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Do Kidney Stone Formers Have A Kidney Disease?

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Abstract

Nephrolithiasis is a highly prevalent disorder affecting approximately one in eleven people and is associated with multiple complications including hypertension, cardiovascular disease, and chronic kidney disease. Significant epidemiologic associations with chronic kidney disease and ESRD have been noted and are reviewed herein, but debate persists in the literature as to whether kidney stone formation is a pathogenic process contributing to kidney disease. Corroborating evidence supporting the presence of kidney disease in stone formers includes the variability of renal function by stone type, the positive association of stone size with renal dysfunction, the presence of markers of renal injury in the urine of even asymptomatic stone formers, and direct evidence of renal tissue injury on histopathology. Proposed pathogenic mechanisms include recurrent obstruction and comorbid conditions such as recurrent urinary tract infections and structural abnormalities. Recent work evaluating the renal histopathology of different groups of stone formers adds further granularity, suggesting variability in mechanisms of renal injury by stone type and confirming the pathogenic effects of crystal formation. Genetic abnormalities leading to stone formation including cystinuria and primary hyperoxaluria, among others, contribute to the burden of disease in the stone-forming population.

Keywords

kidney stone; chronic kidney disease (CKD); histopathology

For many years nephrolithiasis has been viewed as a highly unpleasant nuisance by patients and doctors alike, but there had been little concern regarding long-term ramifications. Over the last several decades, however, there has been an increasing appreciation for the association of nephrolithiasis with negative long-term outcomes including cardiovascular morbidity^{1, 2}, metabolic disturbances³, and renal complications including chronic kidney

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disease (CKD) and End Stage Renal Disease (ESRD)⁴⁻⁷. Guilt by association, however, places nephrolithiasis in a nebulous category – is it simply a bother, a risk factor for other disease states, or is kidney stone formation itself a disease? In the ensuing pages we will consider these issues through the panoramic lens of epidemiology, reviewing data supporting the relationship between nephrolithiasis and impaired kidney function, as well as through the microscopic lens of histopathology, potentially shedding light on the mechanisms leading to kidney injury and dysfunction.

Evidence for Impairment of Normal Kidney Function

While classically renal dysfunction has been thought of as a decrement in the glomerular filtration rate (GFR), renal disease states may present with normal GFR but an abnormality in one of its other functions such as maintenance of blood pressure (through salt and water handling and hormonal regulation) or maintenance of acid /base homeostasis. For example, patients with a renal tubular acidosis may have a normal GFR but have an inability to maintain acid/base homeostasis. Halperin et al⁸ have proposed that the human kidney is designed to maintain systemic acid-base balance while maintaining the “ideal” urine pH of 6 to prevent crystallization within the kidney. Within this framework, any stone former has failed the test of normal renal function, as stone formation has resulted from a failure of the kidney to prevent crystallization.

More recently, international guidelines^{9, 10} have expanded the definition of chronic kidney disease (CKD) from simply a decreased GFR to the presence of any of the following for more than 3 months: eGFR<60 ml/min/1.73 m², albuminuria, urine sediment abnormalities, electrolyte abnormalities due to tubular disorders, structural abnormalities detected by imaging, or history of kidney transplantation, as these have been shown to be predictive of downstream complications. For the purposes of our discussion, we will focus on kidney stone formation as a parenchymal disease of the kidney that may be associated with decrements in GFR, rather than simply a nuisance within the urological tract.

The aforementioned guidelines specifically include abnormal histopathological findings in the renal parenchyma as its own category defining CKD, which, as we will demonstrate, is not an uncommon finding in stone-forming patients¹¹⁻²⁴. Furthermore, recent data highlight the increased prevalence of albuminuria and renal scarring even in asymptomatic stone formers – both considered diagnostic for CKD²⁵. In healthy subjects being evaluated for kidney donation at the Mayo clinic, subjects noted to have asymptomatic kidney stones on computerized tomography (CT) imaging were significantly more likely than donors without a stone to have renal parenchymal thinning and focal scarring²⁵. Furthermore, among subjects who had previously had a symptomatic stone event, 13% had evidence of albuminuria of >30 mg/24 hr, compared to 3.5% and 3.6% of subjects with no stone disease and asymptomatic stone disease, respectively.

While albuminuria is suggestive of glomerular injury, markers of tubular injury are also elevated in patients in nephrolithiasis. Sun et al²⁶ have shown that in a series of 60 stone formers urinary angiotensinogen is significantly higher than in control subjects and is negatively correlated with eGFR. Urinary angiotensinogen concentrations are a marker of

intrarenal angiotensin II levels, a critical modulator of renal injury via its role in potentiating glomerular capillary hypertension²⁷, and activation of signaling pathways associated with inflammation, generation of reactive oxygen species, and endothelial dysfunction²⁸. Urinary angiotensinogen levels were also significantly correlated with urinary α 1-microglobulin, a marker of proximal tubular injury which is believed to be one of the earliest markers of tubular dysfunction²⁹. Urinary excretion of 8-hydroxydeoxyguanosine (8-OHdG), a marker of oxidative DNA damage associated with glomerular and interstitial fibrosis³⁰, is also increased in stone formers³¹. Furthermore, immunohistochemical analysis demonstrates increased 8-OHdG expression in the renal tissue adjacent to stone in subjects with nephrolithiasis³².

Epidemiologic Data

The earliest study to note the relationship between nephrolithiasis and chronic kidney disease in the general population was performed by Vupputuri et al³³. In their case-control study performed in North Carolina, the authors queried 548 patients with newly diagnosed CKD (defined as a creatinine greater than 1.5 mg/dL) and 514 age, sex, and race-matched community dwelling adults without kidney disease regarding history of nephrolithiasis. Among patients, 16.8% of subjects reported a diagnosis of a kidney stone, compared to 6.4% of controls. After adjustment for comorbidities, CKD was nearly twice as likely (OR 1.9) in those with a history of nephrolithiasis.

The following year Gillen et al³⁴ demonstrated that the relationship between estimated GFR and kidney stone history in more than 15,000 subjects (6% stone formers) from the Third National Health and Nutrition Examination Survey (NHANES III) was dependent on weight. Generally, those with a history of kidney stones were more likely to be older, non-African American, male, and have a history of coronary artery disease. After adjustment for potential confounders, overweight stone formers (BMI>27) had a mean eGFR 3.4 ml/min/1.73m² lower than their non-stone forming counterparts. This difference was not noted in those with a BMI<27.

More recent data by Shoag et al using the NHANES 2007–2010 database confirms the association between kidney stones and CKD³⁵. Among 5971 NHANES participants with data on stones and kidney function, 521 subjects admitted to a history of nephrolithiasis. In a multivariate analysis, history of stone disease was strongly associated with CKD (OR 1.5) and dialysis requirement (OR 2.37) in the cohort. Notably, this association appeared driven by women (OR 1.76 for CKD, OR 3.26 for dialysis), as it was not noted in men.

Stankus et al³⁶ compared the incidence of pre-ESRD kidney stones in a cohort of African American hemodialysis patients. In the sample of 300 subjects, 8.2% had a history of nephrolithiasis prior to initiating dialysis, compared to 2.8% of patients matched for age, sex, and race in the NHANES III cohort. Generally, patients of African descent are at a lower risk for kidney stone disease³⁷, but at a higher risk for ESRD³⁸. This data suggest that those already at risk for CKD may have an additive burden in the face of nephrolithiasis.

Several studies out of the Mayo clinic shed further light on the association between stone disease and CKD. In a nested case-control study in residents of Olmstead County, Saucier et al³⁹ compared the characteristics of stone formers with CKD (n=53) and those without CKD (n=106). Predictably, subjects with CKD were more likely to have diabetes (OR 4.27) and hypertension (OR 3.57), as well as recurrent UTIs (OR 5.81). CKD sufferers were also more likely to have had an ileal conduit (OR 7.69) and to have had a documented struvite stone (OR 15.61). Obesity and smoking were also more frequent in the CKD group, but this did not reach statistical significance.

Concurrently, the Mayo group also reported on a much larger population-based cohort study, identifying all incident stone formers (n=4066) in Olmstead County diagnosed between 1986 and 2003 and matched to control subjects (n=10,150) from the local area⁴⁰. Incidence of CKD was determined using both diagnostic codes and lab confirmation of decreased GFR (eGFR<60ml/min/1.73 m²) sustained 3 months. Stone formers were more likely to have underlying hypertension, gout, diabetes, obesity, and coronary artery disease, but even in analyses adjusted for these CKD risk factors, risk of clinical CKD was 50–67% higher in stone formers than in controls.

Most recently, the Mayo group focused on the association of urolithiasis with ESRD⁴¹. The authors identified newly diagnosed stone formers in Olmstead County between 1984 and 2008 and matched each individual by age and sex to up to four controls without stone disease. After adjusting for classic cardiovascular risk factors such as diabetes, gout, obesity, hyperlipidemia, and, notably, CKD, stone formers had more than twice the risk of developing ESRD compared to controls (HR 2.09). The findings were similar (HR 1.95) in a subset of patients who were validated to be symptomatic stone formers by chart review.

The association between stone disease and renal dysfunction does not appear to be limited to the United States. In a registry cohort study of adults living in Alberta, Canada between 1997–2009 encompassing nearly two million subjects, a significant association between one or more episodes of kidney stones and development of new stage 3b-5 CKD (HR 1.74), ESRD (HR 2.16) or a sustained doubling of serum creatinine from baseline was noted (HR 1.94) over a median follow up of 4 years⁴². Across the Atlantic, in a large British population-based cohort study of over 1.5 million designed to develop a prediction model for risk of moderate-to-severe CKD⁴³, the adjusted risk for moderate-to-severe CKD was 1.27 in females, but not males, with a history of nephrolithiasis. The adjusted risk for ESRD was double in females with a history of stone disease (HR 2.1), but the association was not present in males.

Despite these strong associations, however, it is important to note that only 0.2% of incident ESRD patients from 2004–2008 had nephrolithiasis listed as a primary etiology on the CMS ESRD Medical Evidence Form⁴⁴. The complications of CKD should not be discounted, however, as the associations between CKD and cardiovascular disease and mortality are well described⁴⁻⁷. Furthermore, while nephrolithiasis may not be the primary reason for an individual's ESRD, evidence of distorted renal architecture in stone formers^{11,24} could be conceived to predispose to injury from other causes.

Is There a Dose Effect?

If kidney stones are to be linked to a decrement in kidney function, one might expect that greater stone burden would be inversely associated with renal function. This is indeed what Ahmadi et al⁴⁵ noted in their study of 97 kidney stone formers presenting for ESWL. In patients with a total stone burden of <20 mm, each 1 mm increment in cumulative stone size (as determined by the sum of diameters of all stones present) was associated with a 20% increased risk of having chronic kidney disease in a multivariate model. This is particularly striking as urine calcium levels markedly decline with even a small decline in renal function⁴⁶. Thus in the case of calcium stones, it would be likely that the stone formation preceded the decline in GFR, though certainly causality cannot be established by these data.

Determinants of Decreased Renal Function

Kidney loss

Historically, much of the ESRD ascribed to stone disease has been attributed to patients with solitary kidneys. In an elegant study by Jungers et al⁴⁷, the authors reviewed the histories of 1391 consecutive patients with ESRD, of which 45 (3.2%) were attributed to nephrolithiasis. Struvite stones were noted in 19, calcium stones were noted in 12, and uric acid stones in eight, with the remainder due to hereditary stone disease (four with primary hyperoxaluria and two with cystinuria). Interestingly, 40% of subjects in this study had a solitary kidney prior the development of ESRD.

Worcester et al⁴⁸ characterized the etiology for presentation with a solitary kidney in a cohort of 115 patients with nephrolithiasis and a single kidney evaluated at the University of Chicago. The most common cause for loss of a kidney in this group of stone formers was a staghorn calculus or high stone burden (29%), followed by infection (23%), ureteral obstruction (21%), and surgical removal (8%). It should be noted, however, that with advances in surgical techniques, loss of a kidney due to stone disease is likely becoming significantly less common.

Idiopathic stones versus stones associated with systemic disease

If the majority of the burden of kidney disease is not in those with a solitary kidney, is there evidence that renal function is not normal in the routine stone former? Worcester et al⁴⁹ compared pretreatment CrCl values by stone type from 1856 stone formers presenting for their initial evaluation at the University of Chicago. Adjusted for anthropometric measures, CrCl was significantly lower in cystine stone formers compared to all others, while hydroxyapatite, calcium oxalate, and struvite stone formers had significantly lower CrCl compared to normal subjects. Notably, the mean CrCl values for all stone formers were essentially in the normal range (above 100 ml/min), but the discrepant values by stone type may point to variability in the injury mechanism. Similarly, when grouped by etiology of disease leading to kidney stones, patients with nephrolithiasis linked to bowel disease, bariatric surgery, and renal tubular acidosis had lower creatinine clearance than normal subjects.

Mechanisms of Renal Injury

Recurrent obstruction—A reasonable mechanism for renal injury in patients with stone disease is recurrent obstruction. While most often this represents an acute kidney injury (AKI), it is now clear that recurrent AKI episodes are a risk factor for development of CKD⁵⁰. Being unilateral in most cases, stone passage may not produce obvious signs of kidney injury in patients with two kidneys. For example, GFR is not likely to fall and sodium retention may not occur unless the contralateral kidney has CKD and is unable to compensate. Notably, with only one kidney, passage of a stone produces an obvious fall in renal function, sometimes anuria with marked renal failure.

Animal models indicate that ureteral obstruction can lead to renal injury via several mechanisms. Increased intratubular pressure may lead to significant renal vasoconstriction, resulting in a drop in renal blood flow, reduction in GFR, and tissue ischemia^{51, 52}.

Persistence of the ischemic state can lead to glomerulosclerosis, tubular atrophy, and subsequent interstitial fibrosis^{53, 54}. In rodent models, complete unilateral obstruction for 24 hours leads to irreversible dysfunction in 15% of the nephrons in the kidney⁵⁵. Little effect on the overall kidney function would be noted at first, but with repeated episodes it is plausible that the remaining nephrons have to increase their single nephron GFR, with resultant hyperfiltration and potential subsequent injury. In a large human case series of 2073 ureteral stones, Wang et al found the incidence of AKI to be 0.72% (15 patients), with eight of those patients having a unilateral stone⁵⁶. Of those eight subjects, however, seven had a single functioning renal unit, and the remaining subject had underlying CKD.

Associated diseases—In the Mayo study, risk factors identified among stone formers who developed CKD were hypertension and diabetes, diseases associated with both CKD and stone formation. Recurrent UTIs, struvite stones, and allopurinol therapy were other risk factors noted³⁹.

Decreased renal function: importance of stone type and histology

While the epidemiological data certainly indicate a relationship between stone formation and a decrement in kidney function, they are limited by the heterogeneous populations included in the study samples and hampered by use of billing records and diagnostic codes.

Additional limitations include the high prevalence of comorbid conditions such as diabetes and metabolic syndrome, as well as the retrospective nature of nearly all the current work⁵⁷.

In recent years, however, our group has pioneered advanced surgical and histopathological techniques to evaluate potential mechanisms of stone formation. These studies, performed on tissues obtained during percutaneous nephrolithotomy (PCNL) procedures, have revealed a surprising amount of injury in the renal papillae and cortices of many stone formers. It is plausible, however, that the degree of injury is accentuated by the selection bias of obtaining samples from stone formers with a high stone burden requiring PCNL.

Calcium Oxalate (CaOx)

Multiple etiologies exist for CaOx stone formation ranging from idiopathic hypercalciuria, to complications of bowel surgery, to inborn errors of metabolism. While each disorder leads

to the clinical phenotype of the CaOx stone former, recent investigation suggests that the mechanisms of stone formation vary by the underlying etiology, and are associated with strikingly different papillary histopathology.

The most common stones are idiopathic CaOx stones, which are not associated with systemic disease, but may be associated with a number of metabolic abnormalities such as idiopathic hypercalciuria, hypocitraturia, or dietary hyperoxaluria. Stones form as overgrowths on interstitial deposits of calcium phosphate that have come to be known as Randall's plaque, after Alexander Randall, who first described them. Histopathological analyses going back to the time of Randall⁵⁸ suggest that little interstitial inflammation is present surrounding these deposits (Figure 1, panel A). More recently, our group has confirmed the absence of overt inflammation or tissue injury in the interstitial compartment surrounding these deposits in the idiopathic calcium oxalate stone former^{15, 20, 22}.

In contrast, patients with CaOx stones stemming from other causes have calcium deposits in Bellini ducts (BD) and inner medullary collecting ducts (IMCD) which are associated with significant inflammatory changes and evidence of subsequent fibrosis. For example, patients with small bowel resections with subsequent CaOx nephrolithiasis have been shown to have the interstitial deposits classically seen in idiopathic CaOx stone formers, but also to have IMCD plugging with calcium phosphate²¹ (Figure 1, panel B). As in the idiopathic CaOx stone formers, no inflammation is seen in areas of interstitial plaque despite substantial interstitial plaque burden, but significant inflammation and fibrosis was noted surrounding the plugged IMCD. Perhaps more notably, cortical changes including moderate to severe glomerular sclerosis and mild to moderate interstitial fibrosis were noted in the majority of studied patients²¹ (Figure 1, panel F), whereas the cortices of idiopathic stone formers were without abnormalities (Figure 1, panel E).

Not all patients with nephrolithiasis related to bowel pathology show the same histopathological characteristics. Patients with CaOx nephrolithiasis as sequela of bariatric bypass procedures show IMCD plugging with the inflammation and fibrosis similar to those with small bowel resections¹⁸ (Figure 1, panel C). However, these patients do not show evidence of Randall's plaque. Notably, some bypass patients had tiny focal crystal deposits within IMCD lumens (Figure 1, panel D), seemingly attached to cell membranes, whereas all patients demonstrated intratubular IMCD plugging. In addition, hyaluronan expression, a marker of cell injury, was noted in the IMCD tubule epithelium of tubules that were not involved with crystal deposits (Figure 1, panel G), suggesting that injury mediators may have influenced cells far away from actual crystal plugs¹⁸ (Figure 1, Panel H).

Mechanisms of crystal induced tubular damage have been pursued in animal models which most resemble primary hyperoxaluria. In these models, injury is thought to be either direct by crystal induced cellular death or indirect, via the inflammatory cascade⁵⁹. Crystals stimulate innate immunity via the NACHT, LRR, and PYD domains-containing-protein (NLRP)3 inflammasome⁵⁹. CaOx monohydrate (COM) crystals attach to MDCK cells⁶⁰. Once internalized, the crystals interfere with proteins responsible for energy production, resulting in the increased production of reactive oxygen species which are believed to stimulate inflammation⁶¹. Of note, oxalate ion itself, in high concentrations, has been

associated with adverse biologic effects and loss of cell viability in in-vitro experiments with various renal tubular cell lines,^{62, 63} but relevance of these findings to human disease is unknown at this time.

Calcium Phosphate

Calcium phosphate stones come in two varieties: brushite (BR) and hydroxyapatite (HA). Data from our group demonstrate that both stone types are associated with BD tubular plugging, as well as variable stone growth over plaque²² (Figure 2, Panels A and B). BD can be dilated nearly 20-fold. Epithelium of plugged tubules is injured and in many cases lost altogether so that crystals reach the basement membrane. Peritubular fibrosis is invariable. Cortical injury is present in both HA and BR calcium phosphate stone formers at levels above what is found in ICSF (Figure 2, panels E and F).

While the most common stone type in patients with primary hyperparathyroidism is CaOx, as in the general population, the proportion of patients with calcium phosphate stone disease is much higher in those with the endocrine disorder⁶⁴. In our surgical biopsy series, patients with calcium phosphate stone disease stemming from hyperparathyroidism demonstrated findings similar to that of brushite stone formers with ICMD and BD plugging composed of apatite crystals and accompanied by loss of epithelial cells¹¹ (Figure 2, panel C). There was surrounding peritubular interstitial inflammation and fibrosis, with significant retraction of papillae. However, the findings were less pronounced than those seen in BR stone disease and there was more variability in the degree of papillary distortion among patients. Patients with primary hyperparathyroidism demonstrated stone growth on Randall's plaque, more often than idiopathic BR or HA patients⁶⁴.

Another singular group of stone formers with calcium phosphate stones are those with distal tubular acidosis (dRTA). Characterized by calcium apatite stone formation and diffuse nephrocalcinosis, patients in our surgical series also demonstrated plugging of BD and IMCD¹⁶ like their counterparts without systemic illness, but the degree and distribution of plugging was far greater (Figure 2, panel D). The crystals within the plugs were HA and there was a marked degree of associated epithelial cell injury and loss. Furthermore, the degree of fibrosis surrounding the plugged tubules was significantly greater in those with dRTA, and was detected even in the absence of tubular plugging. It is worth noting that while there are genetic causes of dRTA, there is no reason to believe that the histological findings would differ.

Struvite

Struvite (magnesium ammonium phosphate) stones are formed exclusively in the presence of bacteria possessing the urease enzyme to hydrolyze urea to ammonia. The resultant high urine pH and ammonium concentrations predispose to the growth of struvite either alone or admixed with preexisting calcium stones⁶⁵. Struvite stones are particularly hazardous to kidney function as they grow rapidly and can form staghorn stones filling the entire collecting system of the kidney, increasing the risk for significant obstruction. Large staghorn stones may also predispose the kidney to papillary necrosis.

Patients with recurrent urinary tract infections, instrumentation, anatomic abnormalities of the urinary tract, and urinary diversion are at particularly high risk for struvite stones and renal dysfunction⁶⁶. However, even patients without such underlying risk factors who form struvite stones are at risk for reduced renal function. In a series of 75 patients with struvite stones from our center that excluded those with underlying anatomic abnormalities, 25 had serum creatinines that were more than 2 SD above normal for sex⁶⁷. Twenty four of these patients had staghorn stones and 11 had undergone a nephrectomy. Creatinine clearance was significantly reduced in both men and women. The mechanism of injury is almost certainly obstruction and local injury, with loss of functional nephron mass.

Uric Acid

Uric acid nephrolithiasis, accounting for 8–10% of stone disease in the Western world, is becoming increasingly common as populations grow older and more obese⁶⁸. Associated risk factors include diabetes mellitus type 2, hypertension, and obesity with the metabolic syndrome, which is known to be associated with low urinary pH⁶⁸. Low urinary pH is a requirement for the precipitation of uric acid crystals.

Indirect evidence from epidemiologic data suggests that uric acid stone formers are particularly prone to the development of CKD. For example, in the report from Olmstead county³⁹, patients with a documented uric acid stone were three times more likely to develop CKD, though this association was not significant. Subjects receiving allopurinol therapy, presumably for gout and with a likely predisposition to uric acid nephrolithiasis, were 10-fold more likely to develop CKD, which was highly significant. Of course, they may have also been receiving allopurinol due to hyperuricemia stemming from CKD. From a histopathological perspective, uric acid crystals are known to deposit in BD and IMCD⁶⁹, whereas sodium mono-hydrogen urate crystals deposit in the renal interstitial space with associated inflammatory response and fibrosis⁷⁰.

One group of patients particularly prone to uric acid stone disease is those with ileostomies. Due to excessive enteric losses of water and alkali, patients with ileostomies have acidic urine and low urine volumes, optimal conditions for uric acid crystallization. Interestingly, in our surgical series¹⁹ patients with ileostomies were also found to have BD and IMCD plugging with apatite, as well as interstitial apatite plaque, a constellation of findings more characteristic of those with intestinal bypass surgery.

Comparison of Histopathologic Findings with Other Series

Others have begun to explore papillary histopathology in a variety of stone formers. Linnes et al enrolled 78 consecutive stone formers undergoing PCNL at Mayo to evaluate the correlation of stone type to Randall's plaque burden, tubular plugging, and metabolic parameters⁷¹. Generally, findings were similar to our group's with the greatest amount of plaque burden in those with CaOx stone disease and the least in those with uric acid stones, while tubular plugging was greatest in those with brushite nephrolithiasis. Overall the amount of plaque seen in CaOx stone formers was less than seen in our cohort, but the study population was not selected for hypercalciuria as in our series and included subjects with primary hyperoxaluria, primary hyperparathyroidism, and bowel disease. More recently, the

Mayo group compared the histopathology of patients with uric acid stones to those with CaOx disease⁶⁹. As in our series, their subjects with UA stones had a high degree of IMCD plugging, despite a low percentage of patients (<10%) with small bowel resection.

Genetic Diseases with Nephrolithiasis and Kidney Disease

Primary Hyperoxaluria

A small portion of patients presenting with CaOx stones will have underlying Primary Hyperoxaluria (PH). A group of inborn metabolic disorders, the primary hyperoxalurias are characterized by liver enzyme deficiencies that result in overproduction of oxalate, which must be excreted through the kidney.

Patients typically present early in childhood, with 85% of patients diagnosed before age 20⁷². Recurrent stone formation throughout childhood and adolescence, along with nephrocalcinosis, is typical. The median age of progression to ESRD is 33⁷³. While it has been widely accepted that CaOx crystallization can be harmful to cells^{74, 75}, only recently the histopathological changes through the cycle of PH Type 1 from normal renal function to ESRD on dialysis have been demonstrated.

Evaluating differences in the patterns of injury between kidneys of PH1 patients with normal renal function (obtained during PCNL for stone), those just started on renal replacement therapy, and those on long term dialysis, Worcester et al⁷⁵ demonstrated that while renal function is preserved, CaOx crystals in the cortical S1 and S2 proximal tubule segments are present but not accompanied by inflammation or scarring. Papillary findings early in the course of the disease are characterized by IMCD plugging with CaOx crystals and extensive interstitial fibrosis of the papillary tip (Figure 3, panels A and B). By the time the PH1 patient is started on dialysis, intratubular deposits of CaOx are predominately found at the proximal tubule's S3 segment at the corticomedullary junction, as well as in cells and in the surrounding interstitial space. In advanced disease on long term dialysis, intratubular deposits were prevalent throughout the cortex.

Cystinuria

A stone type commonly associated with kidney disease is cystine. While only 5% of patients with cystinuria progress to ESRD, up to 70% of patients develop evidence of renal dysfunction⁷⁶. Biopsies from patients with cystine stones show a variety of histopathologies ranging from normal to tubular plugging, severe injury to BD, and plugging of the IMCD¹⁴ (Figure 3, panel C). Plugging within the BD is typically with cystine aggregates, while the loop of Henle and the IMCD are typically filled with HA crystals (Figure 3, panel D). The mechanism of injury is thought to be secondary to tubular obstruction with the secondary cell injury, interstitial inflammation, glomerular loss, and cortical fibrosis¹⁴.

Adenine Phosphoribosyltransferase (APRT) Deficiency and 2,8-dihydroxyadeninuria

APRT deficiency is a rare autosomal recessive inborn error of adenine metabolism that leads to accumulation of the very poorly soluble dihydroxyadenine (DHA)⁷⁷. Prevalent in Japan, France, and Iceland, among others, this disorder resulting in DHA accumulation can lead to

both discrete stone formation and a crystal mediated nephropathy^{78, 79} (Figure 3, panels E and F). Due to its similarity to uric acid stone disease, with radiolucent stones and a low index of suspicion, stones are often mistakenly identified as uric acid. This is problematic as early identification of the disorder with timely initiation of therapy with a xanthine oxidase inhibitor can prevent the onset of renal failure. Currently, APRT deficiency appears to be a highly unrecognized cause of kidney stones with CKD, which can progress to ESRD in a large proportion of affected patients that are untreated⁷². While recurrent obstruction, hematuria, and recurrent urinary tract infections are common presentations in children, adults are more likely to present with ESRD secondary to crystalline nephropathy^{78, 79}. Several publications report cases of the diagnosis being made only after renal transplantation⁸⁰⁻⁸².

Dent Disease

Dent disease is an X-linked disorder caused by mutations in either the *CLCN5* or *OCRL1* genes and is characterized by low molecular weight proteinuria and the presence of hypercalciuria, nephrolithiasis, or nephrocalcinosis⁷². Typically patients present in childhood with nephrocalcinosis, proteinuria, or unexplained CKD, with subsequent progression to CKD noted by the 3rd to 5th decade in 30–80% of male subjects⁸³. Biopsy findings of nephrocalcinosis and interstitial fibrosis are typical in patients with Dent disease⁷². In recent years, a subset of patients with nephrotic range proteinuria and biopsy findings of focal segmental glomerulosclerosis (FSGS) has been identified^{84, 85}, but the contribution of glomerular disease to renal dysfunction in Dent Disease remains unclear.

Conclusion

The posed question is whether patients with nephrolithiasis have a kidney disease? Using epidemiologic data, the answer is a resounding “yes” given the strong associations with CKD and ESRD.

A more nuanced argument requires a clearer definition of disease. If kidney disease is thought of as a decrement in GFR, indirect evidence using eGFR and creatinine clearance would suggest that some stone types can be thought of as disease states. For example, given the association of PH1, cystinuria, and ileostomy with stone disease with decreased GFR, these states can be thought of as having renal manifestations.

On a broader platform, if disease is defined as a tissue abnormality, nearly all stone formers, with perhaps the exception of idiopathic CaOx stone formers, can be thought of as afflicted.

Perhaps the bigger question in the age of personalized medicine is how we can use our current knowledge to better identify individual stone patients at risk for kidney complications downstream. Does every first time CaOx stone former have a disease? How can we best utilize the metabolic data typically collected during evaluation, in conjunction with surgical imaging, to identify those at risk for CKD down the line? Do histological abnormalities seen in the kidneys of some stone formers portend the same associated risk factors of cardiovascular and bone disease as that in patients with CKD from other causes?

Unfortunately at this time, we have more questions than answers – though without a doubt the answer to the question of kidney stone formers having a disease is certainly “yes.”

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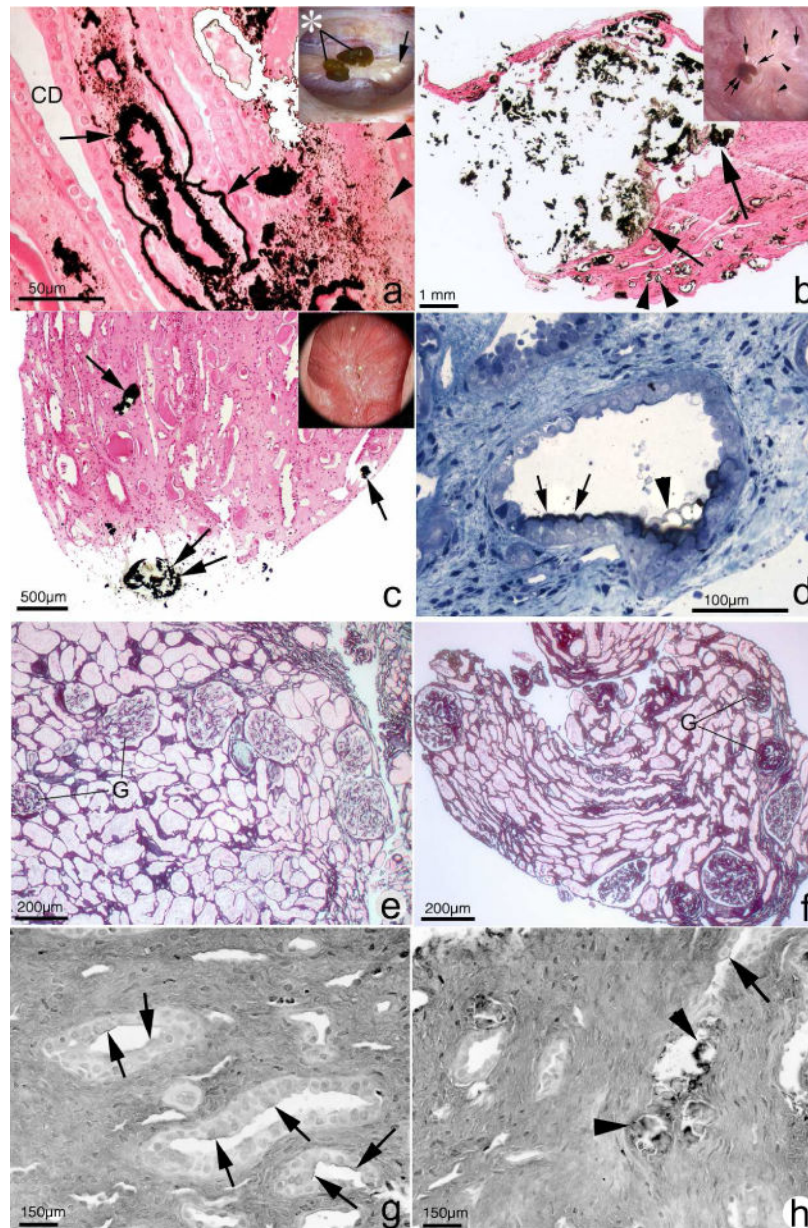


Figure 1. Histopathology of renal papilla and cortex from CaOx stone formers. Papillary tissue of ICSF patients (panel A) shows initial sites of individual calcium phosphate deposits (arrowheads) by Yasue stain (brown-black deposits) in the basement membranes of thin loops of Henle when viewed by light microscopy. These individual deposits coalesce in the interstitial space to form islands of mineral encased in matrix material (arrows) that can extend to the basal side of the urothelium. No evidence of cell injury or inflammation has been noted in the collecting ducts (CD) or interstitium of these papilla. Endoscopic examination of the papilla of ICSF patients reveals small stones (insert panel A, asterisk) attached to the papilla by way of white or interstitial plaque (arrow). In addition to sites of interstitial plaque (panel B, double arrowhead), the papilla of patients with small bowel

resection show intraluminal plugs of varying size in the IMCD (arrows). These deposits contained a mixture of CaOx, apatite and ammonium acid urate. Note the extensive interstitial fibrosis surrounding the IMCD plug. These patients also have attached stones (insert panel B, double arrow) at sites of white plaque (arrows). Areas of yellow plaque are also seen (arrowheads). Papilla of intestinal bypass patients for obesity possesses little to no interstitial plaque (panel C) but have a few intraluminal plugs in IMCD (arrow) and ducts of Bellini (double arrow) composed of apatite and CaOx. The insert in panel C shows a dilated opening to a BD (arrowhead). The initial layer of mineral to coat the apical surface of the lining cells of IMCD of these patients is Yasue positive (panel D, arrows) and particularly clear at the arrowhead. Panel E shows a cortical biopsy from an ICSF patient revealing only minimal interstitial fibrosis and glomerular (G) changes. A moderate level of change is seen panel F from a patient with small bowel resection. Panels G and H show sites of hyaluronan staining (arrows) in papillary tissue from intestinal bypass patients revealing areas of cell surface changes at sites of crystal deposits (panel H, arrowheads) or away from deposits (panel G).

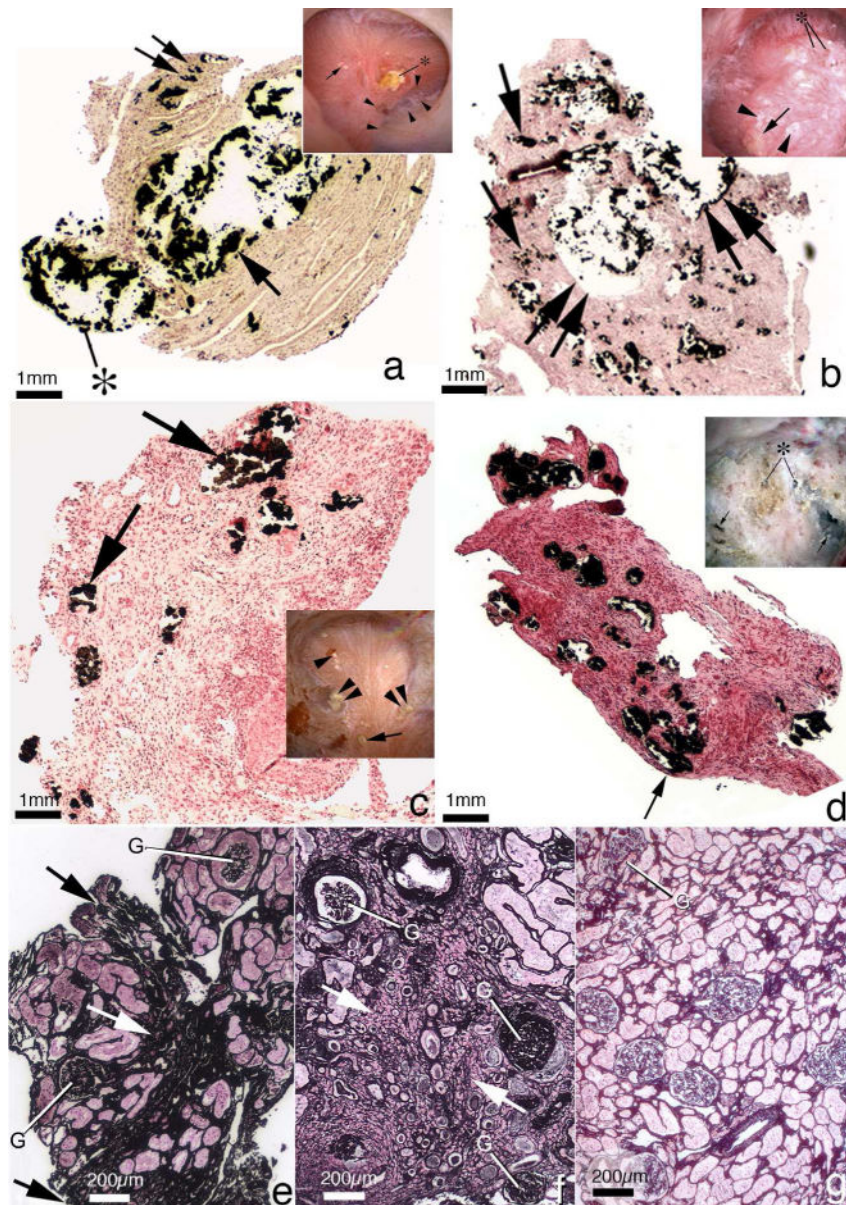


Figure 2. Histopathology of renal papilla and cortex from apatite and brushite stone formers. Panel A is a low magnification light microscopic image of a renal papilla from a brushite stone former showing an enormous amount of Yasue-positive deposits (arrow) filling a grossly dilated IMCD and BD. The crystalline material is protruding (asterisk) from the dilated opening of a BD. Sites of interstitial plaque are noted through out papilla (double arrow). Insert to panel A shows endoscopic view of papillum from brushite patients characterized by areas of white plaque (arrows), yellowish crystalline material protruding from dilated BD (asterisk), pitting (arrowheads) and sites of yellow plaque. Panel B is a histologic section from an apatite stone former with large fields of interstitial plaque termed “novel interstitial plaque structures” (NIPS, arrows) located near greatly dilated IMCD and BD filled with Yasue-positive deposits (double arrows) which are hydroxyapatite. Extensive regions of

interstitial fibrosis surround the dilated IMCD and NIPS. The insert in panel B shows endoscopic view of a papilla from an apatite stone former characterized by sites of white plaque (arrowheads), protruding plugs for dilated opening of BD (asterisk) and an occasional site of yellow plaque (arrow). Panel C is a histologic section from a patient with primary hyperparathyroidism with stones. These patients show numerous IMCD with apatite plugs (arrows), extensive interstitial fibrosis at sites of intraluminal plugs and areas of interstitial plaque. The insert in panel C shows an endoscopic view of a papilla from a patient with primary hyperparathyroidism characterized by attached stone to white plaque, sites of yellow plaque (double arrows), interstitial plaque (arrowhead), and dilated BD with protruding plug (double arrowhead). Panel D is a histologic section from a patient with distal renal tubular acidosis presenting with diffuse IMCD plugging (arrows), severe and diffuse interstitial fibrosis and little to no interstitial plaque. The insert to panel D shows endoscopic view of a papilla from a patient with distal renal tubular acidosis characterized extensive papillary damage with retraction, loss of normal architecture, multiple dilated BD that produce a pitted appearance (arrows), some with protruding mineral deposits (asterisks) and a whitish thickened membrane appearance. Panel E shows a cortical biopsy from an apatite stone former revealing a moderate level of interstitial fibrosis (arrow) and glomerular (G) changes while panel F shows a severe level of interstitial fibrosis (arrow) and glomerular (G) change in a brushite stone former. Panel H shows a cortical biopsy from a patient with distal renal tubular acidosis revealing only a minimal level of change.

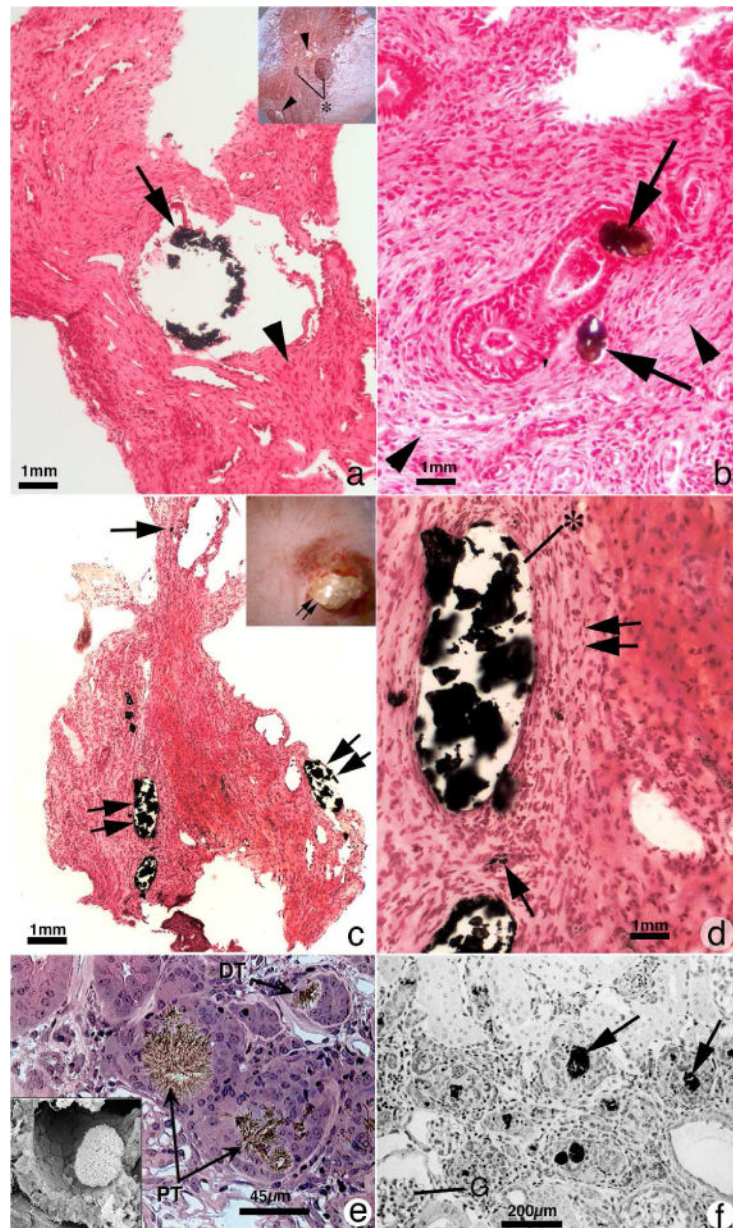


Figure 3. Histopathology of renal papilla from primary hyperoxaluria, cystine and DHA stone formers. Panel A is a histologic section from a primary hyperoxaluric stone former with normal renal function showing isolated dilated IMCD filled with CaOx mineral (arrow) encased in regions of extensive interstitial fibrosis (arrowhead). Sites of interstitial plaque were rare. Insert to panel A shows endoscopic view of papillum from a primary hyperoxaluric stone former characterized by a few dilated ducts of Bellini with and without (asterisk) protruding plugs were seen scattered between sites of yellow plaque (arrowheads). Panel B is a higher magnification Yasue-stained tissue section showing regions of extensive interstitial fibrosis adjacent to and away from (arrowheads) sites of intraluminal IMCD deposits. Panel C is a Yasue-stained histologic section from a patient with cystine stones

revealing numerous dilated IMCD (double arrows) and BD plugged primarily apatite with a few BD containing cystine deposits. Occasionally a thin loop of Henle was noted plugged with apatite deposits (arrow). Panel D is a higher magnification image of a region from panel C showing extensive interstitial fibrosis (double arrow) adjacent to sites of intraluminal IMCD deposits (asterisk) and an occasional site of interstitial plaque (arrow). Panels E and F show the morphology of 2,8-dihydroxyadenine (DHA) crystal in kidneys from adenine phosphoribosyltransferase (Aprt)-deficient mice that resembles human Aprt deficiency. In panel E two proximal (PT, arrows) and a distal tubule (DT, arrow) is seen, each with large brownish-red crystals in the tubular lumens. Interstitial fibrosis is noted around glomeruli and various tubular segments. The insert in panel E shows by scanning electron microscopy an individual DHA crystal in the lumen of a proximal tubule. Panel F shows numerous DHA crystals (arrows) in the cortex of an Aprt-deficient mouse with advanced pathology (score of 4) characterized by interstitial fibrosis and glomerulosclerosis (G).