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Pathogenesis of Nephrolithiasis

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Much has been learned in the last decade regarding the initial steps of crystal deposition and ultimate stone formation. There appear to be 3 basic pathways for crystal formation in the upper urinary tract. The first and most common pathway is the overgrowth of calcium oxalate on suburothelial deposits of hydroxyapatite, so-called Randall plaque.¹ This pathway is germane to the idiopathic calcium oxalate stone former, by far the largest category of stone formers. Randall plaque forms in the basement membranes of the thin limbs of the loop of Henle as fine particles that produce no visible tissue reaction or cell injury. These particles are laminated microspherules of alternating apatite crystals and organic matrix that coalesce in the interstitium to form a syncytium of crystal islands in an organic sea. This migrates to the suburothelial space, where it appears during surgery as a white, irregularly shaped plaque. Randall plaque occupies 5% to 8% of the total papillary surface area in idiopathic calcium oxalate stone formers and on this minor proportion of surface more than 75% of stones are attached, meaning that overgrowth on plaque is of preeminent importance for stone formation.²

Among idiopathic calcium oxalate stone formers plaque abundance is proportional to urine calcium excretion, and inverse to urine volume and pH.³ How urine volume and calcium excretion, ie urine calcium molarity, and pH influence plaque formation so strongly is not known. However, current thinking is that the thick ascending limb of the loop of Henle resorbs calcium without water into the outer medullary interstitium. Given that the vasa recta counter-current mechanism traps solutes there, the calcium molarity must be above blood levels. Blood descending through the vasa recta along the long loops of the juxtamedullary nephrons must then be enriched with calcium so that the outer surface of the thin loop basement membranes can be exposed to a calcium rich interstitium. This loop has a fluid whose calcium molarity is higher than that of blood, at least in rodents,⁴ because of water extraction in the descending thin segments. Thus, the basement membrane of the loop of Henle is essentially sandwiched between 2 calcium rich environments.

In hypercalciuric patients the delivery of calcium out of the proximal tubule is increased above normal, resulting in increased calcium delivery to the limbs of the loop of Henle.⁵ The thin limbs could resorb the extra calcium, raising outer medullary calcium molarity above normal to foster plaque deposits via wash down by the vasa recta. Further, the process of urinary acidification in the collecting ducts requires proton secretion into the collecting duct fluid, balanced by bicarbonate movement into the basolateral side of the collecting ducts, making the interstitium more alkaline. Since plaque is apatite, which forms best in alkaline medium, one can envision a perfect storm driving apatite deposition on the collagen fibers of the basement membrane of the thin limbs of the loop of Henle. There would seem to be no need to impute a role for trace elements in this physiological cascade of events.

The second important mechanism for stone formation involves the overgrowth of stones on tubular crystal plugs. The formation of tubular plugs is uncommon, if it occurs at all in the routine idiopathic calcium oxalate stone former. However, tubular plugging has been documented in patients who are brushite stone formers and idiopathic calcium phosphate

stone formers, patients with ileostomies and small bowel resections, those with cystinuria and patients treated with intestinal bypass for obesity.⁶ Tubular plugging is also seen in patients with primary hyper-parathyroidism, distal renal tubular acidosis and primary hyperoxaluria. How human stones form in relation to plugs is a question that has not been clarified. It is possible that plugs are extruded, providing the nidus for subsequent stone formation, or stones overgrow plugs protruding from the duct of Bellini. A whole school of experimental science concerns the anchoring of crystals to epithelial cell surfaces as a key step in tubular plug formation.⁷ None of this work has suggested a role or requirement for trace elements in the initiating events of nephrolithiasis.

The third pathway for stone formation is likely free solution crystallization. Cystinuria, struvite and perhaps uric acid stones could be examples. Idiopathic calcium oxalate stone formers have shown no evidence to date to suggest that free solution crystallization contributes to stone production in this most common group of stone formers.

In this issue of The Journal Blaschko et al (page 726) report that they are able to detect trace elements in urinary calculi using sophisticated, synchrotron radiation based advanced imaging techniques.⁸ Given our current understanding of stone pathogenesis as outlined, what might be the relevance of the study? The authors suggest that the study of these trace elements and their pivotal role in stone formation is promising. However, they provide no data to support why this might be so. In my view trace elements are just that and likely nothing more. It seems not surprising that such minute amounts of elements such as zinc and lead might be incorporated with time in the months or years required to form a stone of the size removed from patients included in their report. Further, there is no rational physiological mechanism by which one might expect such trace elements to be important in the generation of a urinary calculus. One could just as easily suggest that trace elements are inhibitory to stone formation, given the information offered. The data presented in this study focus on urinary calculi and not on tissues of the renal papillae. Since most human urinary calculi appear to develop due to crystal deposits in the interstitium or tubules of the renal papillae, studies of renal papillary tissue by the University of California-San Francisco group would be of great interest.

Briefly, Blaschko et al present a highly novel technique to analyze urinary calculi, allowing them to report that trace elements can be identified. Whether these trace elements are mere innocent bystanders or have some plausible role in human stone pathogenesis remains to be discovered.

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