Published in final edited form as:
Urolithiasis. 2015 January ; 43(0 1): 1–3. doi:10.1007/s00240-014-0721-9.

FOREWORD

Saeed R. Khan, M.Sc, Ph.D., FASN
Departments of Pathology and Urology, College of Medicine, University of Florida, Gainesville, Florida

Kidney stone formation is a highly prevalent disease with recurrence rates estimated up to 50% within the first five years after the initial stone episode.[4] The risk of recurrence increases with each new episode,[1] and nearly all stone formers are expected to form another stone provided they live long enough.[2] Kidney stone recurrence affects both genders of all ages and ethnicities, and the costs for stone disease care and treatments, estimated at over $10 billion in 2006 in United States, are projected to continue to increase. Current medical preventative therapies reduce stone risk by 50% over short (2–3 years) duration.[7, 13] Furthermore, new epidemiological studies link stone formation to the development of hypertension, chronic kidney disease, and even end-stage renal disease, while other highly prevalent medical conditions, such as obesity, diabetes, and metabolic syndrome, are considered risk factors for stone formation.[3, 5, 6, 8]

Randall wrote a number of articles on the origin and growth of kidney stone [9–12] and suggested that kidney stones are formed attached to two types of pre-calculus lesions. Sub-epithelial deposits of calcium phosphate (CaP) and calcium carbonate, arising from pathologic conditions of the renal papilla, break through the papillary surface exposing themselves to the calyceal urine and establishing, what he called a pre-calculus lesion type 1, which is currently referred to as Randall's plaque (RP). Another type of lesion is formed when excessive urinary supersaturation and necrosis of tubular epithelial cells causes crystallization of stone salts in and plugging of the terminal collecting ducts creating a pre-calculus lesion type 2, and may now be referred 2 to as Randall's plug (RG). Most idiopathic calcium oxalate (CaOx) stones develop from RPs. Considering the severity of the problem, the Editorial Team at Urolithiasis decided to devote a special issue to Randall's Plaques, requesting experts in the area to review the subject from their own perspectives.

Dr. Daudon and colleagues provided information about RPs based on the analyses of 45,774 calculi referred to the Necker Hospital Stone Laboratory, Paris, France. Thirty-nine % of all spontaneously passed stones showed a depression or umbilication on one side, a sign of development attached to the papillary tip. Microscopic examination showed the depression contained calcified tubules. Some of the tubules were plugged with CaP while the others were empty but surrounded with calcified walls. Plaques, as expected, were mostly made of carbonate apatite. Fourteen additional crystalline species, including sodium hydrogen urate, were also identified.

Dr. Williams has pioneered the use of micro-computed tomographic (micro-CT) imaging to study the internal structure of RPs. His group's results show that interstitial plaque contains homogeneously distributed CaPas opposed to the layered arrangement of crystals in the

associated stone growing into the urine. This would suggest the involvement of different mechanisms in the growth of the plaque and the stones attached to it.

Dr. Evans and his colleagues provided a summary of their work investigating various types of stones and proposed four basic mechanisms for their formation. Idiopathic CaOx stones are formed attached to the RPs, with the plaque being apatite and stone mostly CaOx monohydrate. The development of stones on crystalline plugs protruding out of the ducts of Bellini is seen in many types of stones. Other two types of 3 stones are seen in patients with cystinuria and are more likely formed free in urine. Some are seen within the lumens of dilated inner medullary collecting ducts behind the plugged ducts of Bellini, while others in the urine inside the calyces and renal pelvis.

Dr. Grases and associates examined spontaneously passed CaOx monohydrate (COM) and dihydrate (COD) stones. COM stones appeared to have developed attached to the plaque while COD grew unattached. In addition urinary data indicated that COM stone patients showed signs of renal oxidative stress. The authors concluded that oxidative stress may be responsible for papillary injury leading to intra-papillary calcification.

Based mostly on histological analyses, plaques are proposed to start in the basement membrane of the loops of Henle. Dr. Stoller has, however, proposed a vascular hypothesis of RP formation. According to this hypothesis, arenal papillary vascular system with turbulent flow, relative hypoxia and hyperosmolarity is prone to vascular injury and the formation of plaques.

Dr. Tiselius discusses the importance of CaP in the formation of CaOx kidney stones, and tactics to reduce CaP activity products as a preventive treatment for stone recurrence. Calcium phosphate crystals forming in the Loops of Henle or distal tubules are transported into the interstitium depositing in their basement membrane and developing into the RPs. He also raises an important point about permanence of the RP.

Dr. Robertson suggests that the initiation of stone formation can be explained by both the Randall's Plaque theory and the Free-Particle theory. He has updated his program which calculates the supersaturation of tubular fluid at 0.1 cm increments 4 through the renal tubules. This analysis shows that the relative supersaturation of both calcium phosphate and calcium oxalate are increased at the end of the descending limb of the Loop of Henle. The degree of relative supersaturation (RS) of both salts is increased even further in the so-called long Loops of Henle. Spontaneous nucleation of calcium phosphate is more likely than that of calcium oxalate but, once nucleated, the calcium phosphate may then heterogeneously nucleate calcium oxalate under the prevailing conditions. The increase in the RS of calcium phosphate may also account for the formation of Randall's Plaques (type 2). The analysis also shows that supersaturation with respect to calcium oxalate reaches a second much higher peak in the latter section of the collecting ducts. The larger crystals and aggregates of CaOx observed in the urine of recurrent stone-formers are the result of crystals nucleated, perhaps heterogeneously by calcium phosphate, at the end of the descending limb of the Loop of Henle and the smaller crystals of CaOx are those nucleated spontaneously in the latter half of the collecting ducts.

Dr. Gambaro and associates are in agreement with the hypothesis that stones formed attached to RPs have different etiologies from those developing over RGs. It is important to performa clinical work up to determine the etiology for improved treatment options.

Animal models, even when they do not fully mimic the disease, play an important role in elucidating pathogenesis of human diseases. To date it has not been possible to induce the formation of Randall's plaque in animals. A number of genetically engineered mouse models of interstitial papillary nephrocalcinosis have been developed. Dr. Wu provides a comprehensive up to-date review of these mice models including mice 5 deficient in Tamm-Horsfall protein (THP), osteopontin (OPN), both THP and OPN, sodium phosphate co-transporter 2a, and sodium/hydrogen exchanger regulatory factor.

Dr. Gower's laboratory is investigating the role of macromolecules in bio-mineralization. They report that concentrically laminated spherulites similar to those seen in the RPs can be produced in vitro using a polymer-induced-liquid precursor (PILP) process in which acidic polypeptides. These are also similar to those present in renal tissue and urine and they induce a liquid phase amorphous precursor to the mineral. They discuss the hypothesis that kidney stones are formed through non-classical crystallization induced in part by macromolecules present in the urine.

I provide the evidence that deposition of CaP in the renal interstitium and its growth into RP formation is similar to pathological biomineralization seen elsewhere in the body. Under abnormal urinary conditions the renal epithelial cells acquire an osteoblastic phenotype. The production of bone-specific proteins is increased and that of crystallization inhibitors is decreased. Crystals of biological apatite are produced at the basal aspect of the epithelium. Mineralization continues through the interstitium by heterogeneous nucleation supported by collagen fibers and membranous cell degradation products. Once the front reaches the papillary surface, epithelial integrity is breached through a combination of physical force and matrix metalloproteinases thus exposing the plaque to the urine which is metastable with respect to the CaOx. Stone formation begins either by the transformation of outer layer of CaP crystals into the CaOx crystals or by matrix supported nucleation of CaOx on the plaque surface.

It is apparent that RPs, RGs, and kidney stones are different entities. RPs are formed inside the kidneys, in the renal interstitium. RGs are formed in the urine of 6 the terminal collecting ducts. Stones are formed in the urine of the renal pelvis. RPs are common while RGs and stones are not. Since RGs and stones start and grow in a urinary environment, urinary supersaturation and crystallization inhibitory potential are obvious targets for therapeutic interventions. But what about the plaques? Can we stop the production of RPs? As pointed out by Dr. Tiselius, is there RP turn over? Does urinary supersaturation affect the formation of RP? Some have theorized that CaP crystals forming in the tubular lumen are responsible for the formation of RPs. In that case supersaturation will be expected to be involved in RP formation. But RPs themselves appear to be innocuous, as long as RPs are covered with an intact papillary epithelium. It is unclear, why and how do the sub epithelial RPs become exposed to calyceal urine. What causes the epithelial breach? We have come a

long way since Randall proposed his hypothesis about the origin of renal calculi. We have a much better understanding. But we still have some way to go.

References

1. Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, Novarini A. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med. 2002; 346:77–84. [PubMed: 11784873]
2. Coe FL, Keck J, Norton ER. The natural history of calcium urolithiasis. JAMA. 1977; 238:1519–1523. [PubMed: 578220]
3. Daudon M, Jungers P. Diabetes and nephrolithiasis. Current diabetes reports. 2007; 7:443–448. [PubMed: 18255008]
4. Fink HA, Wilt TJ, Eidman KE, Garimella PS, MacDonald R, Rutks IR, Brasure M, Kane RL, Ouellette J, Monga M. Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an american college of physicians clinical guideline. Ann Intern Med. 2013; 158:535–543. [PubMed: 23546565]
5. Jungers P, Joly D, Barbey F, Choukroun G, Daudon M. ESRD caused by nephrolithiasis: prevalence, mechanisms, and prevention. Am J Kidney Dis. 2004; 44:799–805. [PubMed: 15492945]
6. Khan SR. Is oxidative stress, a link between nephrolithiasis and obesity, hypertension, diabetes, chronic kidney disease, metabolic syndrome? Urol Res. 2012; 40:95–112. [PubMed: 22213019]
7. Lipkin ME, Preminger GM. Demystifying the medical management of nephrolithiasis. Reviews in urology. 2011; 13:34–38. [PubMed: 21826126]
8. Obligado SH, Goldfarb DS. The association of nephrolithiasis with hypertension and obesity: a review. Am J Hypertens. 2008; 21:257–264. [PubMed: 18219300]
9. Randall A. The Origin and Growth of Renal Calculi. Ann Surg. 1937; 105:1009–1027. [PubMed: 17856988]
10. Randall A. The etiology of primary renal calculus. International Abstract of Surgery. 1940; 71:209–240.
11. Randall A. Papillary pathology as a precursor of primary renal calculus. Journal of Urology. 1940; 44:580–589.
12. Randall A. Recent Advances in Knowledge Relating to the Formation, Recognition and Treatment of Kidney Calculi. Bull N Y Acad Med. 1944; 20:473–484. [PubMed: 19312406]
13. Raynal G, Petit J, Saint F. Which efficiency index for urinary stones treatment? Urol Res. 2009; 37:237–239. [PubMed: 19513704]