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,[1,2] metabolic disturbances,[3] and renal complications including chronic kidney 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

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.*[8] 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 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^2, 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 patients.[11–24] Furthermore, recent data highlight the increased prevalence of albuminuria and renal scarring even in asymptomatic stone formers—both considered diagnostic for CKD.[25] 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.[25] 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.*[26] 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[27] and in activation of signaling pathways associated with inflammation, generation of reactive oxygen species, and endothelial dysfunction.[28] Urinary angiotensinogen levels were also significantly correlated with urinary α1-microglobulin, a marker of proximal tubular injury that is believed to be one of the earliest markers of tubular dysfunction.[29] Urinary excretion of 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage associated with glomerular and interstitial fibrosis,[30] is also increased in stone formers.[31] Furthermore, immunohistochemical analysis demonstrates increased 8-hydroxydeoxyguanosine expression in the renal tissue adjacent to stone in subjects with nephrolithiasis.[32]

EPIDEMIOLOGIC DATA

The earliest study to note the relationship between nephrolithiasis and CKD in the general population was performed by Vupputuri *et al.*[33] 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.*[34] 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^2 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.[35] 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.*[36] 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[37] but at a higher risk for ESRD.[38] 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.*[39] 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.[40] Incidence of CKD was determined using both diagnostic codes and lab confirmation of decreased GFR (eGFR <60 ml/min per 1.73 m^2) sustained $\geqslant 3$ 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.[41] 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,