decrease urinary uric acid excretion by blocking the conversion of xanthine to uric acid by xanthine oxidase. Allopurinol serves as a second-line agent used when patients either refuse treatment or diet and when alkali therapy fails. Furthermore, it may be of benefit when uric acid loads are large, such as prior to chemotherapy for large volume rapidly growing tumors, or if the urinary uric acid excretion rate is more than 1 g per 24 hours. In the treatment of hyperuricosuria due to chemotherapy, a brisk diuresis should still be maintained because xanthine, the precursor of urate, may accumulate and cause acute renal failure, as can other products of tumor lysis.

The potential role of Oxalobacter formigenes in the treatment of primary hyperoxaluria has shed some light on the role of the intestine in maintaining oxalate balance. The use of the intestine to alter oxalate balance when kidney excretion alone is inadequate is among the therapeutic options on the horizon for the treatment of primary hyperoxaluria. Studies in rats have shown that intestinal colonization with O. formigenes can induce colonic secretion of oxalate, in part by producing a favorable concentration gradient through oxalate degradation.[281] Hoppe et al.[282] reported efficacy of oral O. formigenes administration in humans with primary hyperoxaluria. The majority of subjects with normal kidney function showed a 22% to 92% reduction in urinary oxalate. Two of three dialysis patients had a significant reduction in plasma oxalate levels as well, and with improvement in clinical symptoms.[283]

STRUVITE STONES

Struvite stones are composed of magnesium ammonium phosphate with variable amounts of carbonate apatite. This compound forms only in the presence of chronic urinary tract infection with bacteria capable of producing urease. The action of bacterial urease on urine urea yields ammonia and carbon dioxide. These are further hydrolyzed to ammonium and carbonate, resulting in a urine pH above 7.2—ideal conditions for struvite formation. Most species of Proteus and Providencia produce urease. Klebsiella, Pseudomonas, Serratia, Haemophilus, Staphylococcus, and Corynebacterium species are all capable of urease production. Escherichia coli does not possess urease activity.

Struvite now accounts for less than 10% of all stones and occurs most often in women and patients with spinal cord injury, neurogenic bladder, urinary diversion, or chronic indwelling bladder catheters due to their increased frequency of chronic urinary tract infection. Clinical findings may include evidence of urinary tract infection, hematuria, flank pain, or obstructive uropathy. Rarely, infection stones may cause xanthogranulomatous pyelonephritis. Struvite, when calcified, presents radiographically with a

characteristic multilobulated shape and laminated appearance and may extend to involve all calyces forming so-called staghorn calculi.

Because struvite formation occurs in the region surrounding bacterial colonies, all struvite stone material is infected. In addition, antimicrobial agents are unable to adequately penetrate struvite and achieve bactericidal levels. Therefore, the only curative treatment is eradication of infection with antimicrobials and removal of all stone material. Combined percutaneous nephrostolithotomy and extracorporeal shock wave lithotripsy is recommended as the first line treatment choice.[284] In those patients who are not candidates for surgery, a conservative approach may be indicated. Chronic antibiotic therapy may limit stone growth and result in partial dissolution[285] in nonsurgical patients. Another potentially useful agent is acetohydroxamic acid (AHA), which is a potent inhibitor of bacterial urease and can limit stone growth.[286] Despite the potential usefulness of AHA, it has been associated with frequent side effects, including potentially carcinogenic effects,[287] particularly in patients with renal insufficiency. For these reasons, use of AHA should be limited to patients with normal renal function who are unable to undergo surgical intervention.

CYSTINE STONES

Cystinuria is an inherited abnormality in amino acid transport affecting the gastrointestinal and proximal renal tubular epithelia. As a result of abnormal renal tubular transport of cystine and the other dibasic amino acids (ornithine, lysine, and arginine), abnormally large amounts of the amino acids are excreted in the urine. Cystinuria accounts for 1% of renal calculi in adults, but up to 10% in children.[288] Even with medical management, long-term outcome is poor due to insufficient efficacy and low patient compliance. The solubility of cystine in urine is approximately 300 mg per L. When overexcretion leads to higher concentrations than the solubility limit, cystine stones tend to form. Biochemically, it has been known for decades that different phenotypes in cystinuric populations exist. The disease has been differentiated by amino acid excretion in obligate heterozygotes as type I (normal urinary amino acids), type II (high excretion of dibasic amino acids), or type III (modest elevation in dibasic amino acids). Given the identification of only two affected genes, a new classification scheme is now utilized.[289] Mutations in SLC3A1 and SLC7A9 are responsible for all three phenotypic subtypes of cystinuria. To date, all mutations of SLC3A1 produce the type I phenotype whereas mutations in SLC7A9 can cause all phenotypic subtypes.

In the new classification, cystinuria is defined as type A if mutations are found in both SLC3A1 alleles, type B if mutations are found in both SLC7A9 alleles, and putative type AB if one mutation is found in each gene.[289] Heterozygous type AB individuals have been identified,[290] but cystinuric patients from families of such individuals have two mutated alleles in the same gene in addition to a mutated allele in the other gene. Because type AB double heterozygous individuals do not produce stones, and two mutations in the same gene were found in patients from these families, digenic inheritance of cystinuria was ruled out.[291]

The amino acid transport system b(o)+AT is the main effector of cystine reabsorption in the kidney. This system was identified by expression cloning of renal cDNA (related to bo,+ amino acid transporter [rBAT]) that induces the $b^{o,+}$ system in Xenopus oocytes. In oocytes, the rBAT ($b^{o,+}$-like) system acts as a tertiary active transport mechanism. A cloned "light" subunit ($b^{o,+}$AT) coexpresses system $b^{o,+}$ activity in heterologous expression systems. Both proteins are expressed in brush-border membranes of proximal straight tubule and small intestinal mucosa. Whereas all renal $b^{o,+}$AT is disulfide bound with rBAT, there is an excess of rBAT covalently bound to an unidentified "light" subunit (X) in renal brush-border membranes. The rBAT/$b^{o,+}$AT heterodimer shows a gradient of expression along the proximal tubule: higher in the convoluted tubule and lower in the straight tubule. In contrast, the rBAT/X heterodimer has the opposite gradient of expression along the proximal tubule.

More than 50 unique SLC3A1 /2p16.3-p21 mutations have been identified in cystinuria patients. Missense mutations show loss of transport function in oocytes, apparently due to trafficking defects during transfer from endoplasmic reticulum to plasma membrane. Null SLC3A1 mutations are fully recessive in cystinuria heterozygotes. Mutational analysis and linkage studies have demonstrated genetic heterogeneity in cystinuria. The SLC3A1 gene is only associated with type I (fully recessive) cystinuria. A second locus, accounting for types II and III cystinuria (incomplete recessive forms), has been identified by linkage analysis at chromosome 19q13.1–13.2. The gene for the non-type I cystinuria (SLC7A9) codes for the "light" subunit ($b^{o,+}$AT) of rBAT, where 37 unique cystinuria-specific mutations have been identified. This strongly supports the notion that rBAT/$b^{o,1}$AT heterodimer (system $b^{o,+}$) is the main apical reabsorption system for cystine.

In non-type I cystinuria, the urinary hyperexcretion of cystine and dibasic amino acids among heterozygous carriers of SLC7A9 mutations correlates well with the severity of defective amino acid transport in vitro. In some cases, mild SLC7A9 mutations account for heterozygous type I cystinuria. Patients with the mixed form of cystinuria (type I/III) excrete slightly lower levels of cystine and appear to have a lower risk of nephrolithiasis in the first decade. An SLC3A1 mutation is rarely identified on the fully recessive allele in these patients.[292]

While the molecular physiology of the renal cystine transport mechanism is being worked out, additional clarification is needed. In particular, we need to understand the physiologic role of the SLC3A1 gene, why mutations in the "heavy" subunit (rBAT) of system $b^{o,+}$ produce a silent phenotype in carriers whereas mutations in the "light" subunit ($b^{o,+}$AT) produce a dominant negative effect, and which genes modulate urolithiasis in patients with cystinuria.

Additionally, three similar, but distinct, syndromes are associated with cystinuria. The 21p21 deletion syndrome, hypotonia-cystinuria syndrome (HCS), and atypical HCS are associated with deletions of/and genes contiguous to SLC3A1.[293–298]

Pathobiology

Although a kidney biopsy is not usually performed, examination of renal tissue obtained during stone removal procedures reveals associated parenchymal abnormalities that may partly explain the loss of kidney function associated with this disorder.[299]

The ducts of Bellini are plugged with cystine crystals, and apatite crystals can be seen in the inner medullary collecting ducts and in the thin loops of Henle. Focal areas of dilatation with varying degrees of surrounding interstitial fibrosis are present. These findings are in contrast to the histopathology of routine calcium oxalate formers (interstitial deposits of apatite without intratubular crystals). The crystallization of cystine in terminal ducts of Bellini may cause local obstruction and tissue injury contribution to loss of kidney function.

Pathogenesis

Cystine overexcretion raises urinary cystine concentration above the limits of solubility for this relatively insoluble amino acid. Characteristic hexagonal crystals are identified in cystinuric patients particularly in the first voided morning urine, which is concentrated and usually acidic.

All patients with an episode of nephrolithiasis before the age of 30 or a strong family history of recurrent nephrolithiasis should be screened for cystinuria. A rapid qualitative screening test with sodium cyanide-nitroprusside is used for diagnosis when the pathognomonic crystals are not visualized.

Normal adults excrete less than 30 mg of cystine in 24 hours (19 mg per g of creatinine),[300] whereas homozygous cystine stone formers usually excrete more than 350 mg of cystine per day (250 mg per g of creatinine).

Heterozygotes and patients with the Fanconi syndrome generally excrete less than 250 mg per day and usually do not form stones. Given that proximal tubular transport requires maturation, it is frequently difficult to diagnosis cystinuria prior to the age of 1 year.[301]

Treatment

Therapy is designed to reduce the excretion and increase the solubility of cystine. Methionine is the precursor of cystine and dietary restriction of methionine reduces urinary excretion of cystine.[302] However, methionine is an essential amino acid and dietary restriction is, therefore, not a practical mode of treatment. Lowering urinary cystine concentration by increasing urinary volume reduces the likelihood of precipitation and thus provides the basis for clinical treatment. An intake of more than 4 L per day may be required.

The pH of urine alters the level of cystine saturation, but until urinary pH is 7.0 or greater, the effect of pH on solubility is minimal.[303] Dent et al. showed that the solubility of cystine in urine is approximately 250 mg per L up to a pH level of 7.0, but increases to 500 mg per L or more with a pH level of 7.5 or greater. This degree of urinary alkalinization may require up to 3 to 4 mEq/kg/day of potassium citrate or potassium bicarbonate taken in three to four divided doses.[21]

If urinary alkalinization and high fluid intake are ineffective, then a cystine binding drug is added to the regimen.[304] D-penicillamine (DP) and α-mercapto-proprionyl-glycine (MPG) are equally effective in clearing the disulfide bond of cystine into cysteine, which is 50 times more soluble.[305,306] Side effects occur in 20% to 50% of patients and limit treatment success. Typical side effects for both drugs include rash, arthralgia, leukopenia, thrombocytopenia, myositis, and proteinuria (due to membranous nephropathy).

Captopril, a first generation ACE inhibitor, contains free sulfhydryl groups. Captopril cysteine disulfides are 200 times more soluble than cystine alone. Although captopril can reduce cystine excretion by more than 50%, hypotension often limits tolerance.

Medical therapy is beneficial with adequate patient adherence, but there is a high rate of continued stone formation and most patients require multiple urologic interventions. Cystine stone formers have significantly higher procedure rates than other stone formers.[307] Patients may form stones of mixed composition mandating a broader investigation during follow-up.[308]

The response to therapy is monitored both biochemically and radiologically. The preferred imaging test is spine CT. Urinary cystine concentration is measured serially to estimate whether the amount excreted can be held in solution at the urine volume and pH achieved by the patient. The measurement of urinary cystine is imprecise in the presence of thiol drugs. Solid phase assays overcome this barrier and should be used to monitor patients' response to interventions.[309,310]

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