Kidney stone disease

Fredric L. Coe,[1] Andrew Evan,[2] and Elaine Worcester[1]

[1]Renal Section, University of Chicago, Chicago, Illinois, USA. [2]Department of Anatomy, Indiana University, Indianapolis, Indiana, USA.

About 5% of American women and 12% of men will develop a kidney stone at some time in their life, and prevalence has been rising in both sexes. Approximately 80% of stones are composed of calcium oxalate (CaOx) and calcium phosphate (CaP); 10% of struvite (magnesium ammonium phosphate produced during infection with bacteria that possess the enzyme urease), 9% of uric acid (UA); and the remaining 1% are composed of cystine or ammonium acid urate or are diagnosed as drug-related stones. Stones ultimately arise because of an unwanted phase change of these substances from liquid to solid state. Here we focus on the mechanisms of pathogenesis involved in CaOx, CaP, UA, and cystine stone formation, including recent developments in our understanding of related changes in human kidney tissue and of underlying genetic causes, in addition to current therapeutics.

Clinical aspects of stone disease

Stone passage

Nonobstructing stones produce no symptoms or signs apart from hematuria. Stone passage produces renal colic that usually begins as a mild discomfort and progresses to a plateau of extreme severity over 30–60 minutes. If the stone obstructs the uretero-pelvic junction, pain localizes to the flank; as the stone moves down the ureter, pain moves downward and anterior. Stones at the uretero-vesicular junction often cause dysuria and urinary frequency mistaken for infection. Colic is independent of body position or motion and is described as a boring or burning sensation associated with nausea and vomiting. Stones less than 5 mm in diameter have a high chance of passage; those of 5–7 mm have a modest chance (50%) of passage, and those greater than 7 mm almost always require urological intervention. Ideally, stone analysis is performed by infrared spectroscopy or x-ray diffraction. Renal stone burden is best gauged using CT radiographs taken with 5-mm cuts, without infusion of contrast agents. The radiographic appearance and density of stones as measured by CT is a guide to their composition (1).

Urological management of stones

Extracorporeal shock wave lithotripsy (ESWL), in which sound waves are used to break the stone into small pieces that can more easily pass into the bladder, is widely used and valuable for small stones (2). Modern instruments facilitate passage of endoscopes up the ureter into the kidney pelvis and permit local stone disruption with high-powered lasers (3). Percutaneous stone removal via instruments introduced into the kidney through a small flank incision permits disruption and removal of even very large stones (4).

Renal function of stone forming people is reduced

Within the National Health and Nutrition Examination Survey III data set, subjects with a BMI greater than or equal to 27 who had kidney stones had lower estimated glomerular filtration rates than non–stone formers (non-SFs) matched for age, sex, race, and BMI (5). SFs also have higher blood pressures than non-SFs (6). Obstruction of the urinary tract, sequelae of urological interventions, and the processes that cause stone formation may all injure renal tissue, reduce renal function, and raise blood pressure.

Determinants of phase change

Supersaturation

Stones result from a phase change in which dissolved salts condense into solids, and all phase changes are driven by supersaturation (SS), which is usually approximated for such salts by the ratio of their concentration in the urine to their solubilities (7) and calculated by computer algorithms. At SS values less than 1, crystals of a substance will dissolve; at SS values greater than 1, crystals can form and grow. As expected, the composition of stones that patients form correlates with SS values from the urine they produce (8). Although increasing urine volume is an obvious way to lower SS, patients examined in a variety of practice settings have been found to be able to increase their urine volume by an average of only 0.3 l/d (9). Moreover, for unclear reasons, sodium intake and urinary calcium excretion has been found to increase with increased urine volume, partly offsetting the fall in SS. Along with urine volume, urine calcium and oxalate concentrations are the main determinants of calcium oxalate (CaOx) SS; urine calcium concentration and pH are the main determinants of calcium phosphate (CaP) SS; and urinary pH is the main determinant of uric acid (UA) SS.

The upper limit of metastability

Urine with SS greater than 1 is referred to as metastable because the excess dissolved material, being present at a concentration above its solubility, must eventually precipitate. One can add oxalate or calcium to urine and note the SS needed to produce a solid phase of CaOx or CaP. That value, called the upper limit of metastability (ULM), varies with urine SS (10) and is lower among patients with stones than in matched control subjects (11). This suggests that mechanisms that normally protect against solid-phase development are less effective in patients with stones than healthy individuals. Urine contains molecules that retard the for-
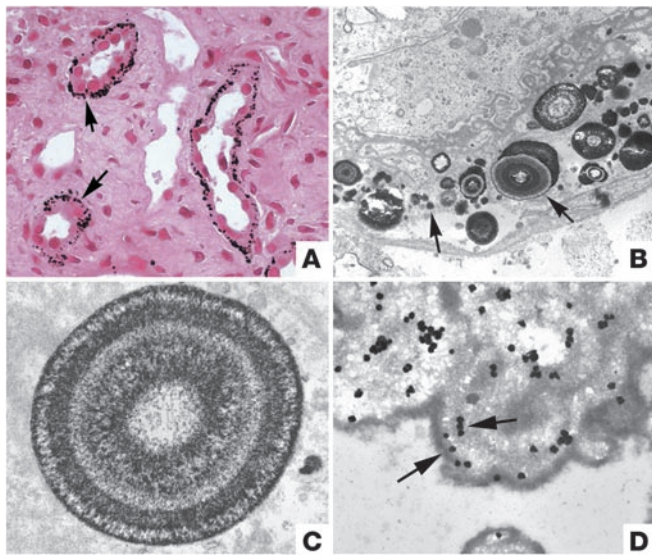
Figure 1
Initial sites of crystal deposition and localization of osteopontin. The initial sites of calcium deposits in the deep papillary tissue of an idiopathic CaOx SF are shown in light (**A**) and transmission electron microscopic (TEM) images (**B–D**). In **A**, Yasue-stained (the Yasue stain detects calcium) biopsy tissue reveals sites of crystal deposits (arrows) within the BM of thin Henle loops and not in nearby inner medullary CDs. By TEM (**B** and **C**), the crystal deposits appear as single spheres with a multi-laminated (6–7 layers) internal morphology consisting of a central light region of crystalline material surrounded by a dark layer of matrix material (arrows). Note that the cells lining this Henle loop appear morphologically normal. Osteopontin (**D**) localizes on either side of the apatite layers, sometimes forming with a clear "tram track"–like appearance (arrows). Magnification: ×1,800 (**A**); ×20,000 (**B**); ×35,000 (**C**); ×37,000 (**D**). **A** and **B** reprinted from ref. 19. **C** and **D** reprinted with permission from *Kidney International* (21).

metabolism, and others present with hyperoxaluria because of bowel disease (enteric hyperoxaluria) and genetic disorders of oxalate metabolism (primary hyperoxaluria [PH]). We discuss these groups separately below.

Pathogenesis of idiopathic CaOx stones
Stones form on interstitial apatite plaque. CaOx stones form on the surfaces of the renal papillae over collections of interstitial suburothelial CaP particles (19) named Randall plaque. The number of CaOx stones formed, adjusted for duration of stone formation, varies directly with plaque surface coverage (20), as would be expected if plaque were a surface that promotes CaOx overgrowth.

Plaque begins in the basement membranes of the thin Henle loops. Basement membrane (BM) plaque comprises a myriad of particles in which crystal and organic layers alternate (Figure 1, A and B); the outer surface of all particles is the organic layer (Figure 1, B and C). The crystal in plaque is always biological apatite, the mineral phase found in bone. Outside the BM, in the interstitium,

mation of solid CaOx and CaP phases (12), and it is precisely this retardation that can permit the transient existence of SS. The measurement of ULM is not currently used in clinical practice.

Modulators of the ULM, crystal growth, and aggregation
Urine citrate reduces SS by binding calcium and inhibits nucleation and growth of calcium crystals (13); it is measured clinically, and low levels are treated as a cause of stones. Osteopontin (14), prothrombin F1 fragment (15), the inter-α-trypsin inhibitor molecule (16), calgranulin (17), Tamm Horsfall glycoprotein (18), as well as albumin, RNA and DNA fragments, and glycosaminoglycans have all been identified as urine inhibitors of CaOx and CaP crystallization (12). They have in common long stretches of polyanion chains that can bond with surface calcium atoms and prevent crystal growth. Such blockade prevents measurable phase changes and raises the ULM because newly formed crystals cannot grow beyond extremely minute dimensions. These molecules also prevent clumping of small particles into larger ones (aggregation). Because we do not know which, if any, of these molecules contribute to stone pathogenesis, they are presently of great research interest.
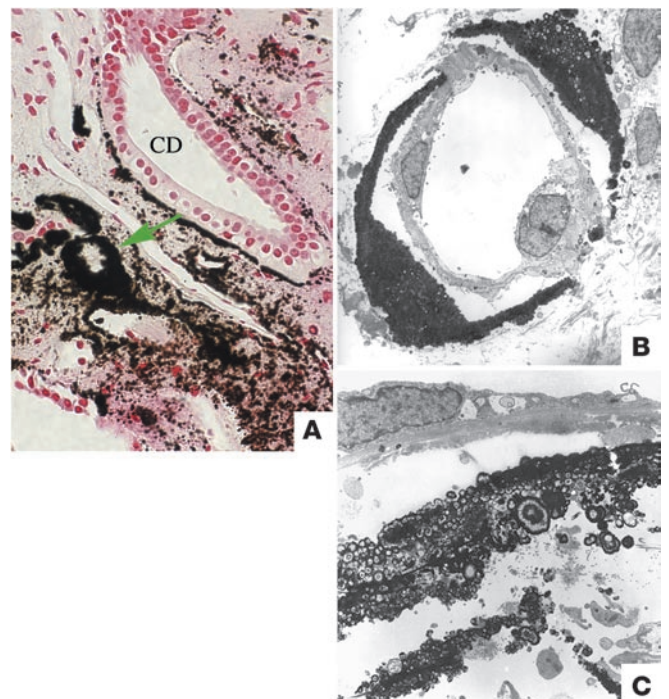
CaOx stones
The vast majority of CaOx SFs suffer from no systemic disease and as such are described as idiopathic CaOx SFs. Some have primary hyperparathyroidism or other disorders of calcium

Figure 2
Accumulation of interstitial crystal deposits as seen in light and TEM images in a papillary biopsy from an idiopathic CaOx SF. (**A**) Light microscopy reveals extensive accumulation of crystalline deposits (green arrow) shown around the Henle loops and nearby vascular bundles and inner medullary CDs. This progressive accumulation of crystalline material in the interstitium results in the formation of incomplete to complete cuffs of plaque. (**B**) TEM reveals a normal thin Henle loop surrounded by a complete cuff of interstitial plaque. (**C**) TEM shows a site of plaque located in the interstitial space, away from a tubular wall. Note that single crystal deposits appear embedded in a sea of matrix. Magnification: ×1,500 (**A**); ×13,000 (**B**); ×13,000 (**C**). **A** reprinted from ref. 19. **B** reprinted with permission from *Urological Research* (123). **C** reprinted with permission from *Kidney International* (21).

Table 1

Monogenic hypercalciuric stone-forming diseases

Disease	OMIM	Inheritance	Locus/gene	Gene product	Functions	Location	Phenotype Renal/urine	Other
Dent disease complex (37–42)	300009, 310468, 300008	X-linked	Xp11.22/ *CLCN5*	ClC-5	Endosomal chloride channel	PT, TAL, CD (type A intercalated cells)	Hypercalciuria, phosphaturia, LMW proteinuria, CRF	Rickets (variable)
Bartter syndrome type I (49)	601678, 600839	Autosomal recessive	15q15–21/ *SLC12A1*	NKCC2	Na-K-2Cl cotransporter (Na absorption)	TAL	Hypokalemic alkalosis, Na wasting, hypercalciuria	Elevated PGE level
Bartter syndrome type II (49)	241200, 600359	Autosomal recessive	11q24–25/ *KCNJ1*	ROMK	K channel (K supply for NKCC2)	TAL, CD	Hypokalemic alkalosis, Na wasting, hypercalciuria	Elevated PGE level
Bartter syndrome type III (49)	607364, 602023	Autosomal recessive	1p36/ *CLCNKB*	ClC-Kb	Basolateral Cl⁻ channel (Cl⁻ absorption Bartter syndrome	TAL, DCT, CD	Hypokalemic alkalosis, hypercalciuria	
Bartter syndrome type V (59–60)	601199	Autosomal dominant	3q13.3–q21/ *CASR* (severe gain of function)	CaSR	CaSR)	TAL, DCT, PT, CD	Hypokalemic alkalosis, hypomagnesemia, hypercalciuria, CRF	Hypocalcemia, tetany, seizures
Autosomal dominant hypocalcemic hypercalciuria (55–58)	146200, 601199	Autosomal dominant	3q13.3–q21/ *CASR* (gain of function)	CaSR	CaSR	TAL, DCT, PT, CD	Hypercalciuria, CRF	Hypocalcemia, hyperphosphatemia, low PTH level, possible tetany
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (61–63)	248250, 603959	Autosomal recessive	3q27/ *PCLN1* (*CLDN16*)	Paracellin-1 (claudin 16)	Tight junction protein	TAL, DCT	Hypercalciuria, hypermagnesuria, polyuria, dRTA, CRF	Low serum magnesium, tetany, seizures

All of the diseases listed cause nephrocalcinosis; stones occur in Dent disease, Bartter syndrome types III and V, and autosomal dominant hypocalcemic hypercalciuria and familial hypomagnesemia. CRF, chronic renal failure; LMW, low molecular weight; NKCC2, sodium-potassium–2 chloride cotransporter; PGE, prostaglandin E; ROMK, renal outer medullary potassium channel. Corresponding references are shown in parentheses.

plaque particles coalesce so that islands of crystal float in an organic sea (Figure 2). It is this coalescent material that extends to the suburothelial region and over which CaOx stones grow. The identity of the organic molecules surrounding apatite in plaque are unknown except for osteopontin, which coats the surface of apatite and positions itself (Figure 1D) precisely at the apatite organic layer interface (21). We envision that plaque forms in the thin limb BM and extends to the suburothelial space and that CaOx stones then form over the organic coating of apatite particles.

Crystals are not found in tubule lumens of the deep or outer medulla or cortex. The lining cells of the tubules are normal in appearance (Figure 2) even when deposits of plaque fill the BM; no lumen crystals have to date been found in tissue from idiopathic CaOx SFs. For this reason, we do not review here the large literature on attachment of CaOx and CaP crystals to renal epithelial cells in culture (22), which does not appear to be relevant to human idiopathic CaOx stone disease. Interstitial cells also show no evident pathology.

Mechanisms of plaque and stone formation. The driving force for CaOx overgrowth on plaque is urine CaOx SS. But the forces that create the plaque are not so clear. The fraction of papillary surface covered by plaque in idiopathic CaOx SFs correlates directly with urine calcium level and inversely with urine volume and pH (23). Given that the initial formation is in the thin Henle loops BM, effi-

cient water extraction in the collecting duct (CD) combined with high deliveries of calcium as a result of idiopathic hypercalciuria (IH) may increase tubule and interstitial calcium concentrations and by as-yet-undetermined mechanisms stimulate apatite deposition in the thin-limb BM.

Clinical implications. High fluid intake may be beneficial not only to prevent CaOx overgrowth, but also to reduce plaque formation itself. Thiazide diuretics, which lower urine calcium, may reduce plaque as well as urine CaOx SS, whereas measures that reduce urine oxalate concentration are important in prevention of overgrowth but have no apparent role with regard to plaque formation. As new technologies permit visualization and quantification of plaque in the kidneys of patients, effects of treatments on plaque may become a matter for prospective trials.

Idiopathic hypercalciuria

Urinary calcium excretion as measured on random diets varies in humans (24), and excretion rates among idiopathic CaOx SFs cluster at the high end of this distribution (25). Lowering urinary calcium levels prevents stone recurrence (12). Conventional upper limits of 250 mg/d (for women) and 300 mg/d (for men) are near the 95th percentiles for our published data sets (26) and are commonly used as diagnostic cutpoints. We believe SFs in the 70th percentiles (170 mg/d for women and 210 mg/d for men)
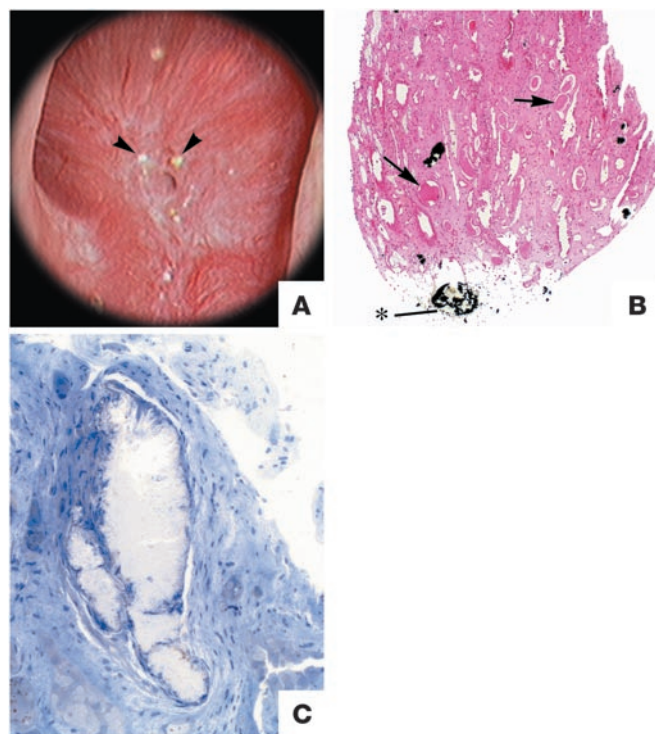
Figure 3
Endoscopic and histological images from a SF following small bowel bypass. The papillary surface (**A**) shows small, round nodular structures (arrowheads) near the openings of the Bellini ducts; distinct sites of Randall plaque material are not found. (**B**) Biopsy through a region that contained nodules reveals crystal deposition in the lumens of a few CDs as far down as the Bellini ducts (indicate by the asterisk). Note dilated CDs (arrows) with cast material in regions of fibrosis around crystal deposit–filled CDs. (**C**) A single CD is shown to be completely filled with crystals with injured lining cells. Magnification: ×100 (**B**); ×550 (**C**). Reprinted with permission from ref. 19.

may well benefit from lower calcium excretion rates. Data linking calcium excretion to stone risk (27) are supportive of the idea that it is a graded risk factor.

Diagnosis of IH requires exclusion of hypercalcemia, vitamin D excess, hyperthyroidism, malignant neoplasm, and sarcoidosis. Pathogenesis and systemic manifestations of IH are well described in standard textbooks (12). About 50% of first-degree relatives of people whose urinary calcium excretion level exceeds the 95th percentile also surpass these limits, establishing the familial and therefore inherited nature of IH. We emphasize here the most salient features and new research concerning this condition.

On average, patients with IH have higher than normal serum levels of $1,25(OH)_2D_3$ (calcitriol) and increased intestinal absorption of calcium (28), and vitamin D receptor expression on circulating blood monocytes may also be increased. High intestinal calcium absorption can raise the load of filtered calcium presented to the renal tubules. The reabsorption of filtered calcium by the renal tubules may also be reduced. Either mechanism can increase urinary calcium level, which can be further increased by glucose or sucrose loads (29), high sodium intake (30), and a high-protein diet (31). Although dietary calcium is the main contributor to high urinary calcium levels in IH, low-calcium diets are not widely used clinically because they are not of proven effectiveness in stone prevention (32) and may predispose to reduced bone mineral content (33). Thiazide diuretics lower urinary calcium levels and promote positive bone mineral balances (34), and multiple prospective trials have documented their effectiveness for preventing calcium stones (see "Treatment trials: stone recurrence outcomes").

*Monogenic disorders that cause hypercalciuria and stones*
These rare disorders illustrate links among genetic variation, urinary calcium excretion, and calcium stones. Two recent reviews (35, 36) have detailed all known mutations that can cause hypercalciuria in humans or animals; here we discuss only those that cause stones in humans. We have excluded mere gene associations with the presence of stones, with the single exception of a cytosolic soluble adenylyl cyclase.

Dent disease. This X-linked hypercalciuric stone-forming disorder (Table 1) is due to mutations in the gene that codes for the voltage-gated endosomal chloride channel 5 (CLCN5) (37–39). Resultant low-molecular-weight proteinuria includes parathyroid hormone (PTH) loss (40, 41). As in IH, hypercalciuria results from increased serum calcitriol levels (42), and thiazide treatment lowers urine calcium concentrations (43). Because some patients with Dent disease lack *CLCN5* (44) mutations, other genetic defects may also contribute to this disease. *CLCN5* mutations are rarely found in IH patients (45). Gene KO studies in mice suggest that defective proximal tubule (PT) endocytosis increases PT lumen PTH levels, which activates 1α-hydroxylase and raises serum calcitriol levels, causing hypercalciuria (46, 47). In one study of *Clcn5*-KO mice (48), urinary $25OHD_3$ levels were high, serum levels of $25OHD_3$ and calcitriol were

Table 2
Primary hyperoxaluria

Disease	OMIM	Locus/gene	Gene product	Functions	Location	Phenotype Renal/Urine
PH type I (77)	259900, 604285	2q36–q37/ *AGXT*	Alanine glyoxylate aminotransferase	Conversion of glyoxylate to glycine; excess glyoxylate oxidized to oxalate	Liver (enzyme may be absent, mistargeted, or nonfunctional)	Hyperoxaluria, CRF; increased urine glycolate excretion
PH type II (77)	260000, 604296	9cen/ *GRHPR*	Glyoxylate reductase/ hydroxypyruvate reductase	Conversion of glyoxylate to glycolate	Liver	Hyperoxaluria, CRF; increased urine L-glyceric acid excretion

Both diseases are autosomal recessive and cause stones and systemic oxalosis. Corresponding references are shown in parentheses.
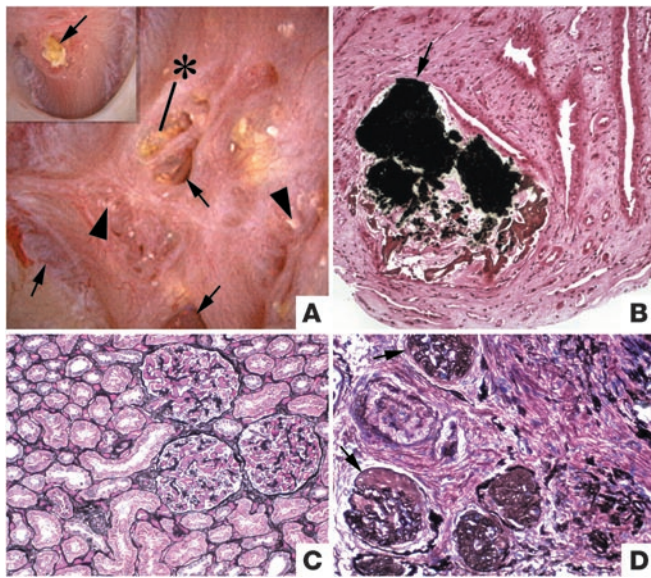
Figure 4
Endoscopic and histological images from a brushite SF. (**A**) Papilla from a brushite SF that was video recorded at the time of stone removal shows depressions (arrows) near the papillary tip and flattening, a phenomenon not seen in CaOx SFs. Like CaOx SFs, the papilla possessed sites of Randall plaque (arrowheads), though lesser in number. In addition, papillae possess sites of a yellowish crystalline deposit at the openings of Bellini ducts (indicated by the asterisk). These ducts were occasionally enlarged and filled with a crystalline material that protruded from the duct (inset, arrow) that might serve as a site for stone attachment. (**B**) Deposits in the lumens of an individual inner medullary CD (arrow) and in an occasional nearby Henle loop are shown. The crystal deposits greatly expanded the lumen of these tubules, and cell injury to the degree of complete cell necrosis was found. A cuff of interstitial inflammation and fibrosis accompanied sites of intraluminal disposition. (**C** and **D**) A cortical sample from a normal human kidney (**C**) compared with that of a brushite SF (**D**) that reveals advanced glomerulosclerosis (arrows), moderate tubular atrophy, and interstitial fibrosis — changes not seen in CaOx SFs. Magnification: ×1,400 (**B**); ×1,000 (**C** and **D**). **A** and **B** reprinted with permission from *Kidney International* (92). **C** and **D** reprinted with permission from *Urological Research* (123).

low, and urine calcium concentration was normal; urinary loss of 25OHD$_3$ was thought to limit the increase in calcitriol from high lumen PTH.

Bartter syndromes. Of the 5 major genetic variants associated with Bartter syndrome (49), cortical and medullary renal calcifications (50) are found in patients with Bartter syndrome types I and II (Table 1), which arise from transport defects that reduce thick ascending limb (TAL) NaCl and calcium reabsorption, creating hypercalciuria. Defects in a TAL basolateral membrane chloride channel, *CLCNKB*, produce only variable hypercalciuria and uncommon crystal deposits (type III). Defects in a chloride channel subunit known as Barttin, encoded by *BSND,* produce Bartter syndrome type IV, in which deafness, but neither stones nor nephrocalcinosis, are observed. Loop diuretic treatment of premature babies, a pharmacological analog of the reduced TAL reabsorption seen in Bartter syndromes, can cause renal calcifications, 50% of which regress over time (51).

Abnormalities of the calcium-sensing receptor. The calcium-sensing receptor (CaSR) regulates PTH secretion in response to blood calcium levels (52) and is also present on the apical membranes of PT and medullary CD principal cells and the basal membranes of TAL and distal convoluted tubule (DCT) cells, where it regulates transport

functions. Gain-of-function mutations of the CaSR reduce serum PTH levels and TAL and DCT calcium reabsorption (53, 54), causing variably symptomatic hypocalcemia (55–57) with low serum PTH levels. Stones usually result from calcium and vitamin D administered in order to raise serum calcium levels. One particular mutation causes multigland primary hyperparathyroidism (58). A severe gain-of-function defect of the CaSR causes Bartter syndrome type V (Table 1), and its clinical symptoms are ascribed to CaSR activation–mediated downregulation of a renal outer medullary potassium channel (ROMK) that is mutated in type II Bartter syndrome (59, 60).

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis. Paracellin-1, a member of the claudin family (61, 62) found only in the TAL and DCT, is essential for normal, voltage-driven paracellular magnesium reabsorption in the TAL. Patients with paracellin-1 defects develop hypomagnesemia, hypercalciuria, polyuria, nephrocalcinosis, stones, distal renal tubular acidosis (dRTA), and renal failure (Table 1). A striking incidence of hypercalciuria and stones has been found in heterozygous family members (63).

Soluble adenylyl cyclase. Among selected IH patients with reduced vertebral bone mineral density, Reed et al. (64) identified linkage to a locus on chromosome 1 (1q23.3–q24). In a specific gene (*human*

Table 3
Distal renal tubular acidosis

Disease	OMIM	Inheritance	Locus/gene	Gene product	Functions	Location	Phenotype
Autosomal dominant dRTA (96–98)	179800, 109270	Autosomal dominant	17q21–q22/ *SLC4A1*	AE1	Chloride-bicarbonate exchanger	CD (type A intercalated cells)	Osteomalacia, low K level
Autosomal recessive dRTA with hearing loss (99)	267300, 192132	Autosomal recessive	2p13/ *ATP6V1B1*	B1 subunit of vacuolar H$^+$-ATPase	Proton secretion	CD (type A intercalated cells); cochlea	Sensorineural hearing loss, growth failure, rickets, low K level
Autosomal recessive dRTA (100)	602722, 605239	Autosomal recessive	7q33–34/ *ATP6V0A4*	a4 subunit of vacuolar H$^+$-ATPase	Proton secretion	CD (type A intercalated cells), PT, DCT	Growth failure, rickets, low K level

All 3 diseases cause metabolic acidosis and hypercalciuria, stones, and nephrocalcinosis. Corresponding references are shown in parentheses.

Table 4
Known gene defects in cysteinuria

Disease	OMIM	Inheritance	Locus/gene	Gene product	Functions	Location	Phenotype
Cystinuria type A (type I) (110, 111)	104614	Autosomal recessive	2p16.3/ SLC3A1	rBAT	Heavy unit of heteromeric aa transporter	PT S3	Heterozygotes: normal urine cystine excretion
Cystinuria type B (usually type non-I) (110, 111)	604144	Incompletely autosomal recessive	19q13.1/ SLC7A9	$b^{0,+}AT$	Light subunit of heteromeric aa transporter	PT S1 and S2	Heterozygotes: elevated urine cystine excretion

Both types cause stones and increased urine excretion of cystine and dibasic amino acids. S1–S3, segments 1–3 of the PT. Corresponding references are shown in parentheses.

soluble adenylyl cyclase [hsAC]) (65), 4 base changes segregated with IH, and bone mineral density decreased as the number of base changes increased. hsAC is a cytosolic enzyme sensitive to bicarbonate concentration in the presence of divalent cations and could explain bicarbonate sensitivity of renal and bone cells (66).

Primary hyperparathyroidism
Clinicians readily distinguish this stone-forming condition from IH because blood calcium levels are high in primary hyperparathyroidism and normal in IH. The two disorders share hypercalciuria and generally elevated serum levels of calcitriol. Diagnosis, pathogenesis, treatment approaches, and the genes related to gland enlargement have been well covered elsewhere (67).

Hyperoxaluria
Urine oxalate concentration affects CaOx SS exactly as does urine calcium concentration (68); therefore, any conditions that increase oxalate absorption from food or lead to increased oxalate production can cause CaOx stone formation.

Dietary hyperoxaluria in idiopathic CaOx SFs. Whereas the 95th percentiles for urinary oxalate excretion for females and males are 45 mg/d and 55 mg/d, respectively, and the corresponding 70th percentiles are 31 mg/d and 41 mg/d (12), values up to approximately 80 mg/d are common among idiopathic CaOx SFs and are often unexplained by a systemic cause (69). A low-calcium diet that reduces CaOx crystallization in the gut lumen, thereby facilitating oxalate ion absorption, is easily identified and corrected (70). High protein or oxalate intake are other causes of this condition (71, 72). Oxalate absorption from food may depend upon gastrointestinal transporters (73, 74), and genetic variations in oxalate transporting proteins in red blood cells have been linked to CaOx stone formation (73).

Enteric hyperoxaluria. If colon is present and receiving small bowel effluent, fat malabsorption of any cause (e.g., small bowel disease, resection or bypass, or exocrine pancreatic insufficiency) results in increased colon oxalate absorption and urine oxalate excretion in the range of 80–140 mg/d (69). Undigested fatty acids promote colon oxalate absorption (75). Diarrheal fluid losses and low urine pH and citrate levels resulting from stool bicarbonate losses increase urine CaOx SS and UA SS; stones usually contain 1 or both of these phases (69).

Among patients with enteric hyperoxaluria resulting from small bowel bypass for the treatment of obesity (19), some terminal CDs are plugged with apatite crystals (Figure 3) and show epithelial cell death and surrounding interstitial inflammation. How the apatite plugs form remains unknown; possibly high oxalate concentra-

tions in tubule fluid injure epithelial cells and disturb pH regulation so that lumen pH increases. Plugging and consequent nephron damage may account for renal function loss in such patients and may benefit from urine dilution.

Treatment involves high fluid intake and reducing dietary oxalate and fat intake to the extent that nutritional requirement guidelines permit. Calcium supplements (500–1,000 mg) taken with each meal can bind food oxalate and hinder absorption. Cholestyramine (2–4 g with each meal) binds oxalate and fatty acids and reduces urine oxalate excretion. If stones contain UA, potassium alkali is needed to increase urine pH (76). No formal trials have validated these treatment approaches.

Primary hyperoxaluria. Mutations in 1 of 2 genes — AGXT or GRHPR (77) — leads to oxalate overproduction and urine oxalate excretion rates above 100 mg/d or even 200 mg/d, resulting in PH (Table 2). When gene alterations divert active enzyme into mitochondria, where it cannot function effectively, pyridoxine may reduce urine oxalate concentration by increasing enzyme activity (78). When loss-of-function mutations inactivate enzymes, actively increasing urine volume and perhaps treatment with orthophosphate supplements may be advised (79). In type I PH, renal failure is frequent and presently treated by combined segmental liver and renal transplantation (80). Type II PH, being milder, seldom causes renal failure.

Hypocitraturia
The 30th percentiles for urine citrate excretion in normal women and men, 424 mg/d and 384 mg/d (26), respectively, correspond well with usual criteria for hypocitraturia (less than 500 mg/d for women and less than 350 mg/d for men). We have already alluded to the role of citrate in binding calcium and inhibiting calcium crystallization (see "Modulators of the ULM, crystal growth, and aggregation"), so it is reasonable to presume that low urine citrate levels could permit CaOx stones.

Regulation of urine citrate. Urine citrate concentration is determined mainly by tubule reabsorption (81), which is increased by acid loads and reduced by alkali loads. Therefore, states of alkali loss such as intestinal malabsorption with diarrhea or any cause of metabolic acidosis reduce urine citrate level (82, 83). Potassium depletion, a common consequence of thiazide intake, also lowers urine citrate level, which can be raised by potassium administration (84). However, in most patients who excrete subnormal amounts of citrate in their urine, no apparent cause can be found, and the underlying mechanisms are presently unknown.

Clinical management. Idiopathic CaOx SFs with low urine citrate levels can benefit from potassium citrate salt administration,

which increases urine citrate level and reduces stone recurrence (see "Treatment trials: stone recurrence outcomes"). Suggested dosages of potassium citrate salts range from 20–60 mEq/d, achieved in 2 or 3 doses. Alkali treatment does not reliably reduce urine calcium levels (85, 86) in IH. If hypercalciuria is present and does not abate with alkali, addition of thiazide is prudent to prevent an increase in CaP SS and development of CaP stones.

Hyperuricosuria

High urine UA excretion in men and women (above 800 mg/d and 750 mg/d, respectively) is associated with the formation of idiopathic CaOx stones (12). Dissolved UA salts appear to reduce the solubility of CaOx (87–89), fostering stones. Although hyperuricosuria results from high dietary intake of beef, poultry, and fish and can be abolished by dietary changes, no clinical trials document the effectiveness of this approach. A single trial has validated the use of allopurinol, an inhibitor of xanthine oxidase, which reduces UA production, as effective in reducing stone recurrence (see "Treatment trials: stone recurrence outcomes").

CaP stones

In a majority of kidney stones, CaOx is the main constituent and CaP is present in amounts ranging from 1% to 10% (90). When CaP becomes the main constituent (>50%) of stones, the stones are called CaP stones, and patients who form CaP stones are referred to as CaP SFs. CaP is present in urinary stones as either apatite (the principal constituent of bones and teeth) or brushite (calcium monohydrogen phosphate). Brushite, but not apatite, stones are physically resistant to ESWL, so repeated treatments may be needed (91). Brushite stones are associated with a distinctive renal disease (92). What drives the development of brushite versus apatite stones is not known.

CD plugging and brushite stones

In patients whose stones contain brushite (92), plugs of apatite fill the lumens of the terminal CD (Figure 4A). Epithelial cells are damaged or destroyed (Figure 4B). Around affected tubules, the interstitium is inflamed and scarred. Idiopathic CaOx SFs do not have intratubular crystals, whereas all brushite SFs we have biopsied to date have exhibited CD plugging. Stone type is therefore a clue to renal pathology. In the cortex of the 10 patients studied thus far (92), glomerular obsolescence and interstitial fibrosis exceeds that in cortical tissue from non-SFs and idiopathic CaOx SFs (Figure 4, C and D). Serum creatinine level was generally higher and 24-hour urine creatinine clearance was lower in the brushite SFs than in healthy controls. In our large clinical series (93), we could not find reduced renal function in brushite versus CaOx SFs, so these biopsied patients may have unusually severe renal disease. Compared with idiopathic CaOx SFs, and adjusted for sex, numbers of stones, and duration of stone disease, brushite SFs require a greater number of ESWL treatments, and this may contribute to their renal injury. Although potassium citrate salts are effective as a treatment for CaOx stones with hypocitraturia, they, along with ESWL, may promote the formation of CaP stones, whose prevalence has risen for the past 3 decades. Use of citrates requires attention in order to avoid increasing CaP SS excessively via high urine pH.

High urine pH as a main risk factor for CaP stones

Idiopathic CaOx SFs and CaP SFs both are hypercalciuric because of IH, but CaP SFs produce urine of higher pH, which favors CaP crystallization (93) by increasing the abundance of urine monohy-drogen phosphate (pKa ~6.7), the ion that combines with calcium. Urine pH rises progressively with increasing CaP percentage in stones (93). The mechanism of increased urinary pH in CaP SFs is unknown. Blood bicarbonate levels are normal, and net acid excretion is not low. High ammonia production and excretion could raise urinary pH (94) but was not obvious in our patients (93).

Management of CaP SFs

CaP SFs are usually treated with fluids and thiazide diuretics to lower urine calcium excretion. Urine citrate excretion can be reduced, as in idiopathic CaOx SFs, but because potassium citrate salts can increase urine pH and CaP SS, careful follow-up is needed. No clinical trials have documented treatment outcomes for CaP SFs.

Hereditary dRTA

dRTA is a syndrome of metabolic acidosis and hypokalemia with alkaline urine pH, low urine citrate excretion, hypercalciuria, and often bone disease (95). Stones are common and usually ascribed to the combination of hypercalciuria, low urine citrate, and high urine pH. If given an acid load, patients cannot reduce urine pH below 5.5, the conventional benchmark (95). Trials have yet to document stone treatment outcomes.

Autosomal dominant dRTA (Table 3) is caused by mutations in a chloride-bicarbonate exchanger encoded by *SLC4A1* on the basolateral surface of type A intercalated cells (96). The abnormal transporter is not targeted to the basolateral cell surface (97) and may form hetero-oligomers with the normal protein, reducing its function (98). Although dRTA is mild, stones and nephrocalcinosis are common and lead to the diagnosis, often in adult life. Autosomal recessive dRTA with sensory hearing loss (Table 3) causes dehydration and growth failure, beginning in infancy or early childhood (99). Hypercalciuria and high urine pH cause nephrocalcinosis. Autosomal recessive dRTA without hearing loss (Table 3) also causes growth failure and dehydration; some patients develop late-onset hearing loss (100). Autosomal recessive dRTA with osteopetrosis and cerebral calcification, caused by carbonic anhydrase II deficiency, does not cause nephrocalcinosis or stones (101).

Acquired and "incomplete" dRTA

Acquired forms of dRTA with stone formation are usually associated with the autoimmune disease Sjögren syndrome and/or use of the carbonic anhydrase inhibitor acetazolamide (102, 103). "Incomplete" dRTA is used as a diagnostic term when urine citrate excretion rate is low despite high urinary pH (pH >6.5) and blood chemistries are normal; given an oral acid load, such patients may fail to lower urinary pH below 5.5 (104, 105). Treatment of the low urine citrate is as already described for CaOx and CaP SFs. Stone treatment outcomes are not known for this condition.

Management of dRTA

Supplemental alkali in the form of potassium citrate salts is required to correct the metabolic acidosis and hypokalemia. Dosage for adults should range between 1 and 3 mEq of alkali per kilogram body weight (95). No trials document stone outcomes with alkali treatment.

UA stones

UA stones form because urine pH is abnormally low. Only 90 mg/l of undissociated UA dissolves in human urine at 37°C; therefore, at a pH of 5.35 (the pKa for the dissociation of the N9 proton of UA), only 180 mg/l of total urate species can be dissolved, whereas the

Table 5

Treatment trials for nephrolithiasis

Treatment	Type	Enrolled			Completed		New stones	
		%F	No. C	No. T	No. C	No. T	No. C	No. T
K citrate, 30–60 mEq/d (115)	RCD	56	28	27	20	18	14 (70%)	5 (28%)
K Mg citrate, 60 mEq/d (116)	RCD	21	33	31	25	16	16 (64%)	2 (13%)
K citrate (variable dose)[A] (117)	RC	38	25	25	22	16	6 (27%)	5 (31%)
Chlorthalidone, 25 mg/d (118)	RCD	12	31	42	26	28	12 (46%)	4 (14%)
HCTZ, 25 mg 2/d (119)	RCD	24	25	25	25	23	10 (40%)	4 (17%)
Indapamide, 2.5 mg/d (120)	RCD	24	25	50	21	43	9 (43%)	6 (15%)
LCD vs. reduced Na and P (diet) (32)	RC	0	60	60	51	52	23 (45%)	12 (23%)
Allopurinol, 300 mg/d (121)	RCD	n/a	31	31	31	29	11 (35%)	5 (17%)

RCD, randomized, controlled, double-blind; RC randomized, controlled; Enrolled, number of controls (No. C) and treated (No. T) subjects entering the study and percent female (%F); Completed, number of subjects who completed the study; New stones, number (%) of subjects who formed stones. All studies were for a period of 3 years except for the diet study, which was 5 years. [A]Dose of sodium potassium citrate varied to maintain urine pH between 7.0 and 7.2. HCTZ, hydrochlorothiazide; P, protein; L, low-calcium diet; n/a, not available. Corresponding references are shown in parentheses.

total urate concentration of healthy individuals and UA SFs approximates 500 mg/l of urine (12). Low urine pH is due in part to low ammonia excretion (106, 107). Low urinary pH and UA stones are common in patients with gout, diabetes mellitus, and the metabolic syndrome, perhaps as a result of insulin resistance that may reduce renal ammonia excretion (108). Urinary pH falls with increasing body weight (109), probably because of insulin resistance. Chronic diarrhea also lowers urinary pH (69) and causes UA stones.

UA stones are not easily seen on kidney, ureter, or bladder x-rays. On CT images, they resemble calcium stones, from which they can be distinguished by their lower density (1). On an i.v. pyelogram radiograph, UA stones appear as filling defects. UA gravel can occlude ureters and produce acute anuric renal failure; UA stones can fill the entire renal collecting system. UA gravel and stones are often orange or red, having adsorbed uricine, a bilirubin breakdown pigment. Prevention and even dissolution of UA stones depends upon the ability to increase urine pH above 6.0, which is accomplished by administration of 20–30 mEq potassium alkali, 2 or 3 times daily. Allopurinol is not usually required or indicated but can be used if alkali does not suffice and urine UA level is increased.

Cystinuria

Genetic abnormalities

Mutations in renal epithelial cell transporters result in reduced reabsorption and increased urine excretion of the dibasic amino acids, including cystine. High cystine SS because of overexcretion causes cystine stones (Table 4). The main apical resorption system for cystine in the kidney is a heterodimer transporter composed of a light chain catalytic subunit, $b^{0,+}$ amino acid transporter ($b^{0,+}AT$), and rBAT (related to $b^{0,+}AT$), a heavy chain subunit (110). rBAT is responsible for targeting $b^{0,+}AT$ to the brush border membrane, and it is $b^{0,+}AT$ that acts as the transporting assembly. Although cystinuria can be subtyped genetically (Table 4), patients of either type A or B are clinically indistinguishable (111). In all forms of cystinuria, urine cystine excretion ranges from 350–500 mg/d.

Clinical management of cystinuria

Treatment of cystinuria aims to reduce SS below 1. Cystine solubility approximates 1 mM (243 mg/l) and rises with urine pH but is variable and higher in urine of cystinuric patients as compared with

CaOx SFs (112) and therefore is best measured directly (113) rather than estimated via a pH nomogram. Management (114) begins with achieving a daily urine volume of 3.5–5 liters, which can dissolve the cystine excreted by some patients. Others also require administration of 40–80 mEq/d of potassium alkali to raise pH. Reduction of sodium and protein intake reduces urine cystine excretion. Those measures failing, D-penicillamine, α-mercaptopropionylglycine, or captopril, all of which form soluble heterodimers with cysteine, can be used. Blood pressure reduction can limit captopril dosing so the drug has little practical utility. D-Penicillamine and α-mercaptopropionylglycine have side effects including loss of taste, fever, proteinuria, serum sickness–type reactions, and even frank nephrotic syndrome. Increasing fluid and alkali intake are therefore preferred therapeutic modalities in as many cases as possible.

Treatment trials: stone recurrence outcomes

To date, 7 of 8 prospective trials, each lasting at least 3 years, have shown that selective treatments have a distinct benefit for idiopathic CaOx SFs (Table 5). Table 5 makes clear that dropout rates were high, and we are not aware that any of the investigators followed up with those individuals that did not complete the trial in order to ascertain their stone status. Therefore, additional trials may not be altogether without merit. Even so, and despite these imperfections, it is difficult to conclude that treatments are without important benefits.

Thiazide and citrate: recurrent calcium SFs. Three prospective trials of potassium citrate salts have been performed to date, and 2 (115, 116) indicate therapeutic benefit (Table 5). The third (117) lacks a double-blind design, and its control subjects formed fewer stones than those in the other studies. All subjects were CaOx SFs with hypocitraturia. Thiazide diuretic agents have been studied in 3 randomized, controlled, double-blind trials. Chlorthalidone (118) at doses of 25 mg/d or 50 mg/d gave equivalent results that are pooled (Table 5). Hydrochlorothiazide gave therapeutic effects equivalent to chlorthalidone (119), as did indapamide (120).

Dietary changes for recurrent calcium SFs. Borghi et al. (32) compared a low-calcium diet to a normal calcium diet reduced in protein and sodium in a 5-year randomized trial (Table 5). The 2 diets gave comparable results during the first 3 years, but by 5 years, the normal calcium, reduced sodium, and protein diet proved superior in that only 23% of patients had formed a new stone.

Allopurinol: recurrent calcium SFs. Allopurinol (121) has been shown to reduce new CaOx stone formation in patients with hyperuricosuria (Table 5).

Patients who have formed only 1 calcium stone. Over a 5-year period, 20% of patients who maintained a urine volume above 2.5 l/d had stone recurrence (122) compared with approximately 50% of patients who were counseled to avoid dehydration and to observe moderate salt and protein intakes. Counseled controls did not actually increase urine volume. We do not combine this trial with the others, as it concerns only SFs with a single stone.

A final word about stones

It is difficult to accept recurrent stone formation as incidental in any patient and allow it to continue without efforts to understand its causes and offer such treatments as seem appropriate. Available trials offer physicians excellent treatment strategies for prevention of calcium stones, and since UA stones are a consequence of low urine pH, physicians can treat them confidently despite the lack of prospective trials for additional therapeutics. Even cystine stones can be prevented, albeit with imperfect remedies. But treatments may pose their own problems. Although potassium citrate salts are effective, they, along with ESWL, may promote the formation of CaP stones, the prevalence of which continues to rise with time. Possibly this means that the use of citrates requires special attention to avoid increasing CaP SS excessively via high urine pH. Although we treat urine SS, the tissue processes of stone formation are complex, not as yet obviously related to solution chemistry within specific nephron segments, and not well understood. This is a significant area of interest that requires new research. Abnormal urine pH and calcium excretion rate are predominant findings in SFs that play a major role in the pathogenesis of stone formation. Their biologies are therefore also of particular research importance. Perhaps most important in the long run will be uncovering the links between genetic variability and urine calcium excretion and pH, for these seem at the very center of the problem of kidney stone disease.

Address correspondence to: Fredric L. Coe, Renal Section MC 5100, University of Chicago School of Medicine, 5841 South Maryland Avenue, Chicago, Illinois 60637, USA. Phone: (773) 702-1475; Fax: (773) 702-5818; E-mail: f-coe@uchicago.edu.

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