# Kidney stones: *KI* at the crossroads of nephrology and urology

*Kidney International* (2020) **97,** 1070–1073; https://doi.org/10.1016/j.kint.2020.03.019



KEYWORDS: calcium oxalate; hyperoxaluria; nephrolithiasis; uric acid; urolithiasis

Nephrolithiasis is among the most common conditions affecting the kidneys (Figure 1), with symptomatic kidney stones reported by approximately 9% of adults in the United States between 2007 and 2010.[2] *Kidney International* has a long history of publishing high impact review articles and original research on kidney stone disease, including large epidemiologic studies, clinical trials, and mechanistic studies.

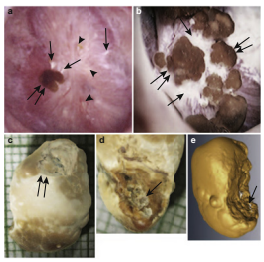

**Figure 1|** Figure 1 shows calcium oxalate kidney stones. (a) An attached stone (double arrow) is seen resting on a region of white plaque (single arrows) and intermixed with areas of white (single arrow) and yellow plaques (arrowheads). (b) Numerous attached stones (double arrow) atop an extensive area of white plaque (single arrow). (c) Light microscopic image of the urinary surface of an attached stone, showing a damaged region (double arrow) generated during stone removal. (d) Light microscopic image of the papillary surface of the stone, with a concave region on the papillary surface (single arrow) consistent with an attachment site. (e) Reconstruction of μ-CT images shows regions of calcium oxalate in yellow and areas of apatite in white. Adapted from Evans AP, Lingeman JE, Worcester SB, et al. Renal histopathology and crystal deposits in patients with small bowel resection and calcium oxalate stone disease. *Kidney Int.* 2010;78:310–317.[1] Copyright © 2010 International Society of Nephrology.

## Estimating the burden of kidney stone disease

***Johnson CM, Wilson DM, O'Fallon WM, et al. Renal stone epidemiology: a 25-year study in Rochester, Minnesota. Kidney Int. 1979;16: 624–631.***

***Stamatelou KK, Francis ME, Jones CA, et al. Time trends in reported prevalence of kidney stones in the United States: 1976–1994. Kidney Int. 2003;63:1817–1823.*** In May 1978, an entire issue of *KI* was devoted to a symposium on urolithiasis, with expert review articles covering common risk factors, specific stone types, and treatment options. The following year, *KI* published the first rigorous epidemiologic study to estimate the incidence of symptomatic kidney stones in a well-characterized population across a range of ages.[3] Between 1950 and 1974, the investigators observed a significant increase in the age-adjusted incidence of symptomatic kidney stones among adult residents of Rochester, Minnesota, with relatively stable incidence in women and much higher and increasing incidence among men. In cases where stone analysis was performed, more than two-thirds of stones were composed of calcium oxalate. Approximately one-half of the cases were evaluated only in an outpatient setting, suggesting that future epidemiologic studies of kidney stone disease should include data from both hospital and ambulatory settings.[3]

Almost 25 years later, *KI* published another high impact epidemiologic study demonstrating a continued rise in the prevalence of symptomatic kidney stones in the US population.[4] Using data from the National Health and Nutrition Examination Survey, the investigators compared the lifetime prevalence of symptomatic kidney stones between 2 survey periods, 1976 to 1980 and 1988 to 1994, and identified potential demographic and dietary risk factors. Overall, the prevalence of symptomatic kidney stones was significantly higher in the

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## Editor's Note

This article is part of the *KI* 60th anniversary series. This month's topic highlights key contributions in the multidisciplinary field of kidney stone disease.

later time period, affecting >5% of the adult population between 1988 and 1994. The prevalence increased in both men and women and across age strata, with persistently higher prevalence of kidney stones in men and individuals of older age, reaching as high as 13% among men 70 to 74 years old. In contrast to many other conditions affecting the kidneys, the prevalence of kidney stones was highest among individuals of non-Hispanic white race. The investigators also noted differences in the regional rates of kidney stones, with the highest prevalence of kidney stones in the Southeastern USA.[4]

### Urine chemistry as a window into kidney stone risk

***Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int. 2001;59:2290–2298.*** In 2001, *KI* published a high-impact study characterizing 24-hour urine chemistries in first-time kidney stone formers.[5] Participants in the Nurses Health Study and the Health Professionals Study were enrolled after a first symptomatic kidney stone and provided a single 24-hour urine collection. Urine chemistries were compared between 807 cases and 239 randomly selected controls with no history of kidney stones. The results highlighted the critical importance of urine volume and the potential for multiple factors to contribute to kidney stone risk in an individual.[5] The investigators' suggestion to view each urine component as a continuous variable is echoed today in the graphical representations that accompany commercial 24-hour urine chemistry reports.

### Identifying risk factors for hyperoxaluria and calcium oxalate stones

***Holmes RP, Goodman HO, Assimos DG. Contribution of dietary oxalate to urinary oxalate excretion. Kidney Int. 2001;59:270–276.***

***Sinha MK, Collazo-Clavel ML, Rule A, et al. Hyperoxaluric nephrolithiasis is a complication of Roux-en-Y gastric bypass surgery. Kidney Int. 2007;72:100–107.*** Publications in *KI* have identified several key risk factors for hyperoxaluria and calcium oxalate stones. In 2001, a small but carefully controlled study demonstrated the important contribution of dietary oxalate and calcium intake to urinary oxalate excretion.[6] Twelve adult participants consumed a fixed amount of oxalate, ranging from 0 to 250 mg per 2500 kcal, and 24-hour urine collections were analyzed. Urinary oxalate excretion decreased in participants fed an oxalate-free formula diet for 5 days. Even modest oxalate intake of 10 mg per 2500 kcal resulted in a nearly 25% increase in urinary oxalate excretion compared with an oxalate-free diet, while high oxalate intake of 250 mg per 2500 kcal resulted in a >40% increase in urinary oxalate excretion (Figure 2). Variation in dietary calcium also influenced urinary oxalate levels, with the highest urinary oxalate excretion observed when participants consumed a high-oxalate and/or low-calcium diet.[6] These results continue to inform clinical practice guidelines, which recommend reduced dietary oxalate and increased dietary calcium intake in patients with documented calcium oxalate stones or hyperoxaluria.[7,8]

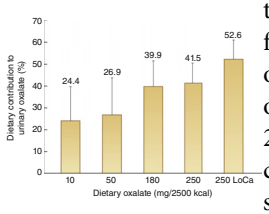


**Figure 2 |**

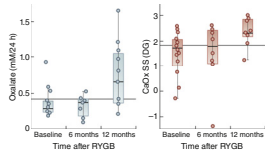


**Figure 3 |**

In 2007, a large case series from the Mayo Clinic identified Roux-en-Y gastric bypass surgery as a potential cause of enteric hyperoxaluria and calcium oxalate kidney stones.[9] The predecessor to gastric bypass surgery, the highly malabsorptive jejunoileal bypass procedure, was known to be associated with a high risk of kidney disease and calcium oxalate kidney stones[10]; in contrast, the Roux-en-Y procedure had not been expected to cause severe fat malabsorption or to increase intestinal oxalate absorption. The investigators identified 60 patients who experienced kidney stones following Roux-en-Y gastric bypass at the Mayo Clinic, including 31 with 24-hour urine chemistries available from the stone clinic. Evaluation of the urine studies identified hyperoxaluria and low urine volume as the primary contributing factors, although hypocitraturia and hypomagnesiuria were also common. In 20 patients with 24-urine collections performed both before and after gastric bypass, the investigators demonstrated a substantial increase in urine oxalate and calcium-oxalate supersaturation at 12 months post procedure (Figure 3).[9] Enteric hyperoxaluria and calcium oxalate kidney stones are now accepted as potential complications of malabsorptive weight loss procedures, including Roux-en-Y gastric bypass and biliopancreatic diversion with duodenal switch.[7,8]

Figure 2 shows the contribution of dietary oxalate to urinary oxalate excretion. Fractional contributions of dietary oxalate to urinary oxalate were calculated assuming that urinary oxalate excretion on days 4 and 5 of the oxalate-free diet represents only endogenous synthesis and that the rate of endogenous synthesis did not vary on any of the diets. The numbers above the bars represent the means. Adapted from Holmes RP, Goodman HO, Assimos DG. Contribution of dietary oxalate to urinary oxalate excretion. *Kidney Int.* 2001;59:270–276.[6] Copyright © 2001 by the International Society of Nephrology.

Figure 3 shows changes in urinary oxalate and calcium-oxalate supersaturation before and after Roux-en-Y gastric bypass. Urine oxalate was above the upper limit of the reference range (horizontal line) in 2 of 20 patients prior to the procedure and in 7 of 13 patients at 12 months after the procedure. At 12 months, all but one patient had a calcium-oxalate supersaturation (CaOx SS) above the reference range (horizontal line). $P = 0.009$ for comparison of CaOx SS between baseline and 12 months. Adapted from Sinha MK, Collazo-Clavel ML, Rule A, et al. Hyperoxaluric nephrolithiasis is a complication of Roux-en-Y gastric bypass surgery. *Kidney Int.* 2007;72:100–107.[9] Copyright © 2007 International Society of Nephrology.

### Linking the metabolic syndrome to kidney stone risk: epidemiology and mechanisms

***Abate N, Chandalia M, Cabo-Chan AV Jr., et al. The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. Kidney Int. 2004;65:386–392.***

***Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. Kidney Int. 2005;68:1230–1235.*** Nearly one-third of patients in the Mayo Clinic series had a history of kidney stones prior to Roux-en-Y gastric bypass, reflecting the increased risk of kidney stones with obesity and related metabolic conditions.[9,11] In 2004 and 2005, *KI* published 2 important studies linking diabetes and insulin resistance to kidney stone disease. In a combined cohort of more than 200,000 participants in the Nurses Health Study and the Health Professionals Study, a diagnosis of diabetes mellitus was associated with significantly increased odds of prevalent kidney stone disease in both men and women and with a significant increase in the risk of incident kidney stones in women.[12] The increased risk of kidney stone disease in women with diabetes was independent of age, body mass index, thiazide use, and diet.

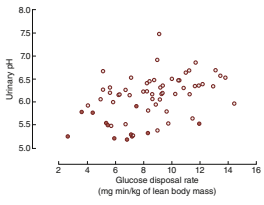


**Figure 4|**

In a small experimental study, insulin resistance was identified as an important correlate and potential driver of low urinary pH in patients with recurrent uric acid kidney stones.[13] Healthy volunteers and patients with recurrent uric acid stones were compared before and during hyperinsulinemic-euglycemic clamp. At baseline, participants with a history of uric acid kidney stones were more likely to have features of the metabolic syndrome and had higher urinary uric acid levels and lower urinary pH and citrate levels than healthy volunteers did. During the experimental phase, lower insulin sensitivity was associated with lower urine pH (Figure 4). In a subgroup of healthy volunteers who had undergone 2-hour urine collections before and during euglycemic clamp, urinary pH, ammonium, and citrate increased in response to hyperinsulinemia. These findings established insulin resistance as a mediator of the observed relationship between metabolic syndrome and kidney stone disease.[13] Although the mechanism was not known, it was hypothesized to involve changes in ammonium and net acid excretion. In support of the proposed mechanism, a recent study published in *KI* demonstrated an increase in urinary pH and urinary ammonium excretion in response to the insulin sensitizer pioglitazone.[14]

Figure 4 shows the relationship between glucose disposal rate during hyperinsulinemic-euglycemic clamp and 24-hour urinary pH. Open dots represent data from non-stone formers and closed dots represent data from patients with uric acid nephrolithiasis. Adapted from Abate N, Chandalia M, Cabo-Chan AV Jr., et al. The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. *Kidney Int.* 2004;65:386–392.[13] Copyright © 2004 International Society of Nephrology.

### Beyond stones: implicating hyperuricemia in hypertension and kidney disease

***Sanchez-Lozada LG, Tapia E, Santamaria J, et al. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal***

***and remnant kidney rats. Kidney Int. 2005;67: 237–247.*** In addition to the contribution of insulin resistance, hyperuricemia also plays an important role in the relationship between the metabolic syndrome and kidney stone disease. High uric acid levels have been linked to hypertension in epidemiologic studies,[15] and a 2005 study published in *KI* helped to elucidate a potential mechanism for this relationship.[16] Induction of hyperuricemia caused thickening of afferent arterioles, glomerular hypertension, and interstitial inflammation in rats fed a standard sodium diet (Figure 5). The changes induced by hyperuricemia were more severe following 5/6 nephrectomy and were ameliorated by allopurinol. The contribution of hyperuricemia to hypertension and interstitial inflammation, kidney stone disease, and gout helps to explain the frequent cooccurrence of these conditions.

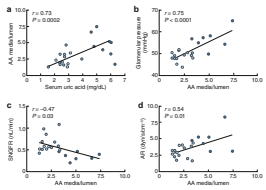

**Figure 5 |**

Figure 5 shows the effect of hyperuricemia on afferent arteriole thickening and glomerular pressure. In normal rats fed a standard sodium diet, values of serum uric acid correlated with afferent arteriolar media/ lumen ratio (a). Afferent arteriolar media/ lumen ratio correlated with glomerular pressure (b). Adapted from Sanchez-Lozada LG, Tapia E, Santamaria J, et al. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. *Kidney Int.* 2005;67:237–247.[16] Copyright © 2005 International Society of Nephrology.

## DISCLOSURE

CMW serves on the academic steering committee for Allena Pharmaceuticals URIROX-2 trial, with financial support to her institution.

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