

Urolithiasis: In Search of New Factors

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Formation of renal stones has been traditionally attributed to risk factors involved in urolithiasis including supersaturation of oxalate crystals, low excretion of citrate and genetic predisposition to certain metabolic disorders. Role of several risk factors suggested to be involved in urolithiasis have been widely investigated, yet they are unable to explain the high prevalence of kidney stone disease in geographical regions of varying environments and life styles.

Factors that have been identified, and are considered to influence the formation of renal stones generally fall into two categories: 1) those present in urine that alter the rate of crystal nucleation, agglomeration and growth, these include various salts, proteins, glycoproteins and phospholipids, 2) cellular surface properties that promote the adherence and/or uptake of nascent crystals by renal epithelial cells.

More recently the interest has been focused on the role of various nontraditional risk factors, such as oxidative stress, role of proteins and genetic polymorphism that influence the process of urolithiasis.

It is well-known that the progression of events leading to urolithiasis is initiated when urine is supersaturated with salts. Crystal nucleation and aggregation with other promoters leads to continued growth.¹ However, the stimuli for these events are not completely known. Proteins are believed to play a major role in the renal stone genesis mainly because of having a potential to promote crystal-membrane interactions.

To date approximately 20 proteins have been detected in the organic matrix of human kidney stones. Proteins associated with renal stones are categorized in three groups, namely, those involved in causation; effectors and bystanders.² With the advent of more sensitive and powerful techniques, recently a number of new proteins have been identified that might be involved in the causation of stone formation. Thus identification of anti inflammatory proteins including myeloperoxidase and interleukin-6 are recent additions to the candidates that could be involved as initiators of urolithiasis.^{3,4} Interaction between calcium oxalate (CaOx) and proteins and their fragments are well documented and therefore it would not be unusual to find many of urinary proteins as

components of organic matrix in CaOx stones. These reports substantiate earlier findings that have demonstrated that renal epithelial cell injury or inflammation promotes crystal attachment. This interaction changes the property of affected cells and leads to unmasking of attachment sites beneath or between cells.⁵ It has also been observed that inflammation and injury of the membrane is associated with excessive calcium oxalate monohydrate crystallization with hyperoxaluria. Reports of Selvam and Khan SR also support the notion that in hyperoxaluria, macrophages migrate towards the site of inflammation, releasing cytokines and some of these proteins particularly Monocytes chemo attractant protein- 1(MCP-1) and calgranulin are also expressed by renal cells, where they play active or passive role in stone genesis.^{6,7} Despite the distinctive role played by the proteins, the process of retention of crystals in the renal organ system, could lead to renal stone formation.

Evidence has also emerged that crystal retention is caused predominantly by the adherence of crystals to the epithelial cells lining the renal tubules. Inflammation is also associated with MCP-1 which is induced in renal cells following exposure to oxalate ions or to calcium oxalate crystals and its expression has been associated with inflammatory responses in a variety of kidney diseases including perhaps, the inflammation produced by crystal deposition in stone disease.⁷

Cell Surface molecules like phospholipid, phosphatidylserine which are normally restricted to the inner leaflet of the membrane, also contribute to the adherence of crystals and promote crystal binding. Thus it would seem that an array of secreted and surface-associated molecules is involved in crystal attachment to cells, and that various pathological conditions can alter the availability and / or orientation of these molecules at the cell surface. Nevertheless, our understanding of the process of stone formation and retention of the crystal is far from complete.

Alterations in gene expression of a variety of secreted proteins that have been shown to alter the rate of crystal nucleation and growth could result in urolithogenesis.⁸ In this regard variants of human

matrix Gla protein, a potent calcification inhibitor in arterial vessels which is also expressed in the kidney have been shown to be associated with genetic susceptibility to urolithiasis. Similarly a high association of osteopontin gene polymorphism at position 9,402 has been suggested to be a likely candidate of genetic marker for evaluating the genetic risk of urinary calcium stone disease.^{8,9}

These new findings suggest that there is significant relationship between the renal cell and its surroundings, and that this interplay between macro molecule, hyperoxaluria and genetic predisposition can greatly influence the stone formation. Factors that alter the surface properties of renal cells and /or that alter the secretion of urinary macromolecules promote urolithiasis. Further studies will be required to determine how this factor interacts with other factors (diet, climate, and genetics) that have been shown to play a role in the stone formation.

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