Anatomy & Physiology: Current Research
ISSN: 2161-0940

Callaghan and Bandyopadhyay, Anat Physiol 2012, 2:4
DOI: 10.4172/2161-0940.1000e118

Editorial Open Access

Calcium Phosphate Kidney Stone: Problems and Perspectives

Daniel Callaghan and Bidhan C. Bandyopadhyay*

Calcium Signaling Laboratory, DVA Medical Center, Washington DC, USA

Acute renal colic due to kidney stones is probably the most excruciatingly painful event a person can endure. This painful event, which starts without warning, is often described as being worse than childbirth, broken bones, gunshot wounds, burns, or surgery. Kidney stone disease, or nephrolithiasis, is a common disease that is estimated to produce medical costs of $2.1 billion per year in the United States. Renal colic affects approximately 1.2 million people each year and accounts for approximately 1% of all hospital admissions. The incidence of kidney stone disease has been increasing in the United States over recent years and it is now estimated that approximately 5% of American women and 12% of American men will be affected at some point in their lives [1]. Since the majority (80%) of these stones are found to be calcium oxalate (CaOx) [2,3], the research conducted over the past three to four decades has largely been focused on delineating the mechanism of formation of CaOx stones [4]. Interestingly, a documented increase in the prevalence of calcium phosphate (CaP) stones in the kidney over the past two decades [5] suggests an epidemiological shift and thus signifies a greater demand for focused research onto such CaP stone formation. Furthermore, the fact that most extraskeletal calcium deposits throughout the body are of CaP origin lends the belief that a better understanding of CaP deposition in the kidneys will compliment scientific research involving other forms of calcinosis. These other diseases associated with idiopathic extraskeletal calcifications are also common medical problems [6,7]. Among them the most common diseases include vascular calcification, dental pulp stones, gall stones, salivary gland stones, testicular microliths, calcification in hemodialysis patients, calcific aortic stenosis, calcific tendonitis and arthritis. Life-threatening calcification may occur after hemodialysis, in scleroderma, and in patients with sclerotic aortic valves.

While the precise stimuli for calcium salt deposition in these diseases are currently unclear, the core idea of the mechanism of calcium biomineralization is centered on the pH and physiologic phosphate and calcium concentrations in tubular fluid. Nephrolithiasis is a multifactorial disease, and while much of the physical chemistry involved in the disease has been delineated, the initiating factor and subsequent steps ultimately leading to stone formation is still unknown [8]. One of the most basic rules governing the physical chemistry of stone formation is that of supersaturation of the urinary constituents. The main determinants of calcium phosphate supersaturation are urine calcium concentration and pH. Calcium can only remain soluble in urine up to a certain point, known as the upper limit of metastability (ULM), above which a solid phase of CaP (or CaOx) forms [9]. While non stone formers have been known to be able to raise the ULM to prevent crystallization, this ability seems to be lost in some stone formers, which leads to crystallization [10]. Factors affecting CaP stone formation mainly include i) supersaturation of free (unbound) ions such as calcium and phosphate, both of which are highly dependent on pH; ii) the presence or absence of inhibitors (i.e., osteopontin, citrate, pyrophosphate, as well as at least a dozen other proteins and glycosaminoglycans) which impede the nucleation, growth and aggregation of crystals; iii) the ability of crystals to anchor to renal tubular epithelium, leading to further growth and aggregation of crystals; iv) the occurrence of various anatomical abnormalities such as horseshoe kidney malformation, polycystic kidney, and obstructions [8]; v) medications such as acetazolamide, calcium antacids, glucocorticoids, loop diuretics, theophylline, and vitamin D [9,11]. In living systems, all of these factors are intertwined with each other, along with the overwhelming complexity of cellular behaviors, regulatory pathways, and differences in renal pathology in individuals. This poses a great challenge in the ability to understand and predict the biomineralization process. To date, the mechanism by which crystals grow into stones is still poorly understood. For instance, some suggest that the attachment of preformed microcrystals to the surface of renal tubular cells leads to the further deposition of crystals and eventual formation of full-sized stones. Other researchers emphasize the free solution crystallization mechanism in which direct crystal growth of stones starts from a nucleolus by means of a continuous crystallization process periodically inhibited by organic molecules [2]. Since the fundamental process of nucleation of CaP stones lies in the regulation of Ca^{2+} and PO_4- ion concentrations, the most important question in future research would be to determine the molecular mechanism of regulation of these ions in the tubular fluid.

While the exact pathogenesis of stone formation remains a mystery, several hypotheses abound. A much abridged one put forward by Hans-Göran Tiselius follows: Stone formation is thought to begin in the thin descending segment of the Loop of Henle due to its high calcium and phosphate concentrations as well as high pH [12]. Depending on the size of the original CaP crystal nucleus formed it can either follow the urine stream or become internalized by the tubular cells in the loop of Henle. The mechanism of crystal internalization has been proposed to occur in one of several ways, including direct translocation to the interstitial tissue or internalization and dissolution by the tubular cells before subsequently re-precipitating in the interstitial tissue [4]. An interstitial plaque such as this is the so-called Randall's plaque which is found in all CaOx-stone formers and less frequently (43%) in individuals who form other types of stones [13]. Once the plaque is in the interstitium, there is erosion of the epithelial cells which are functioning as a barrier between the plaque and the lumen. From here, the exposed plaque acts as an anchor upon which further crystallization can occur. The fate of the plaque, however, depends on several things, the most important of which being urine pH. A low pH creates an environment favoring CaOx stones while a high pH results in pure CaP stones. The complex role of promoters and inhibitors of crystallization should not be discounted

***Corresponding author:** Bidhan C. Bandyopadhyay, Principal Investigator, Calcium Signaling Laboratory, 151 Research Service, DVA Medical Center, 50 Irving Street, NW, Washington, DC 20422, USA, Phone: (202)745-8622; Fax: (202)462-2006; E-mail: bidhan.bandyopadhyay@va.gov

Received February 25, 2012; **Accepted** February 25, 2012; **Published** March 07, 2012

Citation: Callaghan D, Bandyopadhyay BC (2012) Calcium Phosphate Kidney Stone: Problems and Perspectives. Anat Physiol 2:e118. doi:10.4172/2161-0940.1000e118

either, and as noted earlier, is thought to continue to play a role in stone formation here as well [4].

Just as the pathogenesis of CaP stones has remained elusive, there is also ambiguity as to what the best treatment modalities for CaP stones are. As with CaOx stones, there are both nonsurgical and surgical options. Nonsurgical management is usually accomplished using fluids to dilute the concentration of calcium, and thiazide diuretics to lower urine calcium excretion [9]. It has yet to be determined if the potassium citrate salts that are traditionally used to treat CaOx stones do more harm than good for CaP stone formers. This is because while they help inhibit crystallization, they also can raise urine pH, which has been shown to promote CaP stone formation [5,14]. If surgery becomes necessary, the traditional approach for kidney stones has been to use extracorporeal shock wave lithotripsy (ESWL) or percutaneous nephrolithotomy (PCNL) [15,16]. Unfortunately, CaP stones, particularly the subtype of brushite, have been found to have a decreased rate of successful treatment with both PCNL as well as ESWL [15]. While apatite stones may not be intrinsically harder to fragment than CaOx stones, they have also been found to require more ESWL procedures [17]. Furthermore, the number of ESWL sessions received by an individual is itself a risk factor for the formation of CaP stones, possibly due to the fact that ESWL induces an acute traumatic injury to the kidney [3,18].

In conclusion, although past research examining the risk factors for CaP stone formation may have helped streamline future research, the specific pathogenesis still remains a mystery. While research has been conducted to try to highlight the pathological mechanism of stone formation, complementary research is also essential for the elucidation of some currently unknown physiological mechanisms of Ca^{2+} reabsorption in the kidney. For instance, while it is known that 60-70% of $Ca^{2+}$is reabsorbed in the proximal convoluted tubule [19], the mechanisms of Ca^{2+}transport in this part of the renal tubule are still controversial. It is known that considerable reabsorption occurs via the paracellular pathway unregulated by hormones or drugs. However, several lines of evidence indicate that there is also some degree of active transport via a transcellular pathway that could very well be operated through Ca^{2+}-selective channels at the luminal membrane [20]. Although the identification, function, and mechanism of such channels remains elusive, future research in this area will hopefully answer these questions. Judging by the importance of Ca^{2+}concentration in CaP stone formation, a better understanding of these channels may provide further insight into the pathogenesis of CaP stone formation. While this is just one example, it helps illustrate that there are many different angles in which research can, and may have to, take in order to help finally determine the mechanism of CaP stone formation in the kidney and the rest of the body alike.

Acknowledgements

Our research on kidney disease is supported by Research and Development of DVA Medical Center, Washington DC and in part by a grant from National Kidney Foundation of the National Capital Area to BCB.

References

1. Pearle MS, Calhoun EA, Curhan GC, Urologic Diseases of America Project (2005) Urologic diseases of America project: urolithiasis. J Urol 173: 848-857.
2. Evan AP (2010) Physiopathology and etiology of stone formation in the kidney and urinary tract. Pediatr Nephrol 25: 831-841.
3. Parks JH, Worcester EM, Coe FL, Evan AP, Lingeman JE (2004) Clinical implications of abundant calcium phosphate in routinely analyzed kidney stones. Kidney Int 66: 777-785.
4. Tiselius HG (2011) A hypothesis of calcium stone formation: an interpretation of stone research during the past decades. Urol Res 39: 231-243.
5. Parks JH, Coe FL, Evan AP, Worcester EM (2009) Urine pH in renal calcium stone formers who do and do not increase stone phosphate content with time. Nephrol Dial Transplant 24: 130-136.
6. Carson DA (1998) An infectious origin of extraskeletal calcification. Proc Natl Acad Sci USA 95: 7846-7847.
7. Moe SM, Chen NX (2008) Mechanisms of vascular calcification in chronic kidney disease. J Am Soc Nephrol 19: 213-216.
8. Miller NL, Evan AP, Lingeman JE (2007) Pathogenesis of renal calculi. Urol Clin North Am 34: 296-313.
9. Coe FL, Evan A, Worcester E (2005) Kidney stone disease. J Clin Invest 115: 2598-2608.
10. Asplin JR, Parks JH, Coe FL (1997) Dependence of upper limit of metastability on supersaturation in nephrolithiasis. Kidney Int 52: 1602-1608.
11. Bihl G, Meyers A (2001) Recurrent renal stone disease-advances in pathogenesis and clinical management. Lancet 358: 651-656.
12. Asplin JR, Mandel NS, Coe FL (1996) Evidence of calcium phosphate supersaturation in the loop of Henle. Am J Physiol 270: F604-613.
13. Evan AP, Lingeman JE, Coe FL, Parks JH, Bledsoe SB, et al. (2003) Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. J Clin Invest 111: 607-616.
14. Pak CY, Koenig K, Khan R, Haynes S, Padalino P (1992) Physicochemical action of potassium-magnesium citrate in nephrolithiasis. J Bone Miner Res 7: 281-285.
15. Kacker R, Meeks JJ, Zhao L, Nadler RB (2008) Decreased stone-free rates after percutaneous nephrolithotomy for high calcium phosphate composition kidney stones. J Urol 180: 958-960.
16. Morton AR, Wooltorton E (2002) Nephrology in practice: a new series. CMAJ 166: 195.
17. Gault MH, Chafe LL, Morgan JM, Parfrey PS, Harnett JD, et al. (1991) Comparison of patients with idiopathic calcium phosphate and calcium oxalate stones. Medicine (Baltimore) 70: 345-359.
18. Kaude JV, Williams CM, Millner MR, Scott KN, Finlayson B (1985) Renal morphology and function immediately after extracorporeal shock-wave lithotripsy. AJR Am J Roentgenol 145: 305-313.
19. Unwin RJ, Capasso G, Shirley DG (2004) An overview of divalent cation and citrate handling by the kidney. Nephron Physiol 98: p15-p20.
20. Ullrich KJ, Rumrich G, Klöss S (1976) Active Ca^{2+}reabsorption in the proximal tubule of the rat kidney. Dependence on sodium- and buffer transport. Pflugers Arch 364: 223-228.