

## Stones, Bones, and Cardiovascular Groans

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Kidney stones are a major cause of morbidity, and result in >\$5 billion of health care costs annually (1). In the United States, the prevalence of nephrolithiasis increases with age but is approximately 11% for men and 7% for women (2). Although kidney stone composition varies by age, sex, body size, and a variety of comorbidities, calcium-containing kidney stones are the most common and account for >80% of incident and recurrent kidney stones (3).

Awareness of nephrolithiasis as a major public health problem has increased with the recognition that calcium kidney stones are a systemic disorder. Well known conditions that lead to calcium kidney stone formation include primary hyperparathyroidism, Crohn's disease, and renal tubular acidosis (3). However, a wide variety of other common conditions, including obesity (4), diabetes mellitus (5), gout (6), and gallstones (7), has been linked to the development of kidney stones, and a history of kidney stones is a potential risk factor for the development of systemic diseases, such as CKD (8), hypertension (9), osteoporosis (10), and coronary heart disease (11–13).

Interest in the association between calcium nephrolithiasis and osteoporosis has been longstanding. A number of previous studies reported lower bone mineral density in individuals with a history of nephrolithiasis compared with those without (10), and bone demineralization in stone formers may be related to higher urine calcium. In 46 stone formers and their first-degree relatives followed for 3 years, the correlation between higher baseline 24-hour calcium excretion and subsequent decrease in femoral neck z score was  $-0.37$  (14). This relation was independent of calcium intake and 24-hour urine markers of dietary acid load, such as sulfate. Previous reports also suggest that individuals with nephrolithiasis may have higher risk of bone fracture (10). In a longitudinal study of 624 individuals with a history of kidney stones living in Rochester, Minnesota, the risk of an incident vertebral fracture was greater than four times that expected for Rochester individuals of comparable age (15). A recent study using electronic medical record data from the United Kingdom compared >50,000 individuals with diagnostic codes for urolithiasis with >500,000 participants without such codes matched on age and sex. The risk of incident bone fracture in individuals with a history of kidney stones was 10% higher in men, and also, it was higher in some women (the highest hazards ratio in women was 1.52 for those ages 30–39 years old) (16).

Interest in kidney stone disease as an independent risk factor for the development of coronary heart disease has developed more recently. In a case-control study including >15,000 participants with a mean follow-up of 9 years, participants with a history of kidney stones were 31% more likely to have an incident myocardial infarction after adjustment for a wide variety of comorbidities (13). In large prospective cohort studies, a history of kidney stones was associated with an increased risk of incident coronary heart disease in women (but not men) that was independent of age, body size, dietary intakes, and comorbid conditions (12). A prospective study of >3 million individuals in Alberta, Canada found that a history of nephrolithiasis was associated with an increased risk of coronary heart disease and stroke; the risks were higher in women than men and younger than older individuals (11).

In this issue of *CJASN*, Shavit *et al.* (17) report results from a matched case-control study that represent an important contribution to our understanding of the potential relations between calcium nephrolithiasis, lower bone mineral density, and cardiovascular disease. Shavit *et al.* (17) identified 57 patients with recurrent calcium kidney stones from their outpatient nephrology clinic who had previously undergone clinically indicated noncontrast computed tomography (CT) of the abdomen and pelvis and completed a routine metabolic evaluation that included assessment of basic serum chemistries and in most patients, a 24-hour urine collection. The comparison group consisted of age- and sex-matched nonstone formers selected from a list of potential living kidney donors from the same hospital. These nonstone formers all had noncontrast abdominal CT images available as part of the routine pretransplant donor evaluation. The main outcomes of the study were CT-derived measurements of abdominal aortic calcification and vertebral bone mineral density.

Although Shavit *et al.* (17) observed that the prevalence of abdominal aortic calcification was similar in both patients and controls, median abdominal aortic calcification severity scores were significantly higher in stone formers. Mean vertebral bone mineral density was lower in stone formers compared with controls (159 versus 194 Hounsfield Units;  $P < 0.001$ ). As would be expected, the proportion of individuals with a history of hypertension was higher in stone formers than controls (35% versus 9%). However, differences in abdominal aortic calcification scores between stone formers

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and controls remained significant after adjustment for history of hypertension and a variety of other factors. Statistical tests for effect modification by sex were nonsignificant. Shavit *et al.* (17) do not present rates of thiazide use in the stone formers, but in this group, there was no association between abdominal aortic calcification score and 24-hour urine calcium.

The data presented by Shavit *et al.* (17) suggest the possibility that a common biology underlies calcium stone formation, osteoporosis, and vascular calcification. This well performed study has a number of important strengths. Shavit *et al.* (17) used a systematic, well detailed process to generate the abdominal calcification scores used in their study, and they previously assessed the inter- and intraobserver variabilities of their CT scoring technique. Furthermore, abdominal aortic calcification is a relevant study metric. Abdominal aortic calcification is positively correlated with coronary artery calcification, an established predictor of incident nonfatal and fatal coronary heart disease, as well as other validated measures of subclinical atherosclerosis, such as ankle brachial index and carotid intimal medial thickness (18). In previous population-based studies, abdominal aortic calcification was associated with subsequent cardiovascular events and death (19). Finally, Shavit *et al.* (17) are to be commended for using existing clinical data in their practice to address an important scientific question. In particular, their assessment of bone mineral density using CT imaging obtained for other indications holds promise as a clinic-based research tool (20).

This study also has limitations (17). First, several potentially important factors may confound the observed associations. Race is one such factor, and it must be considered, because this study was conducted in London, a city with a large nonwhite population. Kidney stones are much less common in blacks compared with whites (2), and blacks, on average, have less vascular calcification (18,21) and higher bone mineral density (22–24) than whites. Because Shavit *et al.* (17) do not report the racial composition of their study population, it is possible that their findings reflect a greater proportion of blacks in the control group. Body size is another potentially confounding factor. Although higher body mass index is strongly associated with kidney stone formation (4) and greater vascular calcification (25–27), there are no data comparing weight or other measures of body size in stone formers with controls. Second, it is unclear whether the greater severity of abdominal aortic calcification in stone formers was independent of differences in bone mineral density between stone formers and controls. Rather than showing a unique feature of nephrolithiasis, these data, instead, may recapitulate the results of previous studies in nonstone formers showing associations between greater vascular calcification and lower bone mineral density (28,29). Unfortunately, Shavit *et al.* (17) did not include bone mineral density as a covariate in multivariable regression models to see if the positive association between vascular calcification and stone-forming status was attenuated. Third, some important inclusion criteria of the study were unclear, and some relevant data were excluded. For example, Shavit *et al.* state that the participants who formed stones in the study had “a confirmed diagnosis of recurrent calcium nephrolithiasis,” but stone composition was available in only six individuals (17). Reportedly available data

on the number of study participants with heart failure, cardiovascular disease, hyperlipidemia, peripheral vascular disease, and stroke are not included in Table 1, and no mention is made of the association between bone mineral density and 24-hour urine calcium in stone formers.

The study by Shavit *et al.* (17) was not designed to elucidate mechanism(s) and provides, not inappropriately, more questions than answers. The nexus between calcium kidney stone formation, bone demineralization, and atherosclerosis should be an active area of investigation pursued by the clinical investigator and basic scientist alike. Future studies will require careful assessment of calcium-phosphorus regulatory hormones and inhibitors of tissue calcification hypothesized to play important roles in the complex pathophysiology of all three disease states.

In the meantime, clinicians are left to wonder how the current state of research may affect the care of the patient with recurrent calcium stone disease. Nephrologists should ensure that patients with calcium nephrolithiasis are appropriately screened for osteoporosis and modifiable cardiovascular risk factors. Clinicians also should remember existing interventions that simultaneously may prevent kidney stones, bone fracture, and cardiovascular disease. Individuals with calcium stones should be encouraged to consume a healthy diet with more fruits, vegetables, and whole grains and less red and processed meats (30–33), and calcium stone formers with hypertension should be treated with a thiazide diuretic (10,34).

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#### Disclosures

None.

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See related article, “Vascular Calcification and Bone Mineral Density in Recurrent Kidney Stone Formers,” on pages 278–285.