

## **Oxalate in the Kidneys of Human Stone Forming Patients**

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Oxalate excretion rises with meals to higher levels in calcium stone forming patients (SF) than normal subjects eating the same foods in a clinical research center environment; however, concomitant rise in urine volume reduces oxalate molarities to nearly equal levels during the day. Overnight and fasting urine oxalate molarities of SF exceed normal, however, creating a driving force for calcium oxalate (CaOx) stone formation. Idiopathic CaOx SF (ICSF) form their stones attached to renal papillae at sites of suburothelial accumulations of interstitial apatite (Randall's) plaque. The overgrowths begin with layers of urine organic molecules that include osteopontin and Tamm Horsfall protein in which apatite crystals form. Layers of alternating organic matrix and apatite crystals create the tissue-stone interface over which, by about 100-120 microns, successive layers gradually accumulate admixtures of CaOx and apatite and finally pure CaOx. To date, no crystals have been found in the epithelial compartments of ICSF kidneys despite the study of over 7,500 serial sections of biopsies from 45 patients. Brushite (calcium monohydrogen phosphate) SF deposit apatite plugs in their inner medullary collecting ducts (IMCD) and ducts of Bellini (BD); stones can grow as attached extensions of these plugs, or in free solution. Patients with primary hyperparathyroidism and stones form a mixture of attached CaOx stones growing over plaque deposits, and IMCD plugs with attached stones. Patients with cystinuria plug BD with cystine, and also form IMCD apatite plugs that play no evident role in their stone disease, but may reflect ductal obstruction with cystine, with secondary reduction of final tubule fluid acidification—local renal tubular acidosis. Patients with renal tubular acidosis form apatite stones; IMCD are widely plugged with apatite deposits. In rare tubules of one patient, we have found isolated birefringent crystals that are probably CaOx; their significance for stone disease is unknown. Ileostomy patients plug ND with sodium monohydrogen urate, although urine pH values are too alkaline to support formation of such a phase; we postulate that initial plugs of uric acid convert *in situ* to this alkaline urate salt because of a loss of IMCD and ND acidification. This remains to be tested in other experiments. Many IMCD also contain apatite plugs. Stones are CaOx and uric acid, and may form in free solution; this matter presently needs additional research. In patients with intestinal bypass for obesity, we find round CaOx stones that are never attached and almost certainly grow in free solution. IMCD are frequently plugged with apatite, despite a rather low urine pH, suggesting local acidification defects. Rare scattered birefringent scums of crystal are found on apical surfaces of some IMCD; the cells seem otherwise normal. Possibly these scums are pathogenetic in the acidification defect that leads to apatite plugs; this requires additional research. Kidneys from patients with type 1 hyperoxaluria contain large amounts of crystal deposits whose structures have not been determined at the writing of this abstract, but will be available at the final meeting presentation. Finally, in transplanted kidneys, we commonly find CaOx in brush borders of proximal tubules, and apatite in distal convoluted tubules; the causes and consequences of these deposits are as yet unknown. Overall, CaOx is a rare deposit in human kidneys, being documented thus far in intestinal bypass patients, proximal tubules of transplanted kidneys, and in other laboratories, in tubules of patients with primary hyperoxaluria. Apatite deposits are very common in SF kidneys. The most common kind of stone former, the ICSF, have no crystals in their tubule cell compartments, and form their stones as external deposits over interstitial apatite plaque.

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