Recent Advances in the Pathophysiology of Nephrolithiasis

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This is to acknowledge that Khashayar Sakhaee, M.D. has disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Sakhaee will be discussing off-label uses in this presentation.

Khashayar Sakhaee, M.D. is a Professor of Internal Medicine in the Division of Mineral Metabolism.

His interests include clinical evaluation and research in the area of Mineral Metabolism, with a special emphasis on the pathogenetic mechanisms of kidney stone formation and osteoporosis.

Introduction:

The lifetime risk for kidney stone disease currently exceeds 6-12% in the general population [1,2]. In the final quarter of the 21st century, the prevalence of kidney stone disease increased in both gender and ethnicity [2]. Although kidney stone nephrolithiasis is perceived as an acute illness, there has been growing evidence that nephrolithiasis is a systemic disorder which leads to end-stage renal disease (ESRD) [3-5]. It is also associated with an increased risk of hypertension [6-10], coronary artery disease [11,12], the metabolic syndrome (MS) [13-18], and diabetes mellitus [19-22]. Nephrolithiasis without medical treatment is a recurrent illness with a prevalence of 50% over 10 years [23]. Nephrolithiasis has remained a prominent issue which imposes a significant burden on human health and is a considerable financial expenditure for the nation. In 2005, based on inpatient and outpatient claims, this condition was estimated to cost over $2.1 billion [24]. A novel strategy for the development of new drugs has been hampered largely by the complexity of this disease's pathogenetic mechanism and its molecular genetic basis. Our further understanding of these underlying pathophysiologic mechanisms will be the key step in developing more effective preventive and therapeutic measures. In this Medicine Grand Rounds I shall highlight our recent progress in elucidating the pathophysiologic mechanisms of uric acid (UA) and calcium oxalate nephrolithiasis.

Etiologic mechanisms of uric acid stone formation

Three major factors for the development of UA stones are low urine volume, acidic urine pH, and hyperuricosuria. However, abnormally acidic urine is the principle determinate in UA crystallization. The etiologic mechanisms for UA stone formation are diverse, and include congenital, acquired, and idiopathic causes [25]. The most prevalent cause of UA nephrolithiasis is idiopathic. In its initial description, the term "gouty diathesis" was coined [26]. The clinical and biochemical presentation of idiopathic UA nephrolithiasis (IUAN) can not be attributed to an inborn error of metabolism [25,27,28] or secondary causes such as chronic diarrhea [29], strenuous physical exercise [30], and a high purine diet [31].

Physicochemical characteristics of uric acid

In humans and higher primates, UA is an end product of purine metabolism. Due to their lack of the hepatic enzyme, uricase, which converts uric acid to soluble allantoin, their serum and urinary levels of UA is considerably higher than in other mammals [32]. Normally, urinary uric acid solubility is limited to 96mg/L. In humans with a urinary UA excretion of 600mg/day, this should generally exceed the limit of solubility and susceptibility to precipitation [33]. Moreover, urine pH is another important factor in UA solubility. UA is a weak organic acid with an ionization constant (pKa) of 5.5 [34,35]. Therefore, at a urine pH less than 5.5, the urinary environment becomes supersaturated with sparingly soluble, undissociated UA which precipitates to form UA stones [19,36,37].

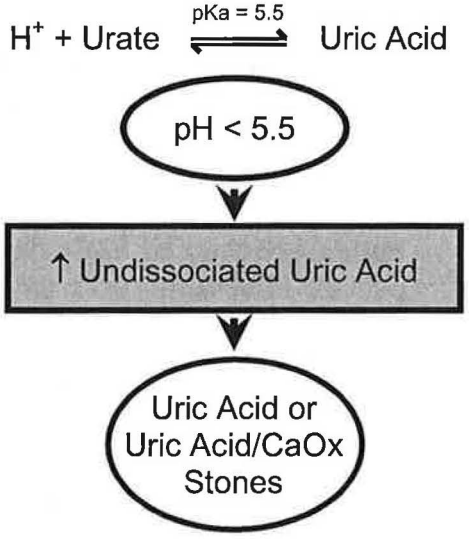


Figure 1. The physicochemical characteristics of Uric Acid

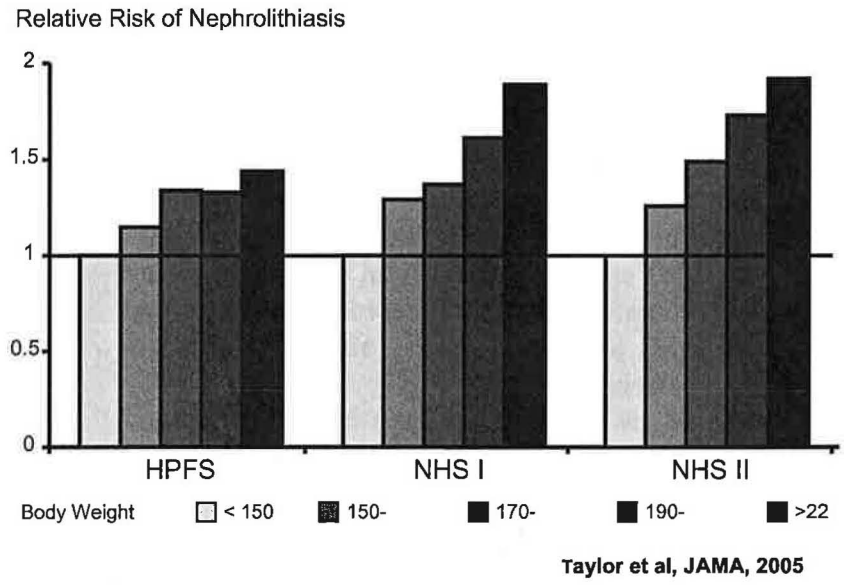


Figure 2. The relationship between body weight and the adjusted relative risk for nephrolithiasis.

Epidemiology of uric acid nephrolithiasis and the metabolic syndrome

The MS is an aggregate of features that increase the risk of type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease [13-15]. In a retrospective analysis of our stone registry, we initially showed a high prevalence of features of the MS in IUAN patients, leading us to determine that patients with IUAN share characteristics similar to those of the MS. Numerous epidemiologic studies have shown that obesity, weight gain, and T2DM are associated with an increased risk of nephrolithiasis (Figure 2) [38,39]. Despite the large sample size, stone composition was not reported among these studies. Our center was the first to report the high prevalence of uric acid stones as the main stone constitute found in T2DM. Additionally, recent retrospective and cross-sectional studies have noted an increased prevalence of UA stones among obese and T2DM patients[21,40-43]. However, T2DM and a greater body mass index (BMI) were shown to be independent risk factors for nephrolithiasis (Figure 3) [43].

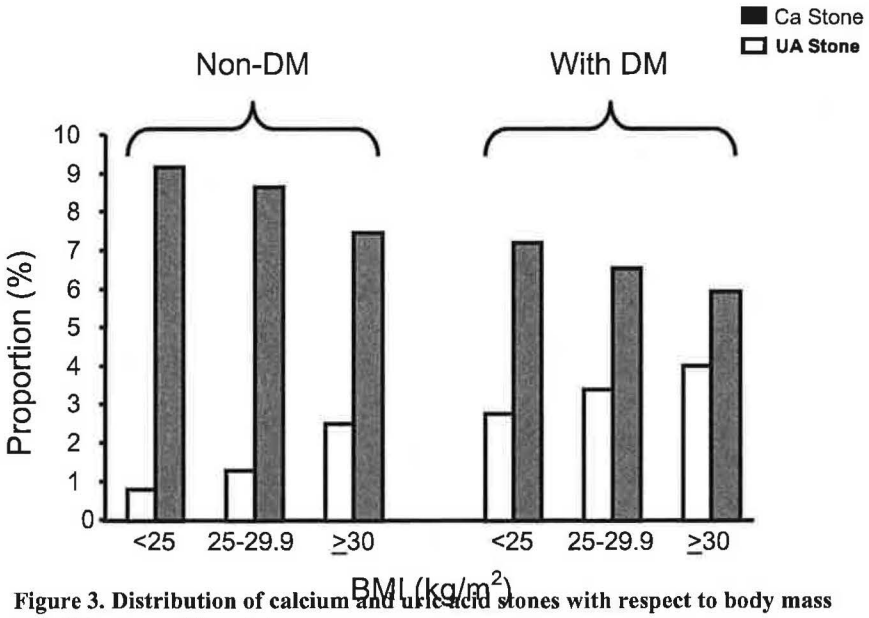


Figure 3. Distribution of calcium and uric acid stones with respect to body mass and diabetes mellitus status

Daudon et al, JASN, 2006

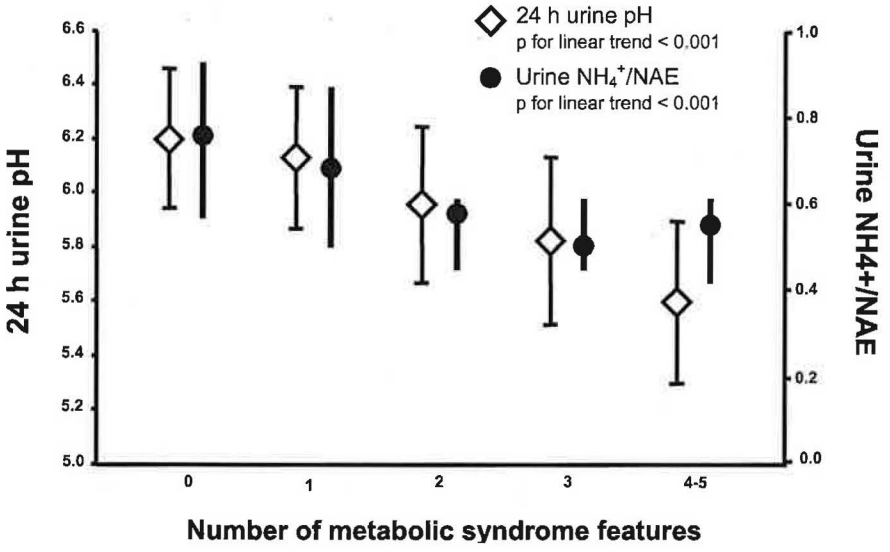
Pathophysiology of low urine pH in idiopathic uric acid nephrolithiasis

The metabolic defect suspected for low urinary pH in UA stone formation was described almost 4 decades ago [44]. Defective ammoniagenesis or excretion was attributed as a possible pathogenetic mechanism. Initial studies showing abnormalities in glutamine metabolism which resulted in the impaired conversion of glutamine to α-ketogluatrate and consequently resulted in reduced renal ammonium (NH_4^+) excretion, were not supported by further investigation [45-48]. Over the past decade,

major progress has been made in the further elucidation of factors resulting in unduly acidic urine pH seen in subjects with IUAN. Mechanistic studies have shown that the two major factors responsible for abnormally low urine pH are a combination of defective NH_4^+ excretion and increased net acid excretion (NAE).

Defective ammonium excretion

Increased acid production alone may not be sufficient in causing abnormally acidic urine, since the excreted acid is neutralized by urinary buffers. Evidence of defective NH_4^+ excretion was provided in IUAN subjects under a fixed, metabolic diet [19,21]. Therefore, an unduly acidic urine pH in the IUAN population is not related to environmental factors but it is, in part, related to the higher body weight in these subjects [49]. The defective NH_4^+ production in these subjects was further explored by the administration of an acute acid load, which amplified the ammoniagenic effect [19]. Similar findings were also demonstrated in IUAN subjects on a random diet [20]. Furthermore, it has been shown that in normal subjects, urinary pH and NH_4^+/NAE ratio falls with increasing features of the MS, indicating that renal ammoniagenesis and low urine pH may be features of the general MS and not IUAN specific [50] (Figure 4).



Modified from Maalouf et al, Clin J Am Soc Nephrol, 2007

Figure 4: The inverse association between 24-hour urinary pH (◊ pH) and the ratio of urinary ammonium to net acid excretion (• NH_4^+/NAE) with the number of features of the metabolic syndrome in 148 non-stone forming individuals. (Significant linear trend for both parameters, p<0.005)

Several studies have provided evidence supporting a relationship between UA nephrolithiasis, obesity, and insulin resistance [19,21,40-43]. The mechanistic connection between peripheral insulin resistance, urinary pH, and NH_4^+, was first demonstrated using the hyperinsulinemic euglycemic clamp technique in subjects with IUAN [22]. These studies support the potential role of insulin resistance in an impaired urinary NH_4^+ excretion and low urinary pH. Insulin receptors are expressed in various portions of the nephron [51,52]. Furthermore, in vitro studies have shown that insulin plays a stimulatory role in renal ammoniagenesis [53,54]. In addition, NH_4^+ secretion is regulated by the sodium-hydrogen exchanger (NHE3) [55]. Since NHE3 plays a key role in the transport or trapping of NH_4^+ in the renal tubular lumen [55], insulin resistance may potentially lead to defective renal

NH_4^+ excretion. One other plausible mechanism may be substrate competition by substituting circulating free fatty acid for glutamine, which is increased in the MS, thereby reducing the proximal renal tubular cell utilization of glutamine and renal ammoniagenesis [56].

Increased net acid excretion

An elevated NAE may occur due to increased endogenous acid production or because of dietary influences such as low dietary alkali or the increased consumption of acid rich foods [35]. Metabolic studies comparing subjects on fixed, low acid-ash diets showed a higher NAE in IUAN patients compared to control subjects, suggesting that endogenous acid production may increase in IUAN [33]. In addition, the urinary NAE for any given urinary sulfate (a surrogate marker of acid intake) tended to be higher in patients with T2DM [20]. These studies also implied that the pathophysiologic mechanism accounting for increased NAE is related to obesity/insulin resistance. Supporting this correlation, additional studies have shown increased organic acid excretion with higher body weight and higher body surface area [57,58]. The nature of these putative organic anions and their link to obesity and/or UA stones has not been fully studied. However, our indirect estimate of organic acid excretion from the urinary anion gap (calculated as the difference between total measured cations and anions) demonstrated a higher value in IUAN and T2DM subjects without kidney stones.

Potential role of renal lipotoxicity

Under normal conditions, when caloric intake and caloric utilization are balanced, triglycerides accumulate in adipocytes [59,60]. A disruption in this tight balance leads to the tissue redistribution of triglycerides which are deposited within parancheymal liver cells, cardiac myocardial cells, skeletal muscle cells, and pancreatic β-cells [60-65]. The process of fat deposition in tissues other than adipocytes is termed lipotoxicity [60]. Cellular injury is primarily due to the accumulation of nonesterified fatty acids (NEFA) and their toxic metabolites including fatty acyl CoA, diacylglycerol, and ceramide [59,66,67]. It has been shown that fat redistribution is accompanied with impaired insulin sensitivity [62], cardiac dysfunction [64], and steatohepatitis [61,68]. There is an emerging interest in the role of renal lipotoxicity in the pathogenesis of renal disease [66,69,70]. A few studies have revealed a mechanistic link between obesity, obesity-initiated MS, and chronic kidney disease [69,70]. Additional studies have displayed a possible role of sterol regulating element binding proteins (SREBP) in renal fat accumulation and injury [71-73]. At the present time, there is insufficient data available to suggest whether renal lipotoxicity influences endogenous acid production and reduces renal ammoniagenesis, consequently leading to abnormally acidic urine.

Calcium oxalate nephrolithiasis

Calcium oxalate is the most prevalent type of kidney stone disease in the United States and has been shown to occur in 70-80% of the kidney stone population [74]. The prevalence of recurrent calcium oxalate stones has progressively increased in untreated subjects, approaching a 50% recurrence rate over 10 years [23]. Although it affects both genders, calcium oxalate nephrolithiasis generally tends to occur in more men than women. In the

calcium oxalate stone former, urinary oxalate and urinary calcium are equally conducive in raising urinary calcium oxalate supersaturation [75].

Hyperoxaluria is encountered in 8% to 50% of kidney stone formers [76-78]. The main etiologic causes of hyperoxaluria can be classified into three groups: (1) increased oxalate production as a result of an inborn error in metabolism of the oxalate synthetic pathway, (2) increased substrate provision from dietary oxalate rich foods or other oxalate precursors, and (3) increased intestinal oxalate absorption (Table 1) [74]. With the study of oxalobacter formigenes [79,80] and the role of putative anion transporter Slc26a6 [81] as potential tools in the treatment of primary hyperoxaluria, our knowledge of the pathophysiologic mechanisms of oxalate metabolism has advanced significantly over the past decade [82]. It is anticipated that these advances will lead to the development of new drugs targeting the intestinal absorption and secretion of oxalate. These targeted treatments could be used rigorously in the treatment of hyperoxaluria in the kidney stone forming population.

Table 1: Causes of Hyperoxaluria

Increased Oxalate Production
Increased substrate provision
Increased intestinal oxalate absorption

Physicochemical properties of oxalate

The human serum oxalate concentration ranges between 1-5μM, however, due to water abstraction in the kidney, its concentration is one hundred times higher in the urine [74,83]. At a physiologic pH, oxalate will form an insoluble salt with calcium. Since the solubility of calcium oxalate in an aqueous solution is limited to approximately 5mg/L at a pH of 7.0, assuming that normal urine volume ranges between 1-2 L/day and normal urinary oxalate excretion is less than 40mg/day, normal urine is often supersaturated with calcium oxalate. However, under normal conditions, the blood is under-saturated with respect to calcium oxalate. As seen in patients with primary hyperoxaluria and renal insufficiency, when the serum oxalate concentration increases to above 30μM, the blood becomes supersaturated with calcium oxalate [84]. In the plasma, oxalate is not significantly bound to protein and is freely filtered by the kidneys. A recent study reported that urinary calcium is as important as urinary oxalate in raising calcium oxalate supersaturation [75].

Oxalate homeostasis

Hepatic production

In mammals, oxalate is an end product of hepatic metabolism [79] (Figure 5). The major precursor for hepatic oxalate production is glyoxalate metabolism within hepatic peroxisomes. This metabolic conversion is mediated by enzyme alanine-glyoxalate aminotransferase (AGT). Under normal circumstances, the metabolism of glyoxalate to glycolate and glycine determines the conversion of glyoxalate to oxalate. Glyoxalate is also metabolized to glycolate by enzyme D-glycerate dehydrogenase, which has both glyoxalate/ hydroxypyruvate reductase (GR/HPR) activity [85]. An inborn error in metabolism with an AGT and GR/HPR deficiency leads to oxalate overproduction, which results in type 1 and type 2 primary hyperoxaluria [79,81,85]. Several other metabolic precursors of oxalate metabolism, including the breakdown of ascorbic acid, fructose, xyulose, and hydroxyproline, have also been incriminated. However, their influences on oxalate production, under normal physiologic circumstances, have not been fully accepted [86-88].

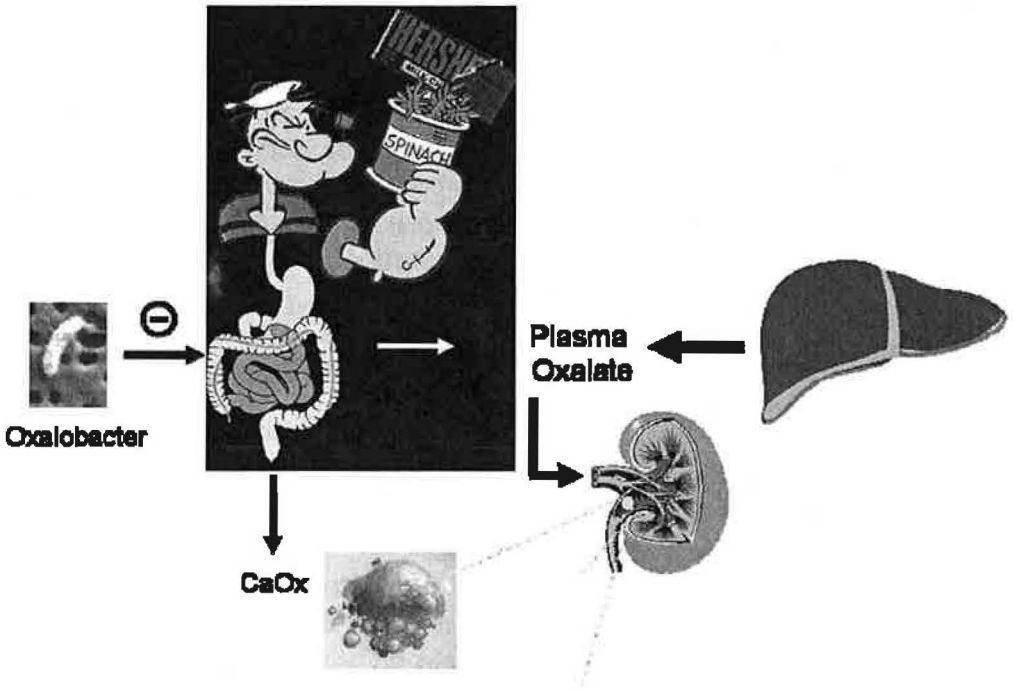


Figure 5: Oxalate Metabolism

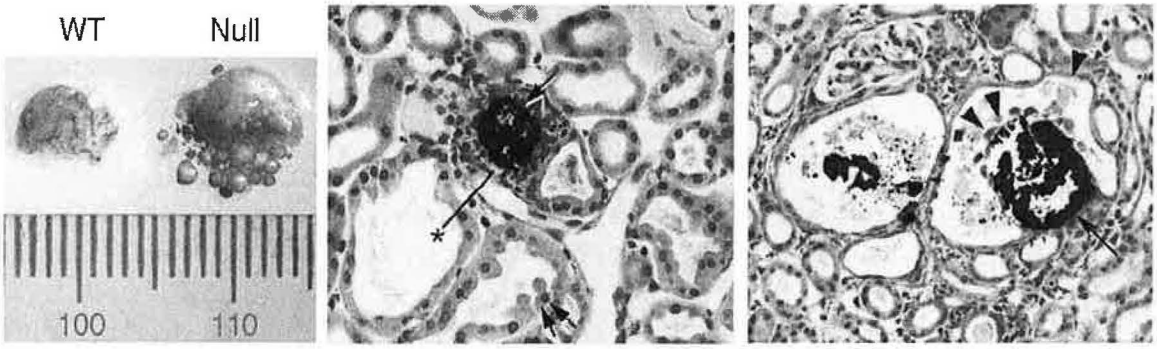
Intestinal absorption

Dietary oxalate intake plays an important role in urinary oxalate excretion. The estimated intake of oxalate ranges between 50-1000 mg/day [77,78,89]. Oxalate rich foods primarily include seeds, such as chocolate which is derived from tropical cacao tree, and leafy vegetation, including spinach, rhubarb, and tea. Approaching approximately 45%, the contribution of dietary oxalate to urinary oxalate excretion has been shown to be much higher than previously described [90]. Additionally, with intestinal oxalate absorption ranging between 10-72%, this relationship between oxalate absorption and dietary oxalate intake has not been shown to be linear [90].

In human subjects, the exact intestinal segment participating in oxalate absorption has not been determined. Indirect evidence suggests that oxalate absorption occurs throughout a large segment of the small intestine. This has been proposed since the main percentage of absorption occurs during the first 4-8 hours after the ingestion of oxalate rich foods [91-93]. This inference has been made based on the reported 5-hour intestinal transit time from the stomach to the colon. However, it has also been suggested that the colon may also

participate in oxalate absorption, but to a lesser extent [93]. In addition, the paracellular intestinal oxalate flux has been suggested to occur in the early segment of the small intestine largely due to the negative intestinal luminal potential and higher luminal oxalate concentration compared to the blood [94].

Recently, the putative anion exchange transporter (Slc26a6) has been shown to play a major role in intestinal oxalate transport [82]. The Slc26a6 is expressed in the apical portion of various segments of the small intestine such as the duodenum, jejunum, and ileum. It can also be found in the large intestine, but to a smaller percentage [95]. *In vitro* studies using the Ussing chamber technique demonstrated defective net oxalate secretion in mice with a targeted inactivation of the Slc26a6 [96]. Moreover, *in vivo* studies in the Slc26a6-null mice on a controlled oxalate diet reported high urinary oxalate excretion, increased plasma oxalate concentration, and decreased fecal oxalate excretion [96]. The differences in urinary oxalate excretion, plasma oxalate concentration, and fecal oxalate excretion were abolished following a 7-day equilibration on an oxalate free diet. These findings suggest that the reduction of net oxalate secretion in Slc26a6-null mice increases net oxalate absorption, raising plasma oxalate concentrations and consequently raising urinary oxalate excretion. These results were also associated with bladder stones and Yasue-positive crystals in the kidney. This study concluded that the Slc26a6 anion exchanger plays a key role in urinary oxalate excretion [96] (Figure 6).



Jiang et al, Nature Genetics, 2006

Figure 6. Urolithiasis and renal tubular changes in Slc26a6-null mice

Role of Oxalobacter Formigenes

Among many other bacteria including *Eubacteruim Lentum, Enterococcus Faecalis, Lactobacillus, Streptoccus thermopilus,* and *Bifidobacterium infantis,* oxalobacter formigenes (OF) have been reported to degrade oxalate [94]. OF was first isolated in ruminates [97] and has since been found in many animal species as well as in humans [98]. However, OF is not found in infancy. The bowel becomes colonized with this bacterium at approximately 6-8 years of age. It decreases in later years and may only be found in the feces of 60-80% of the adult population[99].

OF is a gram-negative obligate anaerobe microorganism which primary utilizes oxalate as a source of energy for cellular biosynthesis [100]. In this process, oxalate enters the

oxalobacter via an oxalate:formate antiporter. It then utilizes its own enzymes, formyl CoA transferase and oxalyl-CoA decarboxylase, to convert oxalate into formate and CO_2[101]. The electrogenic process of heterologous oxalate:formate antiporter activity serves as an ion-motive pump generating ATP synthesis [101].

The clinical importance of OF colonization is primarily suggested for patients with recurrent calcium oxalate nephrolithiasis [102-104], in patients with enteric hyperoxaluria [105,106], and in those with cystic fibrosis [107]. Studies in patients with urolithiasis and cystic fibrosis have shown that the prolonged use of antibiotics may abrogate the bowel colonization of OF and may irreversibly destroy these bacteria. Very recently, a case-controlled study of 274 patients with recurrent calcium oxalate stones and 259 normal subjects matched for age and gender, displayed that the prevalence of OF was significantly lower in the stone formers. In this study, 17% of stone formers were positive for OF vs. 38% of normal subjects. This relationship persisted with age, gender, race, ethnic background, region, and antibiotic use [108] (Table 2).

Table 2: *Oxalobacter formigenes* in stool among patients with recurrent CaOx kidney stones and control subjects

O. formigenes Status	Case Patients (n = 247)		Control Subjects (n = 259)		Crude OR	Multivariate OR (95% CI)[a]
	n	%	n	%		
Positive	42	17	99	38	0.3	0.3 (0.2 to 0.5)
Negative	205	83	160	62	1.0†	1.0[b]

[a]OR based on unconditional logistic regression with the following factors in the model: *O. formigenes*, age, gender, region, education, race, dietary oxalate, antibiotic use, and family history of stones. OR calculated using conditional logistic regression: 0.3 (0.1 to 0.5).

[b]Reference category.

Kaufman et al, JASN, 2008

The colonization of OF may be regulated by dietary oxalate intake. This has been shown in animal models where a significant decrease in urinary oxalate resulted from the administration or in the upregulation of OF colonization [102,109]. Recently, it has been shown that the role of OF in oxalate metabolism not only depends on its capacity to degrade intestinal luminal oxalate but also on its capacity to stimulate the intestinal secretion of endogenously produced oxalate [110]. The result of these animal experiments has recently been conveyed into human diseases [80]. One such study conducted in patients with type 1 primary hyperoxaluria, in subjects with normal renal function, and in patients with chronic renal insufficiency, reported the reduction of urinary oxalate which ensued following the oral administration of OF [80]. The major drawbacks of the use of OF are (A) the lack of large, long-term, controlled studies namely in calcium oxalate kidney stone formers and in subjects with enteric hyperoxaluria such as patients with cystic fibrosis or those following a gastrointestinal bypass procedure, (B) the variable response to OF

administration, and (C) OF's short life span upon the complete utilization of its primary nutrient source, oxalate. Future long-term studies and perhaps the development of target drugs which either upregulate the intestinal secretion of oxalate by stimulating Slc26a6 or provide the enzyme products of OF to allow for its persistent oxalate degrading capacity, are necessary in overcoming these deficiencies.

Renal excretion

The kidney plays an important role in oxalate excretion. With impaired kidney function, plasma oxalate concentrations progressively rise and result in kidney damage. Eventually, with further impairment, there is a robust spike in plasma oxalate concentration which exceeds its saturation in the blood and thereby increases the risk of systemic tissue oxalate deposition. It has recently been demonstrated that Slc26a6 is also expressed in the apical portion of the proximal renal tubule [111] and influences the activity of various apical anion exchangers [112]. In Slc26a6-null mice, it has been shown that Cl-oxalate exchange activity is completely inhibited, and the activity of Cl-/OH- and Cl-/HCO_3 is significantly diminished. However, the significance of this putative anion transporter in calcium oxalate stone formation has not been fully elucidated.

Randall's plaque in the pathogenesis of calcium oxalate stones

Several mechanisms have been proposed for the formation of calcium stones. Firstly, it has been suggested that the increased supersaturation of stone forming salts are responsible for the process of homogenous nucleation in the lumen of the nephron. This process, followed by crystal growth, ultimately results in an obstruction in the distal nephron. Secondly, it has been suggested that crystal forms in the renal tubular lumen adhere to the luminal renal tubular cells. This adhesion then induces renal cell injury resulting in the formation of a fixed nuclei which interacts with the supersaturated urinary environment and results in crystal growth. These processes both lead to nephron obstruction and consequently result in intratubular calcification [113].

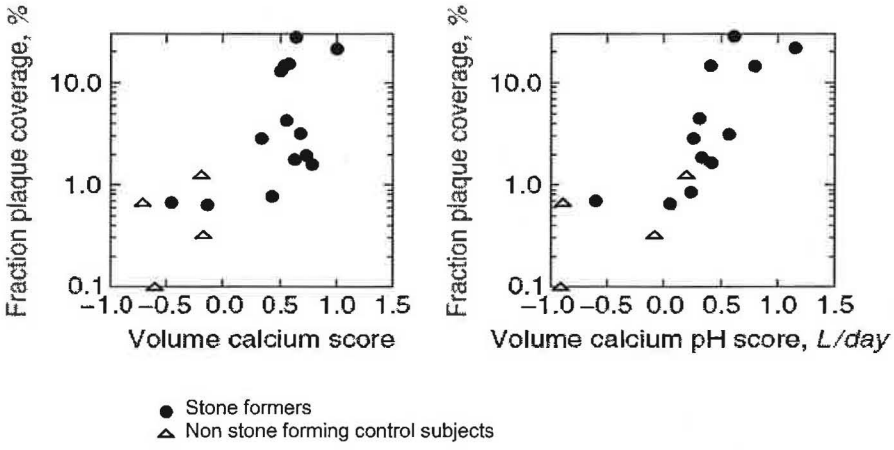
Dr. Alexander Randall was the first to argue that intraluminal plugging is an infrequent occurrence in kidney stone formers [114]. Conversely, he suggested that interstitial calcium phosphate deposits are initial niduses which anchor urinary crystals beneath the normal uroepithelial cells of the renal papilla. The erosion of the overlying uroepithelium exposes these deposits, referred to as plaques, to the supersaturated urine which then propagate calcium oxalate stones. He found these lesions to be interstitial as opposed to intraluminal, and without any inflammatory reactions. He also showed these deposits to be mainly found in the tubular basement membrane and in the interstitial collagen. Randall's hypothesis was primarily disputed since it was carried out in cadaveric kidney specimens and not in a targeted kidney stone forming population [114]. His major discovery, however, was a small stone propagated in the renal pelvis which was attached to a calcium plaque found in the papillae of the kidney.

Characteristics of the interstitial plaques

Randall's initial observations were recently followed with the development of modern techniques for determining mineral composition. These techniques have been used to

characterize the nature of crystals attached to these plaques and to develop novel techniques to visualize Randall's plaque *in vivo* in patients with nephrolithiasis [115,116]. An analysis of over 5000 stones showed the main mineral composition of interstitial plaque to be mainly carbapatite. However amorphous carbonated calcium phosphate, dosium hydrogen urate, and uric acid were found to a smaller extent [117]. Another study utilizing μ-CT determined that apatite crystal surrounded by calcium oxalate was the main mineral composition of Randall's plaque [118].

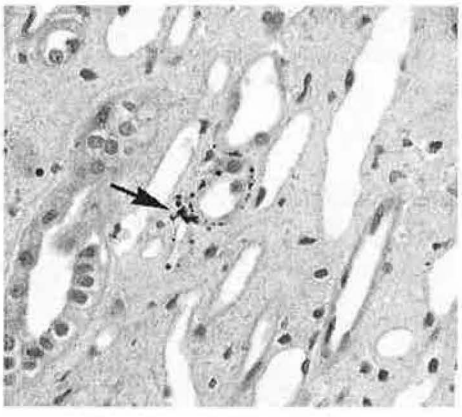
It was first shown that Randall's plaques occur more frequently in patients with kidney stones as compared to non-stone formers undergoing an endoscopic evaluation[119]. Furthermore, a relationship was found between metabolic abnormalities in patients with calcium stones and the number of plaques [120]. The result of this study was reached using digital video and endoscopic techniques to accurately estimate the extent of Randall's plaque in both calcium stone forming and non stone forming subjects [121]. In this study, the main biochemical profiles correlating with the formation of interstitial plaque were urinary volume, urinary pH, and urinary calcium excretion (Figure 7). Higher urinary calcium and lower urinary volume showed an increased coverage of the renal papilla with plaque. This study supports a mechanistic relationship between water abstraction in the renal medulla and papilla with plaque formation. Additionally, a separate retrospective study, using nephroscopic papillary mapping with representative still images and MPEG (Moving Pictures Expert Group) movies in a total of 13 calcium oxalate kidney stone formers, determined the percent of plaque coverage to be directly correlated with the number of kidney stones formed [122].

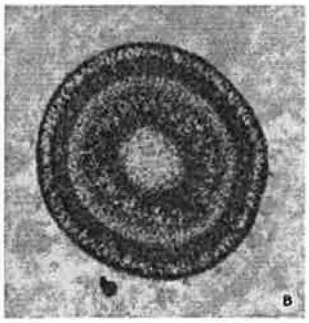


Kuo et al, KI, 2003

Figure 7: Correlation between papillary plaques and urinary profiles

Localization of Randall's plaque





The basement membrane of thin descending loops of Henle is the principle site of Randall's plaque localization [115]. The thin descending limb basement membrane is made up of

Figure 8: Sites and characteristics of crystal deposition Evan et al, JCI, 2003; KI, 2005

collagen and mucopolysaccharides, which attract calcium and phosphate ions [123]. Once attracted to this protein matrix, the crystallization processes begins. In the interaction following, calcium phosphate crystals grow and propagate to the surrounding collagen and mucopolysaccharide-rich renal interstitium [124]. This complex then makes its way through the urothelium and serves as a nidus for calcium oxalate deposition, ultimately resulting in calcium oxalate kidney stone formation. Randall's plaque has only been localized in the basement membranes and in the interstitium. It has never been found in the tubular lumen within epithelial cells or vessels. Within the basement membrane, this plaque consists of coated particles of overlying regions of crystalline material and organic matrix [116] (Figure 8).

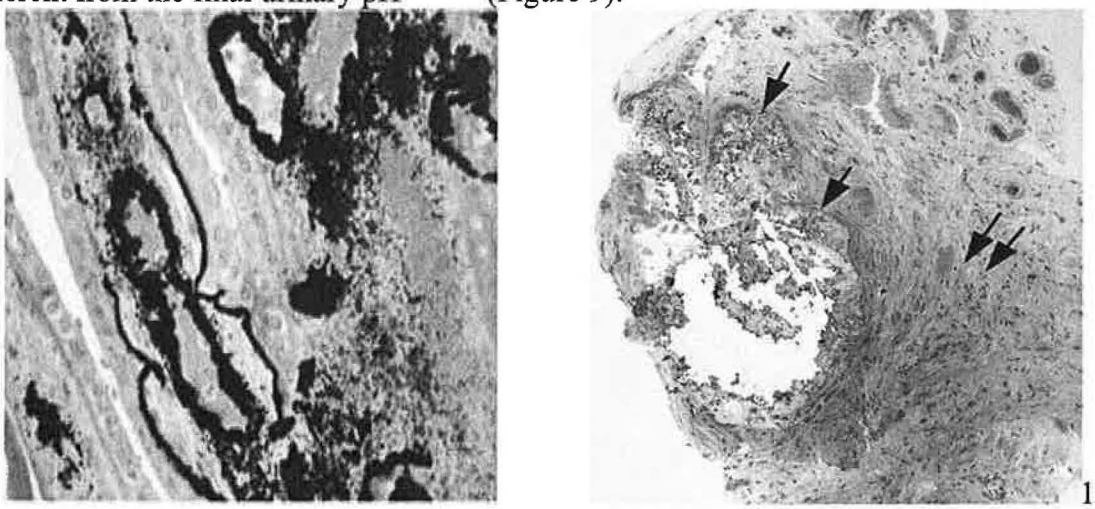
Mechanism of plaque formation

The mechanism of interstitial plaque formation has not been fully elucidated. Our limitations in this area are based on the lack of availability of an animal model which mimics this human disease. A few clinical studies have suggested a correlation between urine volume, urinary calcium, and severity of stone disease with the fraction of papillary interstitium covered by Randall's plaque [119-122]. Although this link is not causal, however, it indicates some correlation between plaque formation and kidney stone disease in idiopathic hypercalciuric patients. It is plausible to propose that plaque formation in the thin descending limb of Henle occurs due to an increase in interstitial calcium and phosphate concentration as well as an increase in renal papillary osmolality as a result of water abstraction in this nephron segmet [125]. Moreover, whether increasing interstitial fluid pH affects the abundance of plaque formation has been suggested but has never been fully explored [116].

Absence of Randall's plaque

Following gastric bypass surgery

Hyperoxaluria and calcium oxalate stones are a common occurrence in patients following intestinal bypass surgery due to morbid obesity [116,126]. In these subjects, there is no plaque observed in the renal papilla. However, crystal aggregates are found in the inner medullary collecting ducts (IMCD). Moreover, in contrast to conditions in idiopathic calcium oxalate stone formers, there is evidence of renal IMCD cell injury, interstitial fibrosis, and inflammation adjacent to the crystal aggregates. The IMCD crystal aggregates are usually composed of apatite crystals. The deposition of these apatite crystals occurs despite an acidic urinary environment, implying that tubular pH may be different from the final urinary pH [116,126] (Figure 9).



Cystine stone formers

In cystinuric patients, there is a blockage of the Bellini duct (BD) with cystine crystal aggregate. Additionally, apatite crystals are also shown to be present in the IMCD and in the thin loops of Henle. Although small areas of plaque formation have been noted in the renal papillae, the cystine stones are attached to cystine deposits in the BD [127]. In this condition, there is evidence of cell injury, interstitial fibrosis, and obstruction. These pathological changes are potentially responsible for the dysregulation of proton secretion and its consequent alkaline microenvironment which is highly conducive to apatite crystal deposition.

Brushite stone formers

In brushite stone formers, similar to calcium oxalate stone formers following gastric bypass surgery, there is evidence of cell injury and interstitial fibrosis in the IMCD adjacent to apatite crystal deposits. Although brushite stone formers, much like idiopathic calcium oxalate stone formers, have plaque in the renal papilla, the stones have not been shown to attach to the plaque [128]. This may be due, in part, to technical difficulties since the high burden of brushite stones may affect the structural integrity of the renal papillae, making it difficult to detect smaller stones that may be attached to the plaque.

Conclusion

Kidney stone disease remains a major public health burden. Its pathophysiologic mechanisms are complex, mainly because it is a polygenic disorder, and it involves an intricate interaction between the gut, kidney, and bone. Additionally, an exact animal model to recapitulate the human disease has not yet been defined. Despite these limitations, our comprehension of uric acid stone formation's link to insulin resistance and renal lipotoxicity, the underlying mechanisms of intestinal oxalate transport, and the role of renal papillary plaque in idiopathic calcium oxalate stone formation, has advanced significantly over the past decade. These elucidations can potentially lead us to the development of novel drugs targeting basic metabolic abnormalities which abrogate stone formation.

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