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MINIREVIEWS

# Kidney stone matrix proteins: Role in stone formation

#### Armando Luis Negri, Francisco Rodolfo Spivacow

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# Abstract

Stone formation is induced by an increased level of urine crystallization promoters and reduced levels of its inhibitors. Crystallization inhibitors include citrate, magnesium, zinc, and organic compounds such as glycosaminoglycans. In the urine, there are various proteins, such as uromodulin (Tamm-Horsfall protein), calgranulin, osteopontin, bikunin, and nephrocalcin, that are present in the stone matrix. The presence of several carboxyl groups in these macromolecules reduces calcium oxalate monohydrate crystal adhesion to the urinary epithelium and could potentially protect against lithiasis. Proteins are the most abundant component of kidney stone matrix, and their presence may reflect the process of stone formation. Many recent studies have explored the proteomics of urinary stones. Among the stone matrix proteins, the most frequently identified were uromodulin, S100 proteins (calgranulins A and B), osteopontin, and several other proteins typically engaged in inflammation and immune response. The normal level and structure of these macromolecules may constitute protection against calcium salt formation. Paradoxically, most of them may act as both promoters and inhibitors depending on circumstances. Many of these proteins have other functions in modulating oxidative stress, immune function, and inflammation that could also influence stone formation. Yet, the role of these kidney stone matrix proteins needs to be established through more studies comparing urinary stone proteomics between stone formers and non-stone formers.

**Key Words:** Stone formation; Kidney stone; Matrix proteins; Uromodulin; Calgranulin; Proteomics

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**Core Tip:** Several urinary proteins have been found in kidney stone matrix. In vitro and in vivo studies have shown that they have an important role in various processes of calcium oxalate crystallization. Many of them have other functions in modulating oxidative stress, immune response, and inflammation that could also influence stone formation. Yet, the exact role of these kidney stone matrix proteins needs to be established through more studies comparing urinary stone proteomics between stone formers and nonstone formers.

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#### INTRODUCTION

Healthy people regularly excrete calcium oxalate crystals in urine. Calcium oxalate stones are formed only in a small part of the population[1]. Stones develop from crystals that form in the urine, which contains a mixture of ions, salts, macromolecules, and metabolites<sup>[2]</sup>. Crystals undergo different stages (nucleation, growth, and aggregation) until they produce a stone.

Induction of stone formation is produced by an increased level of crystallization promoters in the urine and reduced levels of its inhibitors<sup>[3]</sup>. Crystallization promoters are those substances that may constitute the crystals by which stones are formed, in particular calcium and oxalate. Idiopathic hypercalciuria is probably the principal condition underlying stone formation that produces increased levels of urinary calcium<sup>[4]</sup>. Crystallization inhibitors include citrate, magnesium, zinc, and organic compounds produced by renal tubular epithelial cells as glycosaminoglycans. Several proteins, such as uromodulin [UMOD; Tamm-Horsfall protein (THP)], calgranulin, osteopontin (OPN), bikunin, and nephrocalcin (NC), are present in the urine<sup>[5]</sup>. These proteins that are frequently found in the kidney stone matrix will be the subject of this review (Table 1).

### MACROMOLECULES AND CRYSTALLIZATION

We do not know the exact role of many macromolecules present in urine in calcium salt crystallization. The normal level and structure of these macromolecules may constitute protection against formation of large, intratubular precipitates of calcium salts. Paradoxically, most of them may act as both promoters and inhibitors depending on circumstances (for example urine pH).

Back in the 1970's, Gill et al<sup>[7]</sup> showed an inhibitory effect of macromolecules from human urine on crystallization of calcium oxalate[6]. The presence of several carboxyl groups in these macromolecules reduces calcium oxalate monohydrate crystal adhesion to the urinary epithelium<sup>[7]</sup>. The findings showed that macromolecules could potentially protect against lithiasis and that affected patients with lithiasis may have a different composition from that in healthy subjects.

Among macromolecules, proteins are present in all stones in a slight proportion, commonly < 5%. Several proteins rich in the urine proteome, have been examined in relation to their possible role in renal lithiasis. The most abundant component of kidney stone matrix are proteins, and their presence indirectly shows the process of stone formation. Urinary stones proteomics has been analyzed in several studies [5,8-10]. In a recent study, Kaneko et al [11] conducted a bioinformatic research on the proteomics of urinary stones to identify the most frequent stone matrix proteins present and afterwards performed immunohistochemistry to detect the top five of those matrix proteins expressed in renal tissue. Among the stone matrix proteins, the most frequently identified were UMOD, S100 proteins (calgranulins A and B), OPN, and several other proteins that participate in inflammation and immune response. Several proteins determined by immunohistochemistry in kidney stones showed increased expression, such as S100A8, S100A9 (calgranulins A and B), and OPN, while others such as UMOD decreased. Proteomic analysis of exosomes from kidney stone patients also showed higher expression of S100 proteins[12] while they were difficult to detect in urine.

#### Uromodulin

UMOD, originally known as THP, is a kidney-specific protein synthesized at the thick ascending limb of the loop of Henle[13,14]. Nearly 100 mg of this protein is excreted daily, and it is the most abundant of all urinary proteins. UMOD is a complex protein with several domains including a zona pellucida domain, essential for protein polymerization, and a special anchoring domain[15]. It is composed of 640 amino acids with 48 cysteine residues that form 24 disulphide bonds and glycosylation accounts for



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Matrix protein name	Primary function	Celular origin	Secondary function	Mol. weight (KDal)
Uromodulin	Inhibits crystal aggregation	Epithelial cells of the TALH	Reduces local oxidative stress	87
Calgranulins	Inhibit crystal growth and aggregation	Cells of myeloid origin	Participate in innate immuneresponse	10.9-13.2
Osteopontin	Inhibits/Enhances crystal formation and aggregation	Distal tubular epithelial cells	Regulator of immune response	14
Bikunin	Inhibits crystal nucleation, growth, and aggregation	Proximal tubules and the thin descending segment	Inhibition of the action of many serine proteinases	39
Nephrocalcin	Inhibit crystal nucleation, growth, and aggregation	Proximal tubule epithelial cells and TALH	None	18

#### Table 1 Kidney stone matrix proteins as modulators of crystallization

TALH: Thick ascending limb of Henle.

nearly 30% of its molecular weight. UMOD monomers are produced by epithelial cells present in the thick ascending limb of the Henle loop and then transported and secreted at both cell surfaces. At the apical surface, it is cleaved and released to the tubular fluid. Polymerization occurs depending on the physiological conditions in the urine. Putative functions of this protein include the modulation of salt and water transport, prevention of kidney stone formation by binding calcium oxalate crystals, and defense against urinary tract infection[15]. The role of UMOD in health and disease has been provided by the study of genetic diseases caused by mutations in the *UMOD* gene[16].

Measurements of THP in kidney stone formers and healthy subjects have shown decreased urinary THP in stone formers[17,18]. Urinary excretion of calcium and oxalate ions positively correlates with urinary THP in controls but not in stone formers. Only calcium stone formers show a reduction in THP. More recently, Fraser *et al*<sup>[19]</sup> studied UMOD level in urine of children with stone disease. They did not observe differences in concentration of the protein excreted between the group with symptomatic lithiasis, the group endangered with lithiasis, and the control group. In another study in children, those with lithiasis had increased UMOD excretion<sup>[20]</sup>. Similarly, increased excretion of this protein, with its different composition at the same time, was observed by Jaggi et al[21] in urine of affected adults with high intensity of stone formation. Possible determinants of urinary THP excretion in kidney stone formers and control subjects were studied by Glauser et al<sup>[22]</sup>, assessing 24-h THP excretion and expressing results in the form of THP/creatinine ratio. They found that in both controls and stone formers, urinary THP excretion was related to body size, renal function, and urinary citrate excretion, whereas THP excretion was not correlated with age, urine volume, or dietary habits (dietary calcium supply or protein consumption). An increase in THP in response to increasing urinary calcium and oxalate concentrations was seen only in controls, whereas this self-protective mechanism was absent in stone formers. Therefore, the different publications presenting quantitative differences in UMOD excretion did not have the same findings, which may indicate a random nature of the differences.

Other authors have found that UMOD structure is different between persons with and without kidney stones. Stone formers had lower protein content (32%), sialic acid content (27%), and amino sugar content (nearly 20%)[23]. Viswanathan *et al*[24] have shown that UMOD contains less sialic acid in patients with lithiasis, which leads to reduction of its negative charge. This form of protein promotes aggregation of calcium oxalate monohydrate, whereas the same protein prevents aggregation in healthy subjects with a normal content of sialic residues. Thus, not only UMOD levels but also differences in THP biochemical structure may influence the development of calcium nephrolithiasis.

To better understand the *in vivo* role of THP in kidney stone formation, Mo *et al*[25] inactivated the *THP* gene[25]. The resultant *THP*-/- mice had no THP expression in the kidney. Intratubular crystal aggregates were seen in the collecting ducts at the inner medulla and renal papillae in these mice, while wild type littermates had no crystal deposition in the kidney. This papillary interstitial calcinosis of the THP-/- mice is very similar to Randall's plaques seen in calcium oxalate stone formers, but ureteral stones have been found in this model[26].

Reactive oxygen species (ROS) and inflammation have a critical role in the pathogenesis of kidney stones[27]. ROS production increases when renal tubular cells are exposed to different type of crystals, leading to epithelial cell injury[28] and release of inflammatory mediators[29]. THP<sup>-/-</sup> mouse kidneys have increased ROS accumulation in the kidney, particularly in the S3 segment of the proximal tubules [30]. Targeted proteomic analysis on S3 proximal epithelial cells in these mice showed that free radical scavenging proteins were at the top of the proteins that were differentially downregulated in THP<sup>-/-</sup> mice[30]. Thus, it is possible that one of the mechanisms by which UMOD prevents renal lithiasis is through reducing local oxidative stress.

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#### S100 proteins (calgranulins)

S100 proteins constitute a family of calcium-binding proteins present in the cytosol, characterized by their dissolution in 100% ammonium sulphate[31]. Several of them have been classified as danger-associated molecular patterns (DAMPs) of endogenous origin, including S100A7[32], S100A8, S100A9, and S100A12[31,33]. DAMPs, also known as alarmins, are a group of endogenous intracellular molecules characterized by multiple functions, and they are generally released as inflammatory signal mediators after cell death[34].

S100A8 and S100A9 are also known as calgranulins A and B, respectively. They are constitutively expressed and produced by cells of myeloid origin, such as neutrophils and monocytes[35], and dendritic cells[36]. In other cell types, they can be induced upon activation. S100A8 and S100A9 constitute nearly half of all cytosolic proteins in neutrophils, but only 1% in monocytes[35]. S100A8 and S100A9 in the presence of zinc and calcium ions form a heterodimer called calprotectin that promotes phagocyte migration by polymerization and stabilization of tubulin microfilaments in a calcium dependent manner[37].

Toll-like receptor 4 (TLR4) and RAGE (the receptor for advanced glycation end products) are thought to be the innate immune receptors of calgranulin[38,39]. Upon binding, TLR4 signaling is triggered, which is mediated by MyD88, thus leading to NF-kB activation and secretion of pro-inflammatory cytokines[40,41]. Interaction of calgranulin with TLR4 has been shown to be involved in the pathogenesis of autoimmune diseases, systemic infections, malignancy, and acute coronary syndrome[42-45].

Momohara *et al*[46] showed the ability of calgranulins to inhibit crystallization, aggregation, and adhesion to the urinary epithelium of calcium oxalate monohydrate crystals. Mushtaq *et al*[47] also observed the presence of calgranulin in CaOx deposits but it promoted crystal aggregation. Bergsland *et al*[48] observed that the concentration and composition of calgranulin differed in subjects with a family history of urinary tract lithiasis in comparison with a healthy population. In children with stone disease, no statistically significant difference in calgranulin urine concentrations was observed between the study and control groups.

#### Osteopontin

OPN, also known as secreted phosphoprotein 1 (SPP-1), is a highly phosphorylated, strongly anionic glycophosphoprotein, with a molecular weight that ranges between 41 and 75 kDa, composed of 314 amino acids[49,50]. OPN was originally discovered in bone, as a member of the small integrin-binding ligand N-linked glycoprotein (SIBLING) family of proteins, implicated in bone mineralization and remodeling[51]. OPN suffers multiple post-translational changes that modify the OPN responses in several tissues[50,52].

In addition to bone metabolism, OPN can regulate the immune response through interactions with multiple surface proteins localized in its target cells: Macrophages, dendritic cells, and T cells. Indeed, this protein has chemotactic properties on these cells[50]. Integrin receptor binding to OPN activates the intracellular nuclear factor kappa B (NF-kB)[53]. OPN is also able to stimulate T-cell chemotaxis and adhesion, and it inhibits interleukin (IL)-10 release by macrophages[53]. In the kidney, OPN is produced and secreted into the urine by distal tubular renal epithelial cells, becoming a normal macromolecular constituent of the kidney[54].

Multiple observations support the concept that OPN may play an important role in modulating renal stone formation, such as: (1) OPN is one of the protein components of renal stone matrix[11]; (2) OPN can regulate the renal calcification process[55]; (3) OPN renal expression is altered in hyperoxaluric rats and urinary levels are changed in human subjects with urolithiasis[56]; (4) *In vitro* cell culture based studies and *in vivo* OPN knockout animal models suggest an important role of OPN in various phases of renal stone formation[57-59]; and (5) *OPN* polymorphisms have shown association with urolithiasis in different ethnic groups in candidate gene association studies[60,61].

#### Bikunin

Bikunin is a small chondroitin sulfate proteoglycan with a single glycosaminoglycan chain. It is the light chain of inter-alpha-inhibitor known for its inhibition of the action of many serine proteinases like trypsin and chymotrypsin. It exhibits a strong calcium oxalate crystal nucleation and aggregation inhibitory activity[62]. Immunohistochemical studies have shown that bikunin is localized in proximal tubules and the thin descending segment of the loop of Henle. It is absent in the glomeruli, distal tubules, or collecting ducts[63]. In subjects with lithiasis, bikunin does not prevent crystallization so well as in healthy subjects[64]. In a study by Médétognon-Benissan *et al*[65], strong inhibitory effect of bikunin on CaOx crystallization was confirmed by *in vitro* studies. On the other hand, a comparison of this protein in urine of adults with calcium oxalate lithiasis with urine of healthy subjects by means of the ELISA method, confirmed that bikunin level was 50% lower in affected subjects. On the contrary, a statistically significantly higher excretion of this protein in urine was observed in children with lithiasis [48].

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#### Nephrocalcin

NC was the first urinary protein found to have crystal inhibitory properties[66]. This is a 14-kDa glycoprotein. It is a very potent inhibitor, compared to THP and OPN, the two other inhibitors, and is probably of major importance in protecting the kidneys against urinary supersaturation. NC contains  $\gamma$ carboxyglutamic acid and has been shown to inhibit crystal growth, nucleation, and aggregation. The absence of y-carboxyglutamic acid in the NC molecule from stone forming patients reduces its ability to inhibit nucleation and growth of calcium oxalate crystals[66,67].

To date, four isoforms of NC in urine have been reported. NC A and B isoforms are strong inhibitors, and C and D isoforms act as promoters for kidney stones[68].

A fifth NC was identified, called NC-PreA found in patients with renal cell carcinoma and in calcium oxalate renal extractions. In a recent study in children, Noyan et al[69] included 41 boys and girls with urinary stones and 25 age- and sex-matched healthy controls. The NC-PreA/creatinine ratio is significantly higher in patients with renal stones than in controls. This finding observed in stoneforming patients indicates that this ratio, too, may also be an important stimulatory molecule for urinary stone disease.

#### CONCLUSION

Despite many studies that have explored the proteomics of urinary stones, we still do not know the exact role of many of these matrix proteins found in kidney stones in calcium salt crystallization. The invariable presence of proteins in stones matrix raises the possibility that they play a role in stone formation, like the role that proteins have in healthy biomineralization. Are they protective molecules that were overwhelmed by mineral supersaturation? Can mineralization be promoted by these proteins? Are they merely a response to the disease process, including oxidative stress and inflammation? More studies are needed comparing urinary stone proteomics between stone formers and non-stone formers to elucidate the role of stone matrix proteins in stone formation.

#### FOOTNOTES

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