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Nonrenal Systemic Arterial Calcification Predicts the Formation of Kidney Stones

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Abstract

Background: Recent data indicate that kidney stone formers (KSFs) may have increased biomineralization at anatomic sites throughout the body compared with nonstone formers (NSFs). The objective of this study is to compare the volume of nonrenal systemic calcifications between KSF and NSF by using a standardized system to analyze calcifications in the abdominal aorta (AA) and splenic artery (SA).
Methods: The NSF cohort was obtained from a kidney donor's prospectively maintained database. One hundred ninety-seven NSF were matched to 197 KSF based on age, gender, and body mass index. Noncontrast CT scans were evaluated and semiautomated CT software was utilized to provide an AA and SA calcification Agatston score. Wilcoxon rank-sum test was used on continuous variables and chi-squared test or Fisher's exact test on categorical variables. Odds ratios (ORs) were given for a variable's influence on the formation of stones or calcifications.
Results: AA and SA calcifications were more prevalent in the KSF group ($p = 0.011$ and $p = 0.027$, respectively). KSFs were 1.9 times more likely to have intermediate or severe AA calcification than NSFs (OR = 1.9, $p = 0.004$). Severe AA calcifications had even a greater association (OR = 3.1, $p = 0.019$). KSFs were also more likely to have SA, but this did not reach statistical significance (OR = 3.7, $p = 0.103$).
Conclusion: Patients with increased systemic calcifications, specifically aortic or splenic calcifications, may be at an increased risk for future kidney stone formation. Patients with these imaging findings and additional risk factors for stone disease may be counseled on the future risk of stones.

Keywords: endourology, imaging, urolithiasis

Introduction

The prevalence of kidney stone disease in the United States has been steadily increasing, and is estimated to be nearly 9%.[1,2] A rise in medical comorbidities is thought to be a factor in the increasing prevalence of kidney stones, as several medical conditions are known to be associated with urinary stone disease.[3] Prior studies have shown a link between cardiovascular disease and urinary stone formation, with an increase in the risk of myocardial infarction (MI) in stone patients.[3,4] In addition, research has suggested an association between aortic calcifications and kidney stones, as well as coronary atherosclerosis and recurrent kidney stones, suggesting a possible common pathophysiology between systemic biomineralization and stone formation.[5–8] The objective of this study is to compare the volume of nonrenal systemic calcifications between kidney stone formers (KSFs) and nonstone formers (NSFs) by using a standardized, computerized system. The significance of a link between systemic biomineralization and kidney stone formation could lead to early preventive therapy in patients who are at risk for the formation of kidney stones as well as the inverse of appropriate counseling on the risks of systemic arterial calcifications and the development of medical comorbidities in patients with stone disease.

Materials and Methods

Institutional Review Board approval was obtained for query of our Kidney Stone Registry and Kidney Donor registries. The Kidney Stone Registry includes information on patients seen for the diagnosis of a kidney stone at our tertiary academic center. Similarly, the Donor Registry includes information on patients who underwent a donor nephrectomy at the same academic center. All kidney donors between the years 2010 and 2015 with follow-up data for at least 1 year post-donation were

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included. Any kidney donors with a history of urolithiasis were excluded. KSF were selected and matched to donors based on age, gender, and body mass index (BMI).

Noncontrast CT scans were evaluated and semiautomated CT software (Aquarius iNtuition version 4.4.5; TeraRecon, Inc., San Francisco, CA) were utilized to provide an abdominal aorta (AA), pancreas, and splenic artery (SA) calcification Agatston score, as per previously described methods.[9,10] A detection threshold of 130 HU was used on 3 mm slices. The calcification scores were categorized into four groups: none (score 0), mild (>0–100), intermediate (>100–400), and severe (>400). For the kidney donors, the noncontrast phase of the CT urograms obtained for preoperative evaluation were assessed. For the KSF patients, noncontrast CT scans closest to the date of the CT scan of the donor were evaluated to avoid any significant time difference that could lead to bias. Imaging reviewed ranged from November 2005 to July 2018. A total of 197 pairs of kidney donors and stone formers were matched by age, gender, and BMI. Data on tobacco history and hypertension were collected from the electronic medical records. For between-group comparisons, Wilcoxon rank-sum test was used on continuous variables and chi-squared test or Fisher's exact test, when cell numbers are <5, on categorical variables. Odds ratio (OR) of calcification between the stone groups or of stone formation between the calcification groups, adjusted by tobacco use and hypertension, were estimated by the Cochran–Mantel–Haenszel chi-squared test. All analyses were done using the statistical package R (version 3.3.2; R Development Core Team). Results were considered significant at the significance level of 0.05.

Results

A total of 197 kidney donors were matched to 197 KSF. One hundred and nineteen patients were female and 78 were male (Table 1). The median age of donor at the time of imaging was 43 years (range 19–67) and the median age of the KSF was 43 years (range 19–73). Fifty-one (25.9%) donors were older than 50 and 59 years (29.4%) KSF were older than age 50 years. Median BMI in the donor group was 27.5 kg/m^2 and median BMI of the KSF group was 27.6 kg/m^2. Forty-seven percent of donors had a BMI >28% *vs* 45% of KSF. There was no statistically significant difference between the groups for BMI and age, indicating matching was appropriate ($p=0.962$ and $p=0.3$, respectively). Seventy-three (37.1%) of the donors had a history of tobacco use. Similarly, 83 (42.4%) of the KSF had a history of tobacco use ($p=0.332$). Fifty-two donors (26.4%) had a diagnosis of hypertension *vs* 85 (43.2%) KSF ($p<0.001$).

Only three KSF had pancreatic calcifications so the pancreas was not examined in the NSF cohort. AA and SA calcifications were more prevalent in the KSF group ($p=0.011$ and $p=0.027$, respectively). Treating calcification as an event, KSF patients were 1.9 times more likely to have intermediate or severe AA calcification (OR = 1.9, 95% CI 1.1–3.5, $p=0.004$), or patients with arterial calcifications were 1.9 times more likely to have stones than those who had none. The OR for severe AA calcification was even higher (OR = 3.1, $p=0.019$). KSF patients were 3.7 times more likely to have SA calcification (OR = 3.7, 95% CI 1–14.6, $p=0.103$), or patients with SA calcifications were 3.7 times more likely to have stones than those who had none, but this did not reach statistical significance.

Discussion

Several studies have addressed a link between vascular calcifications and kidney stones. Yasui and colleagues[5] evaluated aortic wall calcifications in KSF and NSF by measuring the circumferential degree of calcification. They found that males 20 to 40 years of age and females older than 60 years had increased aortic wall calcifications. Shavit and colleagues[6] measured the number of calcified aortic segments in 57 KSF and 54 donors. They found that there was a similar prevalence of AC in both groups but the KSF had a higher severity score of AC, based on the average percentage of calcified segments. However, matching was done based on age and gender and did not include BMI. In addition, similar to our study, there was a higher prevalence of hypertension in the KSF group, and the increased risk of vascular calcifications could therefore have been independent of stone disease. However, our analyses were adjusted for both tobacco use and hypertension.

Reiner and colleagues[7] used data from the CARDIA study to evaluate a possible correlation between carotid atherosclerosis and kidney stones. The CARDIA study was a longitudinal study

Table 1. Demographics and Calcification Rates

	Kidney donors (n = *197*)	*KSFs* (n = *197*)	p-*Values, or hypertension adjusted OR (95% CI) and* p-*values*
Sex, n (%)			1
Male	78 (39.6)	78 (39.6)	
Female	119 (60.4)	119 (60.4)	
Median age, years (range)	43 (19–67)	43 (19–75)	0.962
Median BMI, kg/m^2	27.5	27.6	0.3
Tobacco history, *n* (%)	73 (37.1)	83 (42.4)	0.332
Hypertension, *n* (%)	52 (26.4)	85 (43.2)	<0.001
AA calcification (Agatston score), *n* (%)			
Median (range)	0 (0–3790.8)	0 (0–4051)	0.011
Any	43 (21.8)	61 (31.1)	OR = 1.4 (0.8–2.3), 0.191
Intermediate and severe	22 (11.2)	44 (22.4)	OR = 1.9 (1.1–3.5), 0.004
Severe	7 (3.6)	25 (12.8)	OR = 3.1 (1.3–7.5), 0.019
SA calcification (Agatston score), *n* (%)			
Median (range)	0 (0–55.1)	0 (0–479.1)	0.027
Any	3 (1.5)	11 (5.6)	OR = 3.7 (0.95–14.6), 0.103

AA = abdominal aorta; BMI = body mass index; CI = confidence interval; KSFs = kidney stone formers; OR = odds ratio; SA = splenic artery.

looking at the development of cardiovascular risk factors in young adults who were followed for 20 years. Kidney stones were self-reported. There were 200 (3.9%) patients with a self-reported history of kidney stones who completed the 20-year exam, including a carotid ultrasound. The authors found a non-significant increased overall risk of carotid stenosis in KSFs, however, there was a greater carotid wall thickness in patients who had a reported history of symptomatic kidney stones and a 1.6 times increase in the risk of carotid atherosclerosis after adjusting for major risk factors.

Hsi and colleagues[8] analyzed data on 3282 patients with CT coronary calcification scores and a self-reported history of kidney stones. They found that recurrent KSF tended to have moderate or severe calcification *vs* none or mild coronary calcifications in patients without a reported history of stones. The severity of coronary calcifications was a stronger association than the presence or absence of calcifications. The implication of the findings are that a KSF with no prior cardiac history may be at higher risk of severe coronary calcifications and cardiovascular events in the future than a NSF. The risk of increased cardiovascular events in stone patients was previously described by Rule et al.,[4] who found a 31% increased risk of MI in stone formers, independent of chronic kidney disease and other risk factors for cardiovascular disease.

This study confirms an association between systemic biomineralization and kidney stones. Unlike prior studies, we used a standardized system working with our radiology colleagues to quantify the amount of calcifications at two anatomic sites. The semiautomated system was previously described by Patel et al.,[9] who described an association between abdominal aortic calcifications and low urine pH and hypocitraturia. The significant correlation between calcifications and stone disease in this study, along with prior publications, supports a vascular theory of the development of kidney stones. There are three theories described which link vascular etiologies to stone formation.[11] Turbulent flow, which is common in iliac arteries, carotids, and at the bifurcation of the aorta, can predispose to inflammation which can turn into atherosclerosis and calcifications. Blood flow has been shown to be turbulent at the tip of the papilla, where Randall's plaques and stones form. In addition, a hyperosmolar microenvironment can lead to the accumulation of inflammatory cytokines. The third theory involves a decreasing gradient of oxygen capacity from the renal cortex to the tip of the papilla.

Limitations of the study include the retrospective nature and the possibility of medical comorbidities that may make systemic calcifications more common in one cohort, specifically diabetes mellitus. At least eight of the KSF did have a known history of diabetes. Supplementary work in the future should consider additional comorbidities, including diabetes mellitus, in the matching process. Kidney donors typically tend to be in better health than the general population. However, BMI was included in the matching process and tobacco history and hypertension were controlled for in the analysis, unlike previous studies. In addition, with a larger study population, it might have been possible to get additional data on other systemic calcifications, such as the pancreas. This work was done using an existing donor cohort, however future work could include a power analysis to determine the appropriate study population size to further define the statistical significance of small changes in Agatston scores.

Conclusions

Patients with increased systemic calcifications, specifically aortic or splenic calcifications, may be at an increased risk for future kidney stone formation. Patients with these imaging findings and additional risk factors for stone disease may be counseled on the future risk of stones and appropriate follow-up and dietary recommendations should be discussed.

Author Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

AA = abdominal aorta
BMI = body mass index
CI = confidence interval
CT = computed tomography
HU = Hounsfield units
KSFs = kidney stone formers
MI = myocardial infarction
NSFs = nonstone formers
OR = odds ratio
SA = splenic artery