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Beginnings of nephrolithiasis: insights into the past, present and future of Randall's plaque formation research

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Purpose of review

Kidney stones form as a result of heterogeneous nucleation on a calcium phosphate lesion in the renal papilla known as Randall's plaque. Stone disease has plagued humans for millennia with relatively little progress made in the realm of prevention. An understanding of the historical aspects of research into Randall's plaque is necessary to interpret novel correlative imaging discoveries. Focus for the past several decades has been on the distal papillary tip, and the overlooked Anderson–Carr–Randall progression is revitalized with novel supporting evidence.

Recent findings

Novel correlative techniques of three-dimensional micro-XCT imaging combined with electron and light microscopy techniques have revealed that the earliest mineralization event in the papilla is a distinct event that occurs proximal to the region where Randall's plaque has traditionally been identified.

Summary

The history of Randall's plaque research and the Anderson–Carr–Randall progression is reviewed. Proximal intratubular mineral deposits in normal and Randall's plaque affected papillae may be a target for future therapeutic interventions for nephrolithiasis. Further collaboration between nephrologists and urologists is necessary to cure this debilitating disease.

Keywords

correlative microscopy, micro-XCT, nephrolithiasis, prevention, Randall's plaque

INTRODUCTION

Two principal mechanisms of stone formation are recognized [1]. Firstly, stones may undergo homogeneous nucleation by forming in a free solution away from a surface as in the case of cystinuria [2]. Secondly, stones may undergo heterogeneous nucleation from the surface of a plug embedded in the duct of Bellini especially in patients with hyperoxaluria and distal renal tubular acidosis after gastric bypass. Stones can also form by heterogeneous nucleation within the renal collecting system attached to a calcium phosphate nidus within the distal renal papilla known as Randall's plaque. Such mechanisms limit the sequence of stone formation to the classic thought that all large stones were initially an agglomeration of small particles.

Randall's plaque is considered to be the nidus for most calcium-based stones. This review will be substantiated with the recent visualization of bio-minerals in the proximal renal papilla, as precursors and plausible 'seeds' for kidney stones, using higher

resolution correlative imaging techniques. The findings from this interdisciplinary approach will highlight the need to shift the paradigm regarding the knowledge of urinary stone formation and establish a congruency with clinical care through insights that would help prevent future stone 'formation.

DISCOVERY OF RANDALL'S PLAQUE

Reports of kidney and bladder stones span millennia, with documented cases of stone disease occurring as early as 7000 years ago in Egypt [3]. While

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KEY POINTS

- Relatively little progress has been made over 6000 years in understanding and preventing kidney stone disease.
- Randall's plaque begins more proximally than commonly reported, in the form of intratubular mineral deposits.
- Form guides function; the paraboloid architecture of the renal papilla promotes mineral deposition based upon Poiseuille's law and the Venturi effect.
- The Anderson–Carr–Randall progression is reviewed and may represent a tenable sequence of events in the progression of Randall's plaque.
- Proximal intratubular mineral deposits present a temporally distinct opportunity to intervene with future pharmacologic developments that should be developed through collaborative, multidisciplinary approaches.

'cutting for [urinary] stone' is considered one of the earliest surgical procedures, relatively little has changed in our conceptualization of this disease over several hundred years. The epidemiology of the disease was reasonably characterized as early as the 1600s, with physicians remarking on the incidences of uric acid stones among the obese and phosphate/infection stones among the poor [4]. Cursius–Curtius observed in 1662 the role of mucus in the formation of what were likely matrix stones. Inhibitors have been recognized as early as 1879 when Ord investigated calcium oxalate, calcium carbonate and uric acid solubility and noted the inhibitory effects of magnesium [4]. It was not until the 20th century that an inciting lesion, Randall's plaque, was identified.

In 1937, Alexander Randall composed a treatise in which he systematically examined the contemporary theories on the genesis of kidney stones and discovered the lesion now known as Randall's plaque [5]. Due to limited evidence at the time supporting the theories of urinary stasis, infection, vitamin deficiency, colloidal chemistry and parathyroid hyperfunction, Randall and colleagues undertook a multitude of experiments to better define the cause of nephrolithiasis with little success. Finally, they turned to the dissection of 429 pairs of cadaveric kidneys and were able to detect a 'cream colored' papillary lesion in 73, or 17% of those patients who were described as 'a plaque of calcium in the interstitial tissue of the renal papilla, and definitely not intratubular' ([5] pp. 1018). Calcium oxalate stones were even observed to be attached to some of these papillary lesions, which were found to be

composed of calcium phosphate, leading to the supposition that this plaque was the 'initiating lesion' or seed for those kidney stones.

Prior to further discussion on the historical aspects of Randall's plaque research, a brief discussion on the composition of Randall's plaque and the role of Randall's plaque in the formation of stones is necessary to provide sufficient context. In the renal papilla, there is a pH and concentration-driven competition between calcium and various anions, including phosphates and oxalates, as they accumulate. *In vivo*, within the papillary interstitium, phosphate binding to calcium tends to predominate stoichiometrically over oxalates, which may explain calcium, phosphat predominance in Randall's plaque [6]. One of the main challenges in elucidation of the mechanism of calcium phosphate deposition is the incredible complexity that unfolds as calcium and phosphorus along with other elements form clusters and repeatedly shift from one phase to another in a process driven in part by pH and chemical concentration gradients permitting varying organic and inorganic ratios within the higher-ordered mineral deposits [7].

Although Randall's plaque is primarily composed of calcium phosphate, the traditional view of Randall's plaque as an agglomerate of homogeneous mineral has been challenged by the detection of magnesium in calcium phosphate as whitlockite ($\text{Ca}_9(\text{MgFe})(\text{PO}_4)_6\text{PO}_3\text{OH}$), a form of calcium phosphate within Randall's plaque [8,9]. Whitlockite forms in the presence of magnesium and is thought to have a role in defining if the phase of calcium phosphate will be amorphous or crystalline [10]. Therapeutic mechanisms exploiting the inhibitory effect of magnesium towards calcium phosphate mineral formations [7] may have a role in the future treatment of recurrent nephrolithiasis.

Calcium phosphate is a compound with a variety of compositional phases resulting from metastable precursors and precipitating reactions, making a comprehensive understanding of biomineralized lesions challenging. In supersaturated interstitial solutions, there is a precursor phase to hydroxyl apatite ($\text{Ca}_5(\text{PO}_4)_3(\text{OH})$) formation, with brushite ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$) and octacalcium phosphate ($\text{Ca}_8\text{H}_2(\text{PO}_4)_6 \cdot 5\text{H}_2\text{O}$) tending to form in more acidic solutions [2,7]. The least soluble, but most predominant, precursor phase is carbonated apatite. Carbonated apatite tends to form under relatively alkaline conditions [11] and consists of spherical calcium phosphate clusters that aggregate and form larger spheres [12,13]. Spherical structures have been independently described during calcium phosphate precipitation *in vitro*, and in the renal papilla and other tissues several times over the last five decades and

will be referred to here as calcified nanoparticles (CNPs) [13–20].

PROPAGATION FROM RANDALL'S PLAQUE TO STONE

An axiom in the study of crystallization is that particles must be retained at a nidus [2]. In the case of renal stone formation, that nidus is thought to be the Randall's plaque after it has eroded through the surface epithelium of the papilla, exposing the plaque to the urinary space [21]. Patients with traditional risk factors for nephrolithiasis, including low urine volume, high urine calcium and previous stone disease have been found to have more numerous Randall's plaque [22,23]. In fact, stones are often found attached to a renal papilla at the time of endoscopy, and many times retrieved stones exhibit a concavity matching the contour of the papillary surface [5]. At this concavity, a 'cream color' material was described by Randall in 1937 and herein will be referred to as a 'stem' from which a calcium oxalate stone may propagate.

Stems (also at times referred to as 'stalks' [24]) have been shown to consist largely of calcium phosphate, similar to interstitial Randall's plaque and are believed to have eroded through the renal epithelium [24,25]. Upon closer examination, these calcium phosphate plaque deposits are not limited to the surface concavities of oxalate stones but are also in the deeper layers of the stones. Randall's plaque is thought to be a site for heterogeneous nucleation once exposed to urine in the renal collecting system [15,24,26]. Urine, being concentrated and at times supersaturated, offers an ideal solution (depending on pH) from which oxalates, phosphates and uric acid may precipitate on exposed Randall's plaque [27]. Analyses of hundreds of such stone specimens revealed that about 90% of stems are composed of calcium phosphate, but some also contain whewellite ($\text{CaC}_2\text{O}_4\text{H}_2\text{O}$), proteins, glycosaminoglycans and lipids [28]. In some unusual cases, stems were found to contain significant amounts of sodium hydrogen urate and uric acid [28].

Anderson–Carr–Randall progression

Based upon the novel findings of Randall in 1937, work by other scientists through the 1940s and 1950s began a golden age in research on the development of kidney stones and the pathogenesis of Randall's plaque. First, in the 1940s, Anderson was able to histologically identify microscopic calcifications throughout the papilla and classified them as a potentially normal physiologic process [29]. Later, in the 1950s, Carr performed flat plate 2-D

radiography on cadaveric kidneys and identified spherical mineral 'droplets' not just at the tip of the renal papilla but also towards the renal cortex [30]. Carr's proposed mechanism for the proximal deposition and distal interstitial propagation of calcified droplets was through a lymphatic transit process.

Drawing upon these works, Bruwer was able to synthesize a stepwise dogma known as the Anderson–Carr–Randall progression [31]. In this theory, these microscopic calcifications migrate via lymphatic fluid-flow from the proximal papilla to the distal interstitium and subsequently become Randall's plaque. These proximal calcifications were later identified to be within tubules in the proximal renal papilla by transmission electron microscopy [32]. Causative evidence that links the proximally observed *intratubular* mineralization to distal *interstitial* Randall's plaque in support of the Anderson–Carr–Randall Progression has yet to be identified.

Interstitial mineralization

In the following decades, attention was directed primarily to the interstitial plaque itself and Anderson's proximal calcifications were largely forgotten or overlooked except by Bruwer [31]. In the 1970s, Cooke [33] observed calcification within 43 of 62 otherwise normal kidneys, most often in the basement membrane of the thin loops of Henle extending into the surrounding interstitium. In nine of the specimens, small amounts of calcium were detected in the renal cortex. Similarly, in 1971, Haggitt and Pitcock [20] used transmission electron microscopy to identify laminated spherical bodies of mineral (CNPs) within the interstitium and along basement membranes of tubules in the papilla. In 2003, Evan *et al.* [17] confirmed Cooke's observation that, in the renal papillary tip, the basement membrane of the thin loop of Henle is involved with agglomerating CNPs, forming Randall's plaque that can be grossly identified as cream coloured substrate in stone-forming patients. Moreover, the lumens remain patent and spared in Randall's plaque, despite extensive interstitial mineralization. These CNPs have repeatedly been observed to accumulate, forming larger interstitial deposits within a network of globular proteins such as osteocalcin, bone sialoprotein and osteopontin and fibrillar collagen predominantly of type 1 [34]. Although this process has been observed in a variety of biominerals, the mechanisms by which CNPs aggregate to form larger structures such as mineralized plaque remain poorly understood and warrant further investigation [13].

Within the loop of Henle, in-vitro studies have calculated that concentrations of calcium

phosphate tend to reach supersaturation [35]. It is conceivable, given the physiologic stresses of a western diet (high in salt and acid-rich protein), poor oxygenation within the papillary tip due to a paucity of blood vessels relative to the volume of fluid flow, and the steep concentration gradients needed for countercurrent exchange that biomineralization is inevitable in the papillary interstitium. Bushinsky [36] has postulated that, especially in states of poor hydration or hypercalciuria, calcium and phosphate supersaturation can be routinely expected in the renal pyramid. Furthermore, the close approximation of vasa recta and collecting ducts can create a hypertonic and alkaline interstitial environment, promoting calcium phosphate mineralization (with carbonated apatite being distinct from calcium carbonate), despite low transtubular permeability of the thin limbs of the loop of Henle [16].

A variety of pathophysiologic mechanisms have been proposed to explain Randall's plaque development, but none have been proven. Posey and Anderson [37,38] had first hypothesized that perhaps a vascular insult could initiate the Randall's plaque. Later, Stoller *et al.* [39] suggested that Randall's plaque may form in a manner similar to that of an atherosclerotic plaque, due to observed elevations in the levels of free and esterified cholesterol within urinary stones. Along other lines, Lieske *et al.* [40] observed that renal epithelial cells were able to phagocytose calcium oxalate monohydrate crystals, possibly in defense against crystaluria and perhaps resulting in renal papillary mineralization. More recently, attention has turned to the architecture of the renal papilla, which is defined by the property of 'functional zonation' in that each segment, consisting of varied numbers of nephrons and vascular association/densities is also composed of different cell types. These cell types exist in an independent microenvironment and are responsible for distinct functions due to unique physical and physiochemical properties [32^{***}].

Architecture: form and function

The human renal papilla is a protrusion of the medulla and exhibits a paraboloid architecture and shape. The medulla can be subdivided into regions with differing patterns of microvasculature as well as segments containing different nephron cell types. As the vascular network that supplies blood to the medulla travels distally, it becomes increasingly subdivided and sparse by variation in vascular density, contributing to a relative degree of ischemia in the papillary tip. The nephron is several centimetres in length and in some cases traverses multiple regions within the renal papilla of a human

kidney. The glomeruli and convoluted tubules mainly reside within the renal cortex, while the descending limb, loop of Henle and the ascending limbs reside within the medulla.

Two distinct types of nephrons can be identified as well, in varying ratios by species; the short nephron and the long nephron, with the latter being more centrally located and taking advantage of the vertex length of the paraboloid-shaped papilla. The lengths of the nephrons vary based on their central or peripheral locations, distinct cell types and differential expressions of aquaporins and other transporters [41,42]. With the premise of architecture linked to function in mind, Hsi *et al.* [32^{***}] recently sought to link the calcifications first appreciated by Anderson in the proximal renal medulla to the development of distal Randall's plaque by taking into account the unique architecture of the shorter and longer nephrons in the paraboloid-shaped papillary complex.

Integrated theory: multiscale form and function of the renal papilla

Hsi *et al.* [32^{***}] postulated that flow mechanics within the papilla were influenced by the length and diameter of nephrons, which varied as described above. The important fluid characteristics of pressure and volumetric flow rate in a tube with variable radius and length can be described by Poiseuille's law, where pressure is proportional to viscosity, length and flowrate but inversely proportional to the fourth power of the radius [43]. The peripherally located shorter nephrons would be expected to have lower velocity of fluid flow, while the centrally located longer nephrons would have higher velocity of flow. Pressure should increase significantly for a small change in radius between thin and thick limbs of the loop of Henle of any given nephron. So as to maintain continuity of mass and energy, the Venturi effect will apply to the junction of the thick and thin limbs of the loop of Henle. This effect causes fluid velocity in the nephron at the transition to increase (i.e. like a nozzle on a fire hose) and may be a mechanism by which urine is propelled through the nephron and into the collecting system.

Previous research by Asplin *et al.* [35] has shown that the intratubular fluid in the nephron is likely supersaturated with calcium. In the peripheral, shorter nephrons, fluid velocity is lower and would favor particle deposition relative to rapid flow in the longer centrally located nephrons. This particle deposition was found to be the initial site of deposition based on correlative microscopic observations of proximal minerals in human renal papillae without Randall's plaque [32^{***},44]. Human papillae with

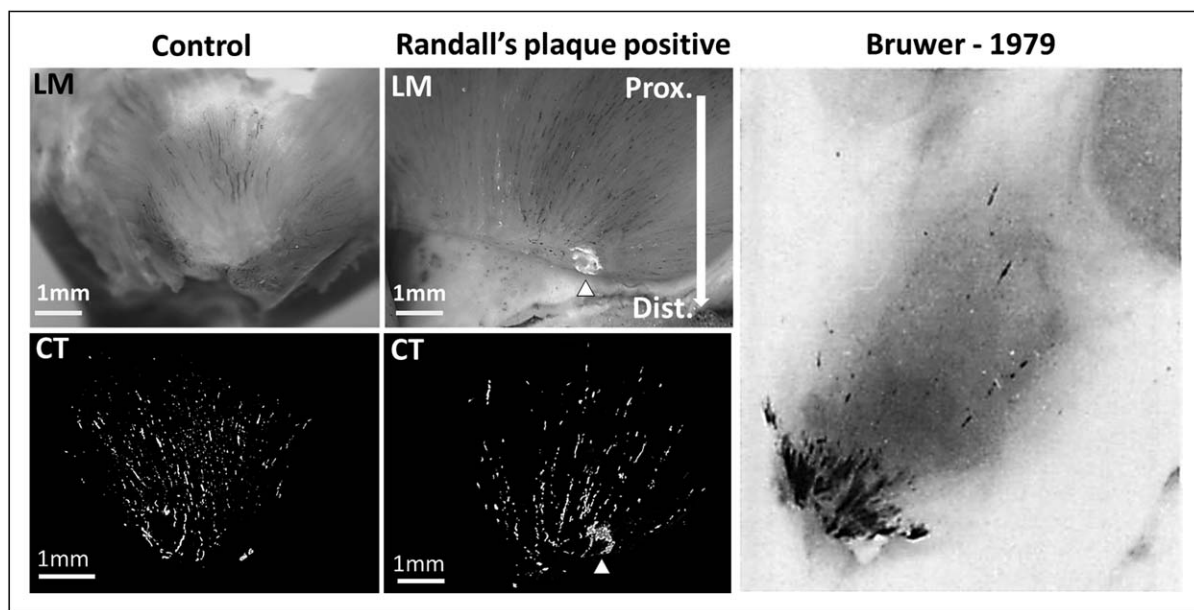


FIGURE 1. Modern and historical identification of proximal intratubular mineral deposits. Top row: Demonstration of intratubular minerals on radiographic imaging. Light micrographs (LM) of excised human papilla (UCSF Institutional review board approval #14-4533) demonstrate a normal papilla (left) and with Randall's plaque (arrowhead, right). Bottom row: micro-XCT reconstructions of those same papillae, with demonstrable intratubular concretions in both specimens, and the grossly visible Randall's plaque again demonstrated. Light and micro-XCT micrographs are contrasted with a flat plate radiograph. Reproduced with permission from [31], showing a similar pattern of proximal mineral deposits in 1979.

Randall's plaque have always been observed to contain initial proximal biominerals (Fig. 1). On the basis of these findings, there appears to be a defined temporal sequence in the progression of renal biomineralization initially from the proximal but peripheral, tubular calcifications and subsequently to the distal but central interstitial biominerals (Fig. 2). Proximal intratubular minerals are hypothesized to be the beginnings of endoscopically appreciated Randall's plaque [32⁴⁴].

CONCLUSION

For many years, the interstitial CNP in the basement membrane of the thin loop of Henle was considered the inciting event in the pathogenesis of Randall's plaque [17]. Studies evaluating this inciting event leading to stone formation within the papilla have been limited by the collection of endoscopic biopsies from the distal papillary tip [15,17,24]. Novel investigative techniques such as high resolution correlative microscopy techniques are allowing for the detection and analyses of mineral from all zones of the human renal medulla in three dimensions. Proximal intratubular mineralization has been observed in contrast to the traditional, distal, interstitial mineral composing Randall's plaque even in specimens without visible Randall's plaque [32⁴⁴].

Recent data presented in this manuscript supports Anderson–Carr–Randall progression (proposed in 1979 by Bruwer [31]), which also views proximal calcifications as precursors to Randall's plaque. The postulates that could promote Randall's plaque formations remain unclear and warrant further investigation through systematic studies. Despite the complexity of the renal papilla, containing a variety of cells, tubules of varying lengths and cross sections, and ion counter-current exchange processes, basic physical processes founded on Poiseuille's law and the Venturi effect could help explain the process of renal biomineralization.

The papilla remains the urologist's window into the world of the nephrologist. Although it has been recognized since the days of Alexander Randall that Randall's plaque bridges the gap between aberrant renal physiology (the domain of the nephrologist) and a soon to be obstructing renal calculus (that of the urologist), there have been minimal interdisciplinary collaborations and approaches to study the pathogenesis of Randall's plaque formation, a nidus from which calcium-based stones form. Perhaps with the identification of anatomically specific intratubular biomineralization as a temporal precursor to Randall's plaque, urologists and nephrologists now have a potential avenue for the collaborative development of a targeted pharmacological intervention.

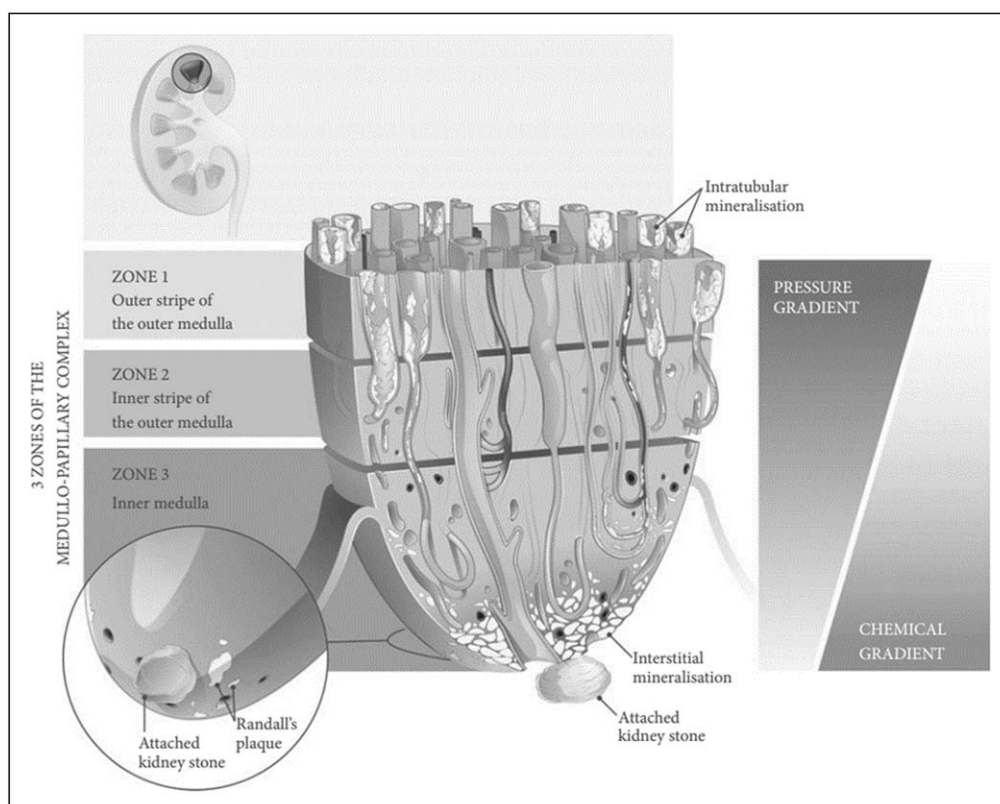


FIGURE 2. Novel concept of biomineralization within the renal medullo-papillary complex. Randall's plaque is seen in the interstitium of the inner medulla (zone 3) with an attached kidney stone, formed by heterogeneous nucleation. Newly identified areas of mineralization are intratubular and seen in zones 1 and 2. As the functional volume of the papilla decreases, pressure gradient alterations drive a mechanoresponsive switch resulting in biomineralization at the papillary tip. Figure reproduced with permission from [32].

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Conflicts of interest

SVW and SPH have nothing to disclose. MLS is the Founder of Applaud Medical.

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