

# Do kidney stone formers have a kidney disease?

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**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.**

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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,<sup>1,2</sup> metabolic disturbances,<sup>3</sup> and renal complications including chronic kidney disease (CKD) and end-stage renal disease (ESRD).<sup>4–7</sup> 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

Although 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 al.*<sup>8</sup> 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<sup>9,10</sup> have expanded the definition of CKD from simply a decreased GFR to the presence of any of the following for more than 3 months: estimated GFR (eGFR) < 60 ml/min per 1.73 m<sup>2</sup>, 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

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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 patients.<sup>11–24</sup> Furthermore, recent data highlight the increased prevalence of albuminuria and renal scarring even in asymptomatic stone formers—both considered diagnostic for CKD.<sup>25</sup> In healthy subjects being evaluated for kidney donation at the Mayo clinic, subjects noted to have asymptomatic kidney stones on computerized tomography imaging were significantly more likely than donors without a stone to have renal parenchymal thinning and focal scarring.<sup>25</sup> Furthermore, among subjects who had previously had a symptomatic stone event, 13% had evidence of albuminuria of  $>30$  mg/24 h, compared with 3.5% and 3.6% of subjects with no stone disease and asymptomatic stone disease, respectively.

Although albuminuria is suggestive of glomerular injury, markers of tubular injury are also elevated in patients in nephrolithiasis. Sun *et al.*<sup>26</sup> 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 hypertension<sup>27</sup> and in activation of signaling pathways associated with inflammation, generation of reactive oxygen species, and endothelial dysfunction.<sup>28</sup> Urinary angiotensinogen levels were also significantly correlated with urinary  $\alpha 1$ -microglobulin, a marker of proximal tubular injury that is believed to be one of the earliest markers of tubular dysfunction.<sup>29</sup> Urinary excretion of 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage associated with glomerular and interstitial fibrosis,<sup>30</sup> is also increased in stone formers.<sup>31</sup> Furthermore, immunohistochemical analysis demonstrates increased 8-hydroxydeoxyguanosine expression in the renal tissue adjacent to stone in subjects with nephrolithiasis.<sup>32</sup>

## EPIDEMIOLOGIC DATA

The earliest study to note the relationship between nephrolithiasis and CKD in the general population was performed by Vupputuri *et al.*<sup>33</sup> In their case-control study performed in North Carolina, the authors analyzed 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 with 6.4% of controls. After adjustment for comorbidities, CKD was nearly twice as likely (odds ratio (OR)=1.9) in those with a history of nephrolithiasis.

The following year Gillen *et al.*<sup>34</sup> 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 (body mass index  $>27$ ) had a mean eGFR of 3.4 ml/min per 1.73 m<sup>2</sup> lower than their non-stone-forming counterparts. This difference was not noted in those with a body mass index  $<27$ .

More recent data by Shoag *et al.* using the NHANES 2007–2010 database confirm the association between kidney stones and CKD.<sup>35</sup> 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 al.*<sup>36</sup> 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 before initiating dialysis, compared with 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 disease<sup>37</sup> but at a higher risk for ESRD.<sup>38</sup> These 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 al.*<sup>39</sup> 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 urinary tract infections (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 area.<sup>40</sup> Incidence of CKD was determined using both diagnostic codes and lab confirmation of decreased GFR (eGFR  $<60$  ml/min per 1.73 m<sup>2</sup>) sustained  $\geq 3$  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 ESRD.<sup>41</sup> 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 with 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 and 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 (HR = 1.94) was noted over a median follow-up of 4 years.<sup>42</sup> 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 CKD,<sup>43</sup> 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 to 2008 had nephrolithiasis listed as a primary etiology on the CMS ESRD Medical Evidence Form.<sup>44</sup> The complications of CKD should not be discounted, however, as the associations between CKD and cardiovascular disease and mortality are well described.<sup>4-7</sup> Furthermore, although nephrolithiasis may not be the primary reason for an individual's ESRD, evidence of distorted renal architecture in stone formers<sup>11-24</sup> 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 al.*<sup>45</sup> noted in their study of 97 kidney stone formers presenting for extracorporeal shock wave lithotripsy. 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 CKD in a multivariate model. This is particularly striking as urine calcium levels markedly decline with even a small decline in renal function.<sup>46</sup> Thus, in the case of calcium stones, it would be likely that the stone formation preceded the decline in GFR, although 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 al.*,<sup>47</sup> the authors reviewed the histories of 1391 consecutive patients with ESRD, of which 45 patients (3.2%) were attributed to nephrolithiasis. Struvite stones were noted in 19 patients, calcium stones were noted in 12 patients,

and uric acid stones in 8 patients, with the remainder attributed to hereditary stone disease (4 with primary hyperoxaluria (PH) and 2 with cystinuria). Interestingly, 40% of subjects in this study had a solitary kidney before the development of ESRD.

Worcester *et al.*<sup>48</sup> 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 a 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 al.*<sup>49</sup> 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 with all others, whereas hydroxyapatite (HA), calcium oxalate (CaOx), and struvite stone formers had significantly lower CrCl compared with 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 compared with normal subjects.

### Mechanisms of renal injury

**Recurrent obstruction.** A reasonable mechanism for renal injury in patients with stone disease is recurrent obstruction. Although most often this represents an acute kidney injury, it is now clear that recurrent acute kidney injury episodes are a risk factor for the development of CKD.<sup>50</sup> 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.<sup>51,52</sup> Persistence of the ischemic state can lead to glomerulosclerosis, tubular atrophy, and subsequent interstitial fibrosis.<sup>53,54</sup> In rodent models, complete unilateral



obstruction for 24 h leads to irreversible dysfunction in 15% of the nephrons in the kidney.<sup>55</sup> 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 acute kidney injury to be 0.72% (15 patients), with 8 of those patients having a unilateral stone.<sup>56</sup> 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 urinary tract infections, struvite stones, and allopurinol therapy were other risk factors noted.<sup>39</sup>

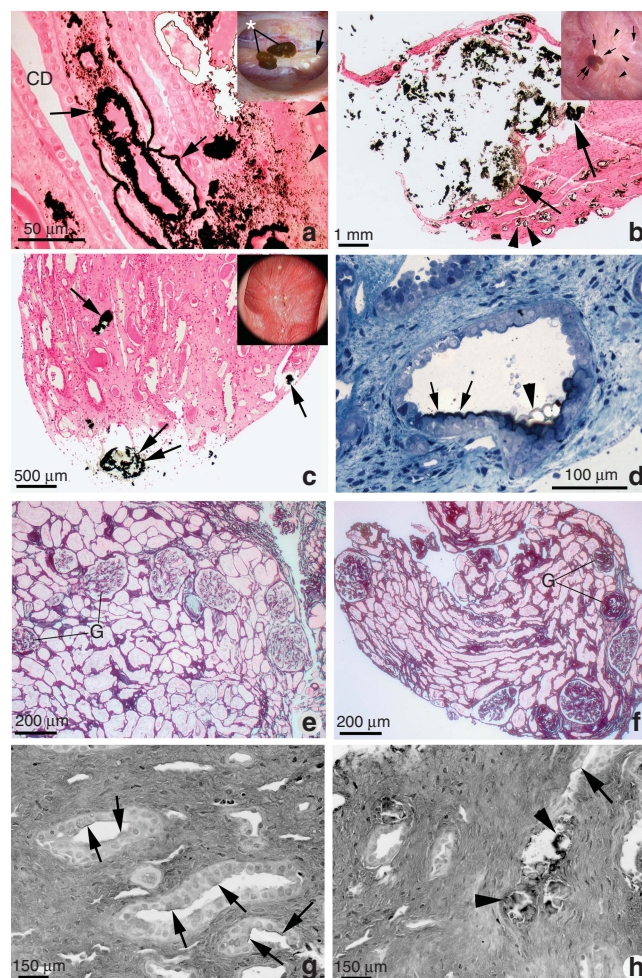
### DECREASED RENAL FUNCTION: IMPORTANCE OF STONE TYPE AND HISTOLOGY

Although 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 the 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 work.<sup>57</sup> 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 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 percutaneous nephrolithotomy.

#### Calcium oxalate

Multiple etiologies exist for CaOx stone formation ranging from idiopathic hypercalciuria, to complications of bowel surgery, to inborn errors of metabolism. Although 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 Randall<sup>58</sup> suggest that little interstitial inflammation is present surrounding these deposits (Figure 1a). More recently, our



**Figure 1 | Histopathology of renal papilla and cortex from calcium oxalate (CaOx) stone formers.** Papillary tissue of idiopathic calcium stone formers (ICSF) patients (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 (CDs) or interstitium of these papilla. Endoscopic examination of the papilla of ICSF patients reveals small stones (inset in a, asterisk) attached to the papilla by way of white or interstitial plaque (arrow). In addition to sites of interstitial plaque (b, double arrowhead), the papilla of patients with small bowel resection show intraluminal plugs of varying size in the inner medullary collecting ducts (IMCDs; 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 (inset in b, double arrow) at sites of white plaque (arrows). Areas of yellow plaque are also seen (arrowheads). Papilla of intestinal bypass patients for obesity possess little to no interstitial plaque (c) but have a few intraluminal plugs in IMCDs (arrow) and ducts of Bellini (double arrow) composed of apatite and CaOx. The inset in c shows a dilated opening to a Bellini duct (BD; arrowhead). The initial layer of mineral to coat the apical surface of the lining cells of IMCDs of these patients is Yasue positive (d, arrows) and particularly clear at the arrowhead. (e) A cortical biopsy from an ICSF patient revealing only minimal interstitial fibrosis and glomerular (G) changes. A moderate level of change is seen in f from a patient with small bowel resection. (g and h) Sites of hyaluronan staining (arrows) in papillary tissue from intestinal bypass patients revealing areas of cell surface changes at sites of crystal deposits (h, arrowheads) or away from deposits (g).

group has confirmed the absence of overt inflammation or tissue injury in the interstitial compartment surrounding these deposits in the idiopathic CaOx stone former.<sup>15,20,22</sup>

In contrast, patients with CaOx stones stemming from other causes have calcium deposits in Bellini ducts (BDs) and inner medullary collecting ducts (IMCDs), 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 phosphate<sup>21</sup> (Figure 1b). 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 were 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 patients<sup>21</sup> (Figure 1f), whereas the cortices of idiopathic stone formers were without abnormalities (Figure 1e).

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 resections<sup>18</sup> (Figure 1c). However, these patients do not show evidence of Randall's plaque. Notably, some bypass patients had tiny focal crystal deposits within IMCD lumens (Figure 1d), 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 1g), suggesting that injury mediators may have influenced cells far away from actual crystal plugs<sup>18</sup> (Figure 1h).

Mechanisms of crystal-induced tubular damage have been pursued in animal models, which most resemble PH. In these models, injury is thought to be either direct by crystal-induced cellular death or indirect by the inflammatory cascade.<sup>59</sup> Crystals stimulate innate immunity via the NACHT, LRR, and PYD domain-containing-protein (NLRP)3 inflammasome.<sup>59</sup> CaOx monohydrate crystals attach to MDCK cells.<sup>60</sup> 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 inflammation.<sup>61</sup> 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,<sup>62,63</sup> 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 HA. Data from our group demonstrate that both stone types are associated with BD tubular plugging, as well as

variable stone growth over plaque<sup>22</sup> (Figure 2a 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 idiopathic calcium stone formers (Figure 2e and f).

Although 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 disorder.<sup>64</sup> In our surgical biopsy series, patients with calcium phosphate stone disease stemming from hyperparathyroidism demonstrated findings similar to those of BR stone formers with IMCD and BD plugging composed of apatite crystals and accompanied by loss of epithelial cells<sup>11</sup> (Figure 2c). There was surrounding peritubular interstitial inflammation and fibrosis, with significant retraction of papillae. However, the findings were less pronounced compared with 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 patients.<sup>64</sup>

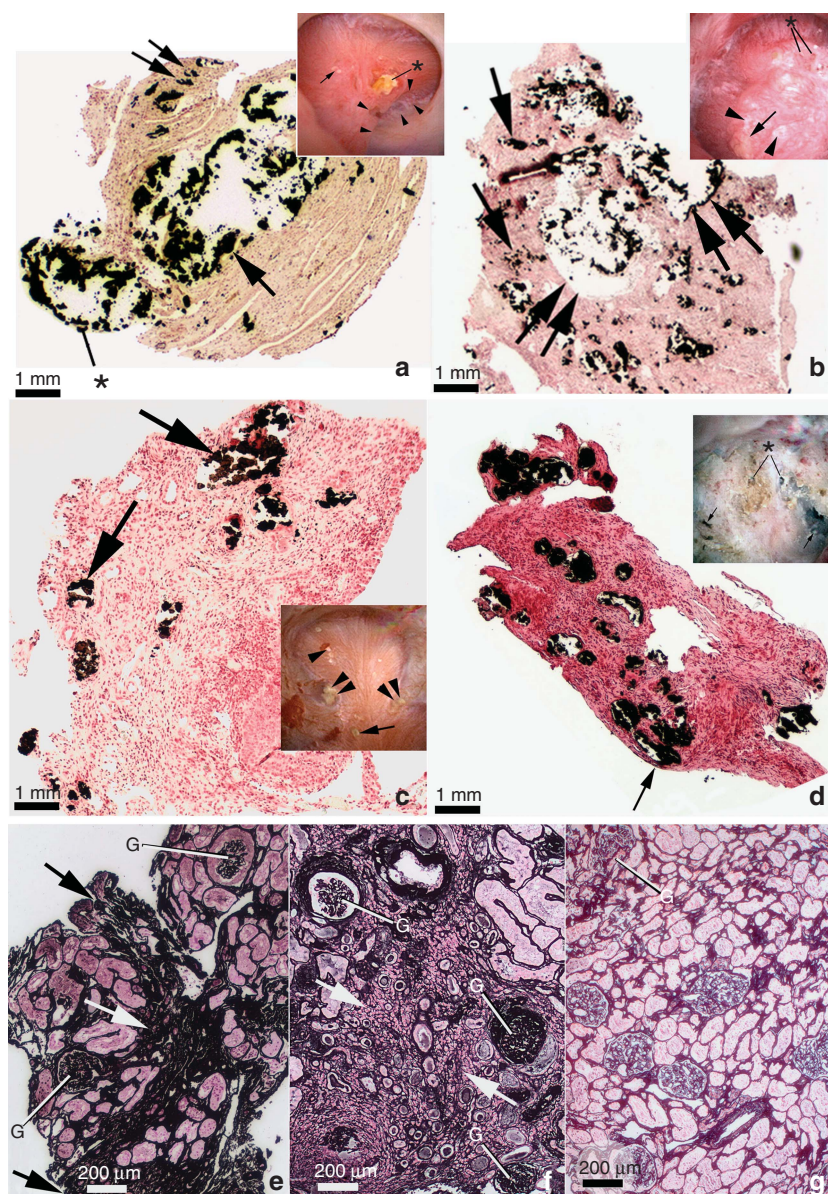
Another singular group of stone formers with calcium phosphate stones are those with distal tubular acidosis. Characterized by calcium apatite stone formation and diffuse nephrocalcinosis, patients in our surgical series also demonstrated plugging of BDs and IMCDs<sup>16</sup> similar to their counterparts without systemic illness, but the degree and distribution of plugging were far greater (Figure 2d). 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 distal tubular acidosis and was detected even in the absence of tubular plugging. It is worth noting that, although there are genetic causes of distal tubular acidosis, 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 stones.<sup>65</sup> 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 dysfunction.<sup>66</sup> 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





**Figure 2 | Histopathology of renal papilla and cortex from apatite and brushite stone formers.** (a) 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 inner medullary collecting duct (IMCD) and Bellini duct (BD). The crystalline material is protruding (asterisk) from the dilated opening of a BD. Sites of interstitial plaque are noted throughout papilla (double arrow). Inset in **a** shows an endoscopic view of papillum from brushite patients characterized by areas of white plaque (arrows), yellowish crystalline material protruding from dilated BDs (asterisk), pitting (arrowheads), and sites of yellow plaque. (b) 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 IMCDs and BDs filled with Yasue-positive deposits (double arrows), which are HA. Extensive regions of interstitial fibrosis surround the dilated IMCDs and NIPS. The inset in **b** shows an endoscopic view of a papilla from an apatite stone former characterized by sites of white plaque (arrowheads), protruding plugs for dilated opening of BDs (asterisk), and an occasional site of yellow plaque (arrow). (c) A histologic section from a patient with primary hyperparathyroidism with stones. These patients show numerous IMCDs with apatite plugs (arrows), extensive interstitial fibrosis at sites of intraluminal plugs, and areas of interstitial plaque. The inset in **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 BDs with protruding plug (double arrowhead). (d) 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 inset in **d** shows an endoscopic view of a papilla from a patient with distal renal tubular acidosis characterized by extensive papillary damage with retraction, loss of normal architecture, multiple dilated BDs that produce a pitted appearance (arrows), some with protruding mineral deposits (asterisks) and a whitish thickened membrane appearance. (e) A cortical biopsy from an apatite stone former revealing a moderate level of interstitial fibrosis (arrow) and glomerular (G) changes, whereas **f** shows a severe level of interstitial fibrosis (arrow) and glomerular (G) change in a brushite stone former. (g) A cortical biopsy from a patient with distal renal tubular acidosis revealing only a minimal level of change.



with struvite stones from our center that excluded those with underlying anatomic abnormalities, 25 patients had serum creatinines that were more than 2 s.d. above normal for sex.<sup>67</sup> 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 obese.<sup>68</sup> Associated risk factors include diabetes mellitus type 2, hypertension, and obesity with the metabolic syndrome, which is known to be associated with low urinary pH.<sup>68</sup> Low urinary pH is a requirement for the precipitation of uric acid crystals.

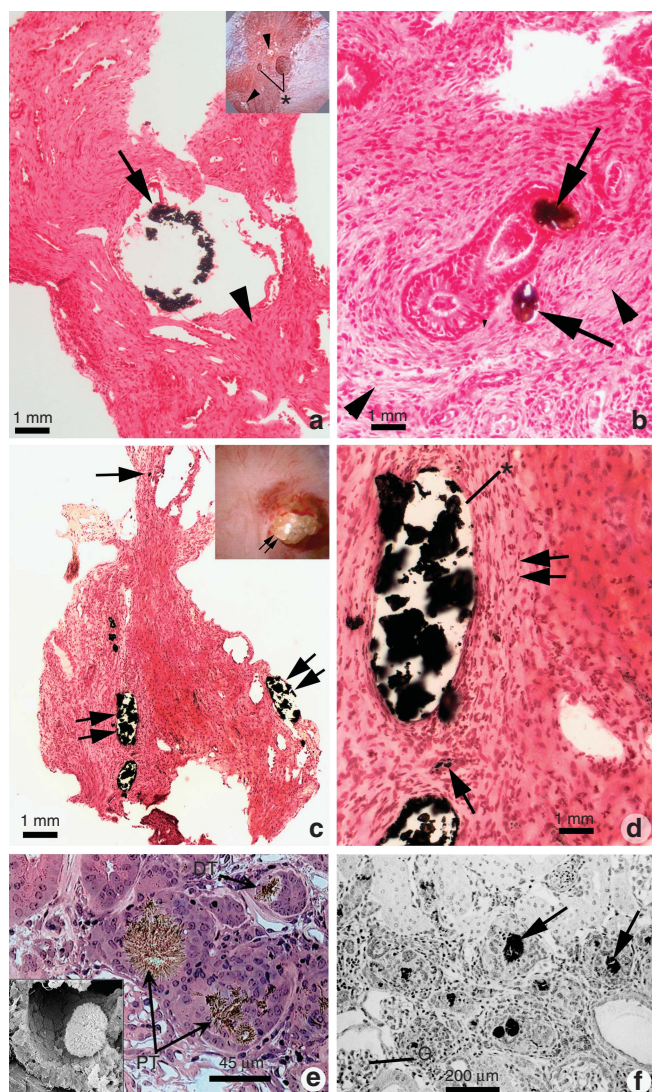
Indirect evidence from epidemiologic data suggests that uric acid stone formers are particularly prone to the development of

CKD. For example, in the report from Olmstead County,<sup>39</sup> patients with a documented uric acid stone were three times more likely to develop CKD, although 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 BDs and IMCDs,<sup>69</sup> whereas sodium mono-hydrogen urate crystals deposit in the renal interstitial space with associated inflammatory response and fibrosis.<sup>70</sup>

One group of patients particularly prone to uric acid stone disease are those with ileostomies. Because of 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 series,<sup>19</sup> 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 percutaneous nephrolithotomy at Mayo to evaluate the correlation of stone type to Randall's



**Figure 3 | Histopathology of renal papilla from primary hyperoxaluria, cystine, and 2,8-dihydroxyadenine (DHA) stone formers.** (a) A histologic section from a primary hyperoxaluric stone former with normal renal function showing isolated dilated inner medullary collecting ducts (IMCDs) filled with calcium oxalate mineral (arrow) encased in regions of extensive interstitial fibrosis (arrowhead). Sites of interstitial plaque were rare. Inset in **a** shows an endoscopic view of papillum from a primary hyperoxaluric stone former characterized by a few dilated ducts of Bellini with and without (asterisk) protruding plugs that were seen scattered between sites of yellow plaque (arrowheads). (b) A higher magnification Yasue-stained tissue section showing regions of extensive interstitial fibrosis adjacent to and away from (arrowheads) sites of intraluminal IMCD deposits. (c) A Yasue-stained histologic section from a patient with cystine stones revealing numerous dilated IMCD (double arrows) and Bellini duct (BD) plugged primarily with apatite with a few BD containing cystine deposits. Occasionally, a thin loop of Henle was noted plugged with apatite deposits (arrow). (d) A higher magnification image of a region from **c** showing extensive interstitial fibrosis (double arrow) adjacent to sites of intraluminal IMCD deposits (asterisk) and an occasional site of interstitial plaque (arrow). (e and f) The morphology of DHA crystal in kidneys from adenine phosphoribosyltransferase (APRT)-deficient mice that resembles human APRT deficiency. In **e**, two proximal (PT, arrows) and a distal tubule (DT, arrow) are seen, each with large brownish-red crystals in the tubular lumens. Interstitial fibrosis is noted around glomeruli and various tubular segments. The inset in **e** shows a scanning electron microscopy image of an individual DHA crystal in the lumen of a PT. (f) 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).

plaque burden, tubular plugging, and metabolic parameters.<sup>71</sup> 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, whereas tubular plugging was greatest in those with BR nephrolithiasis. Overall, the amount of plaque seen in CaOx stone formers was less than that seen in our cohort, but the study population was not selected for hypercalciuria as in our series and included subjects with PH, primary hyperparathyroidism, and bowel disease. More recently, the Mayo group compared the histopathology of patients with uric acid stones with those with CaOx disease.<sup>69</sup> As in our series, their subjects with uric acid 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 20 years.<sup>72</sup> Recurrent stone formation throughout childhood and adolescence, along with nephrocalcinosis, is typical. The median age of progression to ESRD is 33.<sup>73</sup> Although it has been widely accepted that CaOx crystallization can be harmful to cells,<sup>74,75</sup> 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 percutaneous nephrolithotomy for stone), those just started on renal replacement therapy, and those on long-term dialysis, Worcester *et al.*<sup>75</sup> 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 3a 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. Although only 5% of patients with cystinuria progress to ESRD, up to 70% of patients develop evidence of renal dysfunction.<sup>76</sup> Biopsies from patients with cystine stones show a variety of histopathologies ranging from normal to

tubular plugging, severe injury to BDs, and plugging of the IMCDs<sup>14</sup> (Figure 3c). Plugging within the BDs is typically with cystine aggregates, whereas the loop of Henle and the IMCDs are typically filled with HA crystals (Figure 3d). The mechanism of injury is thought to be secondary to tubular obstruction with the secondary cell injury, interstitial inflammation, glomerular loss, and cortical fibrosis.<sup>14</sup>

### Adenine phosphoribosyltransferase deficiency and 2,8-dihydroxyadeninuria

Adenine phosphoribosyltransferase deficiency is a rare autosomal recessive inborn error of adenine metabolism that leads to the accumulation of very poorly soluble dihydroxyadenine.<sup>77</sup> Prevalent in Japan, France, and Iceland, among others, this disorder resulting in dihydroxyadenine accumulation can lead to both discrete stone formation and a crystal-mediated nephropathy<sup>78,79</sup> (Figure 3, panels e and f). Because of 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, adenine phosphoribosyltransferase 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 who are untreated.<sup>72</sup> Although 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.<sup>78,79</sup> Several publications report cases of the diagnosis being made only after renal transplantation.<sup>80–82</sup>

### Dent disease

Dent disease is an X-linked disorder caused by mutations in either the *CLCN5* or the *OCRL1* genes and is characterized by low-molecular-weight proteinuria and the presence of hypercalciuria, nephrolithiasis, or nephrocalcinosis.<sup>72</sup> Typically, patients present in childhood with nephrocalcinosis, proteinuria, or unexplained CKD with subsequent progression to CKD noted by the 3rd to the 5th decade in 30–80% of male subjects.<sup>83</sup> Biopsy findings of nephrocalcinosis and interstitial fibrosis are typical in patients with Dent disease.<sup>72</sup> In recent years, a subset of patients with nephrotic range proteinuria and biopsy findings of focal segmental glomerulosclerosis has been identified,<sup>84,85</sup> 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 those in patients with CKD from other causes? Unfortunately at this time, we have more questions than answers—although without a doubt the answer to the question of kidney stone formers having a disease is certainly a ‘yes.’

#### DISCLOSURE

All the authors declared no competing interests.

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