

The role of Randall plaques on kidney stone formation

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Abstract: Randall's plaque is microscopically a plaque of calcium deposited in the interstitial tissue of the renal papilla. These plaques are thought to serve as a nidus for urinary stone formation. Large amounts of Randall's plaque are unique to idiopathic calcium oxalate stone formers. Although Randall's plaques can be found in other stone formers, only in idiopathic calcium oxalate stone formers, the detailed mechanism of stone overgrowth on plaque was thoroughly studied. Calcification is invariably located in the basement membrane of the loops of Henle and from there plaques spread through the interstitium toward urothelium. Within the basement membrane, mineral deposits are individual laminated particles in which zones of crystal and organic matrix overlay each other. In the interstitium, the particles appear to fuse on the collagen bundles to form a syncytium of crystal islands in an organic sea. By loss of integrity of urothelium, regions of plaque are exposed to urine. The exposed surface will touch and be covered by molecules of urine origin, including osteopontin, Tamm Horsfall protein, and crystals formed under urine supersaturations, resulting in a ribbon of alternating matrix and crystal. Eventually crystallization escapes from matrix modulation and crystals extend outward into the space of urine and begin to form a calcium oxalate stone proper. Randall's plaque plays an important role and is prerequisite of kidney stone formation in idiopathic calcium oxalate stone formers.

Keywords: Randall's plaque; kidney calculi; nephrolithiasis

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Introduction

Critical function of the urinary system is the maintenance of normal composition and volume of body fluids; this is accomplished by glomerular filtration, tubular reabsorption, and tubular secretion of soluble and filterable plasma components. By such means, urine contains water, electrolytes, minerals, hydrogen ions, end products of protein metabolism, and other compounds that are not useful to the metabolism, energy requirements, or structure of the body. Under normal circumstances, urine will not contain solid particles (stones). Why do humans suffer from urinary stone disease? The underlying etiology of stone formation remains a mystery, although urinary stones have been noted in human remains up to 7,000 years old (1).

Theory of renal stone formation

Renal stones are solid concretions formed within the collecting system of kidney. They are usually composed of calcium oxalate monohydrate, calcium oxalate dehydrate, calcium phosphate, uric acid, cystine, etc. and organic debris or a mixture of two or several of previous components. They result from the growth of crystals into stones. Although the precise pathogenesis of urinary stone formation is unknown, most believe it is related to crystal formation, especially in the early stages. Crystals in the urine result from nucleation, the initial step whereby the urinary constituent transforms from a liquid to a solid phase in a supersaturated solution. Crystal nuclei will bind to each other to form larger particles. This process is called aggregation or agglomeration. Crystals grow via aggregation and epitaxy,

the process of oriented growth of one crystalline lattice over another crystalline lattice whose dimensions are similar (2). The presence of multiple inorganic and organic constituents in urine; interactions between promoters and inhibitors and all modulate the already complicated pathogenesis of stone formation. These particles grow into the size range of, or even greater than the inner diameter of the collecting ducts and thus might be retained (3). The aggregated particles may also adhere to the renal epithelium through the mechanism of crystal-renal cell interaction or may be retained by anatomic abnormalities, such as ectatic tubules or ureteropelvic junction obstruction. Either way, these particles will have chance to grow into clinically significant stones which may be unable to pass through the urinary tract in a spontaneous fashion.

Randall's plaque

None of these crystals would result in urinary stone formation if the nucleated crystals were flushed out by urinary flow. Crystal retention is therefore a key factor. Crystal retention will result if the crystals grow large enough to be trapped in renal tubules or if they adhere to urothelium prior to excretion. The earliest evidence of crystal retention was the finding of macroscopic plaques of subepithelial deposits of calcium crystals in renal papillae by Randall in 1937 (4,5). Randall, in his postmortem series, examined urinary calculi using hand lens. He regularly found that these calculi had a surface highly crystalline but also a portion presenting smooth and somewhat depressed, resembling a facet, suggesting mural attachment of calculi. Then he studied the location of small stones using roentgenograms and concluded that such early calculus shadows were proven to occur most regularly in the minor calices. These findings drew his attention to renal papillary lesions. He described the lesion having cream-colored area near the tip of the papilla, which appeared to be sub-epithelial. It was microscopically a plaque of calcium deposited in the interstitial tissue of the renal papilla, and definitely not intratubular. Randall implicated the renal papilla as the primary site of renal calculi unrelated to urinary stasis, infection, vitamin deficiency, hyperparathyroidism or urinary hypersecretory states. He proposed that these calcific deposits originate in damaged renal tubule epithelial basement membranes and later erode into the urinary collecting system. These plaques, now known as Randall's plaques, are thought to serve as a nidus for urinary stone formation (6,7). The incidence of calcified papillary plaques

was 17% of cadaveric renal units (4). Stoller *et al.*, by using high resolution radiography, demonstrated papillary calcifications in 57% of radiographically imaged cadaveric kidneys (7). They also showed a correlation between a history of hypertension and papillary calcifications. Based on the analysis of the cholesterol content of renal stones and the review of literature, they proposed a new hypothesis of primary stone formation event involving a vascular etiology. To further investigate the association between papillary calcifications and urinary stone formation, the presence, pattern, and distribution of Randall's plaques were mapped endoscopically in patients (6). This study revealed the incidence of plaques varied with the primary composition of extracted stones. In addition, the incidence of papillary plaques was significantly more common in patients with calcium oxalate (88%) and calcium phosphate stones (100%) than in patients without a history of urinary stone disease (43%) (6). These findings suggest that the presence of papillary plaques is associated with calcium nephrolithiasis and may contribute to the pathogenesis of calcium urinary stones.

Characteristics of Randall's plaque

Randall's plaque begins in basement membranes of thin loops of Henle (8,9). Several electron microscopic studies of Randall's plaque have led to the understanding today (10-12). Calcification was invariably located in the basement membrane of the loops of Henle, from which it extended into the medullary interstitium (8). Stoller *et al.*, by using high resolution radiography of cadaveric kidneys, found that subepithelial Randall's plaque were intimately associated with vasa recta and collecting ducts (7). Evan *et al.* reported that the basement membrane of the thin loops of Henle is the original formation site of Randall's plaques and from there plaques spread through the interstitium toward urothelium (8,13-15). Bushinsky thought it is reasonable and proposed a sequence of events to try to explain it, including diet calcium increasing absolute loop of Henle calcium delivery, medullary countercurrent mechanism concentrating calcium extracted from the thick ascending limb of the loop of Henle into the hypertonic papilla, increased calcium concentration in the vasa recta not allowing its removal from the interstitium, increased serum calcium stimulating calcium receptor and decrease reabsorption of water in the collecting duct, vectorial proton transport into collecting duct increasing alkalization of the interstitium decreasing the solubility of calcium phosphate

complexes, systemic and probably vasa recta pH increase following gastric secretion resulting in less bicarbonate removal from medullary interstitium, the pH increase in the medullary interstitium decreasing the solubility of calcium phosphate complexes, and an extracellular matrix protein providing the site for heterogeneous nucleation (9,16).

Within the basement membrane, mineral deposits are individual laminated particles in which zones of crystal and organic matrix overlay each other (8,14,15,17,18). The mineral in the individual particles was always determined to be calcium phosphate (8,15). In the crystal matrix interface, osteopontin was identified (15,19), while heavy chain 3 of the inter-alpha-trypsin molecules was located in the matrix (15,20). In the interstitium, the particles appear to fuse on the collagen bundles to form a syncytium of crystal islands in an organic sea (15,17,18). There was no evidence of cell injury, inflammation, interstitial fibrosis or intratubular crystal deposition in the renal biopsies of idiopathic calcium oxalate stone formers (15,21). The calcification processes like physiological, primarily in the extracellular matrix bone, cartilage, and teeth, and ectopic, common in soft tissue in response to injury and mineral imbalance, calcification processes. The original formation of Randall's plaques in the basement membrane of the thin loops of Henle resembles the ectopic calcification process. It was thought as a passive process before but was recently reported to be a regulated process. Crystal deposition at various sites in the body is a result of an imbalance between forces that inhibit precipitation and those that promote it (18,22).

Stone overgrowth on Randall's plaque

In 1937, Randall noticed that some renal stones attached to interstitial plaques in renal papillae (4,5). This finding was subsequently confirmed endoscopically (17,23). These interstitial plaques (Randall's plaque) seem to be benign calcification process because on biopsy of renal papillae, no tissue inflammatory reaction or cell injury could be identified (15,21). This occurs primarily in idiopathic calcium oxalate stone formers, calcium oxalate stone formers without systemic disease apart from familial hypercalciuria. Large amounts of Randall's plaque are unique to idiopathic calcium oxalate stone formers and correlate with urine volume, urine calcium level, and urine pH (15,24) as well as the number of stones adjusted for duration of stone formation (15,25). Although Randall's plaques can be found in other stone formers, such as primary hyperparathyroidism stone formers, stone formers with ileostomy or small bowel resection, and

brushite stone formers, only in idiopathic calcium oxalate stone formers, the detailed mechanism of stone overgrowth on plaque was thoroughly studied (14).

Evan *et al.* made a great contribution to this field and lead to our understanding at present (8,13-15,17,19-21). To quote their findings, when Randall's plaque grows and penetrates urothelium, either due to urothelial cell damage or cell death, into space of urine, the exposed surface will touch and be covered by molecules of urine origin, including osteopontin, Tamm Horsfall protein, and crystals formed under urine supersaturations, resulting of a ribbon of alternating matrix and crystal. The crystallization process continues under the drive of urine supersaturations. Enough crystallization eventually escapes from matrix modulation, more calcium phosphate forms and calcium oxalate comes to predominate. Transition from calcium phosphate with some calcium oxalate crystals to only calcium oxalate crystals, the actual stone is progressively developing (8,13-15,17,19-21). For calcium oxalate stones formation and growth in idiopathic calcium oxalate stone formers, Randall's plaques play an important role and are prerequisite. The majority (approximately 75%) of calcium oxalate stones is formed attached to sites of Randall's plaque and represents all idiopathic calcium oxalate stone formers. In other kidney stone diseases, the stone formations are through different pathways (13-15).

Conclusions

Randall's plaque plays an important role and is prerequisite of kidney stone formation in idiopathic calcium oxalate stone formers. It begins in the basement membrane of the loops of Henle, from which it extended into the medullary interstitium. By loss of integrity of urothelium, regions of plaque are exposed to urine. The urine molecules, osteopontin and Tamm Horsfall protein, and crystals in urine, driven by supersaturations, react with the exposed plaque to form a ribbon of alternating matrix and crystal layers by repeated coating and crystallization. Eventually crystallization escapes from matrix modulation and crystals extend outward into the space of urine and begin to form a calcium oxalate stone proper. Although Randall's plaque can be found in other stone formers, its role on kidney stone formation might not be important as its role in idiopathic calcium oxalate stone formers.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

- Menon M, Resnick MI. Urinary lithiasis: etiology, diagnosis, and medical management. In: Walsh PC, Retik AB, Vaughan ED, et al. eds. *Cambell's Urology*, 8th ed. Philadelphia: Saunders, 2002:3229-305.
- Mandel NS, Mandel GS. Epitaxis in Renal Stone. In: Wickman JEA, Buck AC. eds. *Renal Tract Stone: Metabolism Basis and Clinical Practice*. London: Churchill Livingstone, 1990:87-101.
- Kok DJ, Khan SR. Calcium oxalate nephrolithiasis, a free or fixed particle disease. *Kidney Int* 1994;46:847-54.
- Randall A. The origin and growth of renal calculi. *Ann Surg* 1937;105:1009-27.
- Randall A. Papillary pathology as precursor of primary renal calculus. *J Urol* 1940;44:580-9.
- Low RK, Stoller ML. Endoscopic mapping of renal papillae for Randall's plaques in patients with urinary stone disease. *J Urol* 1997;158:2062-4.
- Stoller ML, Low RK, Shami GS, et al. High resolution radiography of cadaveric kidneys: unraveling the mystery of Randall's plaque formation. *J Urol* 1996;156:1263-6.
- Evan AP, Lingeman JE, Coe FL, et al. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. *J Clin Invest* 2003;111:607-16.
- Sepe V, Adamo G, La Fianza A, et al. Henle loop basement membrane as initial site for Randall plaque formation. *Am J Kidney Dis* 2006;48:706-11.
- Cooke SA. The site of calcification in the human renal papilla. *Br J Surg* 1970;57:890-6.
- Haggitt RC, Pitcock JA. Renal medullary calcifications: a light and electron microscopic study. *J Urol* 1971;106:342-7.
- Weller RO, Nester B, Cooke SA. Calcification in the human renal papilla: an electron-microscope study. *J Pathol* 1972;107:211-6.
- Coe FL, Evan AP, Lingeman JE, et al. Plaque and deposits in nine human stone diseases. *Urol Res* 2010;38:239-47.
- Coe FL, Evan AP, Worcester EM, et al. Three pathways for human kidney stone formation. *Urol Res* 2010;38:147-60.
- Evan AP. Physiopathology and etiology of stone formation in the kidney and the urinary tract. *Pediatr Nephrol* 2010;25:831-41.
- Bushinsky DA. Nephrolithiasis: site of the initial solid phase. *J Clin Invest* 2003;111:602-5.
- Evan A, Lingeman J, Coe FL, et al. Randall's plaque: pathogenesis and role in calcium oxalate nephrolithiasis. *Kidney Int* 2006;69:1313-8.
- Khan SR, Rodriguez DE, Gower LB, et al. Association of Randall plaque with collagen fibers and membrane vesicles. *J Urol* 2012;187:1094-100.
- Evan AP, Coe FL, Rittling SR, et al. Apatite plaque particles in inner medulla of kidneys of calcium oxalate stone formers: osteopontin localization. *Kidney Int* 2005;68:145-54.
- Evan AP, Bledsoe S, Worcester EM, et al. Renal inter-alpha-trypsin inhibitor heavy chain 3 increases in calcium oxalate stone-forming patients. *Kidney Int* 2007;72:1503-11.
- Evan AP, Coe FL, Gillen D, et al. Renal intratubular crystals and hyaluronan staining occur in stone formers with bypass surgery but not with idiopathic calcium oxalate stones. *Anat Rec (Hoboken)* 2008;291:325-34.
- Giachelli CM. Inducers and inhibitors of biomineralization: lessons from pathological calcification. *Orthod Craniofac Res* 2005;8:229-31.
- Matlaga BR, Williams JC Jr, Kim SC, et al. Endoscopic evidence of calculus attachment to Randall's plaque. *J Urol* 2006;175:1720-4; discussion 1724.
- Kuo RL, Lingeman JE, Evan AP, et al. Urine calcium and volume predict coverage of renal papilla by Randall's plaque. *Kidney Int* 2003;64:2150-4.
- Kim SC, Coe FL, Tinmouth WW, et al. Stone formation is proportional to papillary surface coverage by Randall's plaque. *J Urol* 2005;173:117-9; discussion 119.

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