Pathophysiology-Based Treatment of Idiopathic Calcium Kidney Stones

Fredric L. Coe,* Andrew Evan,† and Elaine Worcester*

Summary
Idiopathic calcium oxalate (CaOx) stone-formers (ICSFs) differ from patients who make idiopathic calcium phosphate (CaP) stones (IPSFs). ICSFs, but not IPSFs, form their stones as overgrowths on interstitial apatite plaque; the amount of plaque covering papillary surface is positively correlated with urine calcium excretion and inversely with urine volume. The amount of plaque predicts the number of recurrent stones. The initial crystal overgrowth on plaque is CaP, although the stone is mainly composed of CaOx, meaning that lowering supersaturation (SS) for CaOx and CaP is important for CaOx stone prevention. IPSFs, unlike ICSFs, have apatite crystal deposits in inner medullary collecting ducts, which are associated with interstitial scarring. ICSFs and IPSFs have idiopathic hypercalciuria, which is due to decreased tubule calcium reabsorption, but sites of abnormal reabsorption may differ. Decreased reabsorption in proximal tubules (PTs) delivers more calcium to the thick ascending limb (TAL), where increased calcium reabsorption can load the interstitium, leading to plaque formation. The site of abnormal reabsorption in IPSFs may be the TAL, where an associated defect in bicarbonate reabsorption could produce the higher urine pH characteristic of IPSFs. Preventive treatment with fluid intake, protein and sodium restriction, and thiazide will be effective in ICSFs and IPSFs by decreasing urine calcium concentration and CaOx and CaP SS and may also decrease plaque formation by increased PT calcium reabsorption. Citrate may be detrimental for IPSFs if urine pH rises greatly, increasing CaP SS. Future trials should examine the question of appropriate treatment for IPSFs.


Introduction
The common measures of reduced diet sodium and protein, increased fluids, thiazide, potassium citrate, reduced diet purine, and allopurinol have until now been viewed from the perspective of altering urine supersaturations and inhibitors of crystallization. Here, we add to this familiar theme the new work concerning how stones actually form and how the mechanisms that drive their formation actually function. The result is a new level of understanding in the use of accepted treatments that should bring to physicians and their patients a greater confidence and subtlety of management.

The new work has divided calcium stone-formers not only by their clinical appearances but also their renal pathology. We have always distinguished patients who form calcium stones because of systemic disease from idiopathic calcium stone-formers. However, we now know that idiopathic calcium stone-formers whose stones are predominantly calcium oxalate differ markedly from those whose stones are not. This new distinction has real clinical effects and calls for a new trial.

Idiopathic Calcium Oxalate Stone-Formers

Stones Grow over Deposits of Interstitial Apatite (Plaque)

In the most common kind of patient, calcium stones arise from no systemic disease but are, rather, “idiopathic.” Among these, most (1) form stones for which the most abundant crystal is calcium oxalate (CaOx). The kidneys of idiopathic CaOx stone-formers (ICSFs) are normal except for papillary interstitial apatite deposits (2,3) that appear as white clouds (Figure 1A) under the urothelium during ureteroscopy (URS) or percutaneous nephrolithotomy (PERC). The kidney stones grow over these deposits, often called “white plaque,” on the outside of the papilla (Figure 1B). No crystals are seen within the epithelial compartments (4). The deposits evoke no obvious inflammation, and renal papillae are completely normal in appearance except for plaque and overgrowing stones.

Plaque begins as collections of tiny microspherules that form in the basement membranes of the papillary thin limbs of the loops of Henle (Figure 1C) and spread from there into the interstitium and eventually beneath the urothelium and basement membranes of inner medullary collecting ducts (IMCDs) and terminal ducts of Bellini (BDs), where they appear as white plaque (Figure 1D).

In a prospective study of ICSFs, all stones visualized using PERC were classified as attached or not, and those attached were further classified as attached or not to plaque (5). Most stones were attached, and of those, all were attached to plaque or their attachment site could not be fully verified. Verification required that intraoperative classification during surgery agree with subsequent classification from intraoperative
Physiologic Links between Urine Findings and Plaque. How these urine factors affect plaque requires a deeper look into the renal physiology involved, and such a look increases the nuance and subtlety of clinical management. In the papillae, thin limbs are surrounded by three to four capillaries each (Figure 3, lower panels). The calcium concentration of thin limb fluid exceeds that of blood levels because of water extraction (9), but the epithelium possesses very low calcium permeability and does not transport calcium at all (10). Even so, thin limb fluid is always in contact with its epithelium, so calcium must move into the basement membrane at a higher concentration than blood, especially in the ascending portion that does not permit extensive water movement. However, the outer side of the basement membrane can lose calcium into the surrounding interstitium at a rate that is inversely related to the calcium molarity of the interstitial fluid, and that molarity will inevitably be dominated by the calcium concentration of the blood delivered to the capillaries. That blood comes down in the descending vasa recta, which form bundles in the inner stripe of the outer medulla that are surrounded by a ring of thick ascending limbs (11) (Figure 3, upper panels). Thick ascending limbs absorb calcium without water mainly via a lumen positive trans-epithelial potential created by the sodium-potassium-chloride cotransporter 2 and the renal outer medullary potassium channel. (10). Delivery of calcium without water must enrich the inner stripe interstitium with calcium, and this must in turn raise the calcium concentration of blood in the descending vasa recta. So, in all conditions, the basement membranes of the papillary thin limbs will be bathed on both sides by fluid with a calcium concentration above that of blood: lumen fluid via water extraction, interstitial fluid via vasa washdown.

This probably accounts for why interstitial plaque forms even in normal people and initiates in this particular site; however, so far we have not explained why plaque would be more abundant in ICSFs than in normal people because the anatomy and functions of thin limbs and thick ascending limbs are essentially alike.

Idiopathic Hypercalciuria. The crucial difference lies in how calcium is managed in ICSFs as opposed to normal people. Populations of men and women exhibit a wide range of urine calcium excretions from as low as 50 to as high as >500 mg daily, with mean values in the range of 130 to 170 mg daily for both genders (12). ICSFs appear to have been selected from the high tail of this distribution because their mean values are twice that of normal individuals. Like height, calcium excretion is seemingly genetically determined because high values run in families (13) and rodents can be bred for it (14). Such high urine calcium excretion is not a disease, but merely the cause of high stone risk in more hypercalciuric people. ICSFs are said to have idiopathic hypercalciuria (IH), but a better way to think about the matter is that they simply are drawn from one end of the normal genetic endowment of humankind.

In humans and in animals, IH reflects increased tissue vitamin D activation: intestinal calcium absorption and bone mineral mobilization are increased, and a low-cal-
The thin limbs do not reabsorb calcium appreciably, so increased distal delivery means increased calcium enters the thick ascending limbs where it is reabsorbed via mainly electrogenic forces. This means that more delivery will generally result in correspondingly more reabsorption, without water, into the interstitium of the outer stripe of the inner medulla. In turn, descending vasa recta will be more preloaded with calcium, and the capillaries of the papillum will enrich the interstitium with calcium to a...
greater degree, thereby fostering crystal nucleation in thin limb basement membranes. In the broadest sense, one would expect plaque abundance to parallel urine calcium excretion, which it does. Of course, interstitial calcium concentrations must be measured in human tissues if this hypothesis is to be properly tested; such measurements can be made, and we hope that investigators take on this specific test as a research aim. Failure to find increased interstitial calcium would defeat our hypothesis.

Effects of Urine Volume on Plaque. This model also predicts that plaque abundance will be generally inverse to urine volume. Vasopressin, a major agonist of medullary thick ascending limb transport, acting via the V2 receptor, is highest when urine volume is low, and the converse. Moreover, medullary washout from high urine flows will tend to reduce the concentrations of all papillary interstitial solutes, including calcium.

Limitations of This Model. We present this work as in progress and of value because it leads to further tests. For example, lithium clearance is not a direct measurement of proximal tubule reabsorption and may be subject to errors. Other tests (e.g., increase of urine calcium after blockade of the thick ascending limb by furosemide) would be valuable confirmation (17), as would, perhaps, studies of free water clearances. Likewise, Figure 4 makes it clear that not all of our ICSFs display the same degree of proximal tubule alteration, but we cannot presently correlate proximal reabsorption with plaque abundance measurements. This latter comparison would be a critical test of the hypotheses we propose and can be performed in human subjects.

Clinical Measures That May Reduce Plaque Formation

Because plaque cannot be quantified in patients except during surgery, randomized controlled trials (RCTs) for plaque prevention are not as yet practical, but from what we have already presented clinicians can derive some reasonably sound directions that have no risk and high potential benefit.

Reduced diet sodium and protein, long mentioned for moderation of hypercalciuria (18), may increase proximal tubule reabsorption. The first acts via reduction of extracellular fluid volume. The second reduces endogenous acid production from oxidation of sulfur on methionine and cystine; acid loads reduce proximal reabsorption (19). Thiazide-type diuretics are a mainstay in stone prevention (20) because they lower urine calcium excretion. In rodents, and presumably humans as well, they increase proximal reabsorption by reducing extracellular fluid volume (21). High water intake, an obvious stone prevention supported by RCTs (22), will reduce vasopressin, and therefore medullary thick ascending limb reabsorption (23), and foster medullary solute washout. One might consider

Figure 3. | Schematic drawing of outer medulla and papillary tip. Vasa recta descend in bundles through the inner stripe of the outer medulla (upper panels) surrounded by rings of thick ascending limbs. In the papillary tips, where plaque forms in basement membranes of thin limbs (lower panels), thin limbs are each surrounded by three to four capillaries that derive from the descending vasa recta.
once-a-night nocturia for patients whose stones recur despite all other measures because urine volume is lowest and vasopressin is presumably highest overnight.

After only one stone, we advise only modest treatment efforts (24), but one might consider that plaque needs to form before ICSFs can make stones and that stone recurrence tends to parallel plaque abundance (7). Given this point, high fluids and reduced diet protein and sodium would be reasonable as soon as possible in the natural history of stone disease, meaning with the first stone. Even at the first stone, and often during the course of the disease, surgeons will have access to at least a coarse-grained visual assessment of plaque abundance via URS or PERC. We see every advantage in asking surgeons to share their best impression with us. Given a lot of plaque, stone prevention efforts may best be pushed as far as possible and patients made aware of a higher underlying risk of recurrence. This latter may increase their desire to maintain prevention treatments, especially those pertaining to diet and fluid intake.

How Stones Grow on Plaque

At the attachment site of a 1-mm CaOx stone (Figure 5) the urothelium over a plaque deposit was disrupted, and the plaque surface was exposed to urine (25). The exposed surface was sealed by an inner boundary of organic material of urine origin, containing Tamm–Horsfall protein and osteopontin as well as other molecules. Apatite crystals nucleated in the layer, were covered by more organic matrix, new nucleation occurred, and ultimately alternating crystal and organic layers formed a laminated ribbon. The ribbon terminated when crystallization spread out into the urinary space forming the stone base. In this transmission electron micrograph, plaque is at the lower left, white arrowheads show the inner boundary layer, and crystals are shown at the stone base by an asterisk and double arrows. The inset shows the details of the ribbon and its crystals at higher magnification.

The crucial steps in the process, in addition to formation of plaque itself, are disruption of the urothelium, about which we know nothing at the present time, and the initial apatite nucleation, which drives the formation of the new stone. This nucleation depends entirely upon urine calcium phosphate (CaP) supersaturation (SS), meaning that even in CaOx stone-formers, CaP SS is a critical clinical variable to control as best one can.

In ICSFs, CaP SS far exceeds normal (Figure 6, lower right panel), to an even greater extent than for CaOx SS (Figure 6, upper right panel). Normal people do not, on average, achieve CaP SS values >1, meaning that the initial apatite nucleation might be rare indeed, whereas values in ICSFs are >1 virtually all of the time (26). The highest
values of CaP SS are late afternoon and overnight for ICSFs, when the SS of normal people declines modestly. The high CaP SS is driven by high urine calcium molarity (Figure 6, upper left panel), itself arising from IH without any corresponding increase of urine volume (Figure 6, lower middle panel). Differences in urine pH are minimal between ICSFs and normal individuals (Figure 6, lower left panel).

One must think it odd that urine volume is not higher in ICSFs than normal people given that the apical collecting duct calcium receptor (CaSR) should sense the rising calcium molarity and reduce water reabsorption; however, the facts are simply that this does not occur. For example, overnight, calcium molarity among ICSFs reaches near 6 mM whereas normal is 2 mM, but urine volumes are identical. The CaSR is probably protective, but only at higher levels of urine calcium excretion. The human CaSR studied in vitro is half stimulated at calcium ion molarities of 6 at the pH and ionic strength of urine, but in human urine a total calcium molarity of 6 means only approximately 3 mM calcium ion. The remaining urine calcium is bound in complexes that help create SS, such as with phosphate and oxalate. So the lack of effect in our patients is not actually divergent from what one might expect.

Clinical Measures That May Reduce Stone Overgrowth on Plaque

Reduction of CaP SS may be as important as reduction of CaOx SS even in ICSFs. High urine volume should help, as might all measures to reduce urine calcium, including reduced diet sodium and protein and thiazide. Overnight is so remarkably a time of high CaP SS, 1× nocturia could be important in refractory patients. In other words, means of treatment are the same as for plaque.

However, potassium citrate is complex, if of probable value. Alkalis reduce urine calcium excretion and increase proximal tubule reabsorption via reduced diet net acid load (27), and two RCTs document benefits for calcium stone-formers with hypocitraturia, among whom ICSFs would statistically have predominated (20). Citrate is an excellent inhibitor of apatite nucleation and growth (28,29); however, citrate can raise urine pH and CaP SS, so we believe it is prudent to dose enough to reduce urine ammonia by one half to two thirds; more will almost certainly raise pH. For example, the initial dose in millimoles per day could be one half to two thirds of the urine ammonia, in millimoles per day, as derived from standard commercially available 24-hour urine kidney stone risk panels.

Urine oxalate is far from trivial in any ICSF, so even in this CaP-oriented discussion we note that even with fixed
and identical diets oxalate excretion is higher than normal in ICSFs, and CaOx SS is also higher, especially overnight (30). Moreover, ICSFs not infrequently exhibit renal oxalate secretion compared with normal control subjects eating the same diet (31), suggesting new mechanisms by which CaOx crystallization might be promoted. Lowering CaOx SS should reduce bulk nucleation and growth of CaOx on the new CaP stone nidus and is therefore very important. Urine oxalate excretion rates >45 mg/d often arise from low-calcium or high-oxalate diets that can be corrected. Values >65 to 70 mg/d may reflect primary hyperoxaluria or enteric hyperoxaluria (20). No RCTs support reduction of urine oxalate as a treatment for ICSFs.

Finally, hyperuricosuria may reduce CaP and CaOx solubility via salting out and therefore raise the propensity for both nucleations (32-34). This is perhaps why a single RCT with allopurinol was so positive (35). Reduced diet purine should do as well, but no trial has been done.

**RCTs Accord with the Model of Plaque Formation and Overgrowth**

In an RCT of male ICSFs, a low sodium and protein diet was more effective in stone reduction than a low-calcium diet, which would not increase proximal tubule reabsorption (18). All three fully powered, 3-year thiazide trials (36–38) have been highly positive, as have the two RCTs with potassium citrate in hypocitraturic calcium stone-formers (39,40) and the one RCT with allopurinol in hyperuricosuric calcium stone-formers. The thiazide, citrate, and allopurinol RCTs concerned idiopathic calcium stone-formers, wherein ICSFs must have predominated, but some CaP stone-formers were surely also present.

**The ICSFs Have a Specific Disease**

Because IH can be linked to plaque via the known anatomy and physiology of the kidney, because their stones grow on plaque through a well defined series of nucleations, and because mechanisms and origins of IH itself also are becoming well known, the stone disease of IH can be understood from its etiology, through its pathogenesis to its eventual tissue expression. Given that the final disease, stones, can be so well explained in mechanistic terms, ICSFs appear to satisfy reasonable criteria of a cohesive disease of mineral metabolism. We note in leaving this subject that a generation of researches has established the remarkable abilities of urine to inhibit nucleation and growth of calcium crystals (41); abnormalities of inhibition may well be part of the ICSF phenotype, but evidence for this is scanty at best, and much more must be done before the matter has clinical relevance.

**Idiopathic CaP Stone-Formers**

Idiopathic CaP stone-formers (IPSFs) whose stones contain >50% CaP differ so radically from ICSFs that their stones might well come from an entirely different etiology and pathogenesis. However much they may resemble ICSFs on superficial analysis, they do not have that disease. Instead, their kidneys are involved in a far more destructive local process. IPSFs could form stones of apatite or brushite (calcium monohydrogen phosphate); to date, we have data only on the latter group, brushite IPSFs, and what follows applies only to them.

**IPSFs Plug BDs and IMCDs with Apatite Crystals**

During PERC or URS, white plaque is present (Figure 7A, arrow); papillae show areas of scarring (arrowheads) and scattered hugely dilated BDs plugged with apatite crystals.
that often protrude out of the duct opening (42) and project into the urinary space (asterisk). On biopsy (Figure 7, B through F) affected BDs can be 20-fold dilated; epithelial cells are absent (arrow). Interstitial fibrosis surrounds affected BDs (legend details changes in each panel). Crystal-mediated injury essentially creates a focal papillary tubulointerstitial nephropathy.

The mechanism for plugging and high stone CaP abundance seems simply to be a high urine CaP SS (43). Mean urine CaP SS (Figure 8, left panel) of calcium stone-formers increases smoothly as the fraction of phosphate in stones analyzed increases (Figure 8, x-axes of both panels). This occurs because of rising urine pH (Figure 8, right panel). The reason for the increasing pH is not known. All groups of patients on these plots have equivalent IH. Because IMCD and BD tubule fluid approximates the final urine, CaP SS must be higher at both sites, leading to sporadic and damaging crystallizations.

**The Less Abundant Plaque in IPSFs Raises Important Research Questions**

Urine calcium excretion is slightly higher in IPSFs versus ICSFs, and urine volume is approximately the same, but the higher pH is predictive of less plaque. Vas washdown should operate the same way for both groups. However, at least two alternative mechanisms can reduce plaque. Reduced net proton secretion in IMCDs would be expected in IPSFs compared with ICSFs, and this would reduce bicarbonate entry into the papillary interstitium and therefore reduce interstitial fluid pH. Higher pH would foster CaP nucleation in basement membranes of thin loops.

Alternatively, medullary thick ascending limb may have reduced absolute calcium reabsorption in IPSFs compared with ICSFs. Although both exhibit the same urine calcium losses and even reduced overall tubule reabsorptive changes, IPSFs would not load descending vasa recta with calcium to the extent found in ICSFs. Because thick ascending limbs reabsorb approximately 15% of filtered bicarbonate (44), reduced reabsorption would increase distal bicarbonate delivery to IMCDs and BDs, raise the pH there, and foster CaP crystallization. In other words, IH may have several tubule expressions, one centered mainly in proximal tubules and one in thick ascending limbs with perhaps a spectrum in between these extremes. In inbred hypercalciuric rats, proximal tubule and thick ascending limb calcium reabsorptions are abnormally low (17). Comparison of nephron physiology in IPSFs versus ICSFs therefore offers remarkable opportunity for new human discoveries.

**Management of IPSFs**

The value of reduced diet sodium and protein, and of high fluid intake and thiazide, is the same as in ICSFs—what differs is the role of potassium citrate. Citrate is an inhibitor of CaP nucleation and growth, as mentioned already, but if urine pH and therefore CaP SS rises, stones and plugging can increase. An RCT is badly needed for this exact kind of patient. Given that IPSFs are hardly rare, this trial is long overdue.

One does not have to wait for stone analysis. Any URS or PERC is an opportunity for surgeons to observe plugging, which is not present in ICSFs. The urologists who serve our patients should always be asked if plugging is seen and if even a crude estimate can be given of amounts of plugging and papillary retraction and scarring.

**Summary**

Information drawn from operative biopsies of the renal papillae in stone-formers is altering our understanding of the ways in which calcium stones form. The importance of plaque in formation of CaOx stones means that methods to reduce plaque formation should become a goal of stone prevention.
prevention. The role that CaP SS plays in the formation of CaOx and CaP stones means that lowering CaP SS should be a goal for ICSFs and IPSFs. The marked histopathologic differences between ICSFs and IPSFs highlight the need for a trial to evaluate treatments for stone prevention in each group. As our understanding of the pathophysiology of stone formation improves, it will inform our ability to choose appropriate treatments for our patients.

Disclosures
None.

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