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Coronary Artery Calcium Score and Association with Recurrent Nephrolithiasis: The Multi-Ethnic Study of Atherosclerosis

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Purpose: Subclinical coronary artery calcification is an established predictor of cardiovascular events. While a history of kidney stones has been linked to subclinical carotid atherosclerosis, to our knowledge no study has examined its relationship with coronary artery calcification. We studied the association between kidney stone history and prevalent coronary artery calcification in MESA (Multi-Ethnic Study of Atherosclerosis).

Materials and Methods: MESA is a multisite cohort study of participants 45 to 84 years old without known cardiovascular disease at baseline from 2000 to 2002. Computerized tomography was done in 3,282 participants at followup in 2010 to 2012 to determine coronary artery calcification and kidney stone history was assessed by self-report. Coronary artery calcification scores were categorized as none—0, mild—1 to 99, moderate—100 to 399 or severe—400 or greater. Cross-sectional analysis was performed adjusting for demographic and dietary factors related to kidney stones.

Results: The prevalence of kidney stone disease history was approximately 9%, mean ± SD participant age was 69.5 ± 9.3 years, 39% of participants were Caucasian, 47% were men and 69% had detectable coronary artery calcification (score greater than 0). No difference in the score was seen between single stone formers and nonstone formers. Recurrent kidney stone formation was associated with moderate or severe calcification on multivariable logistic regression vs none or mild calcification (OR 1.80, 95% CI 1.22–2.67). When coronary artery calcification scores were separated into none, mild, moderate and severe calcification, recurrent stone formation was associated with a higher score category on multivariable ordinal logistic regression (OR 1.44 per category, 95% CI 1.04–2.01).

Conclusions: Recurrent kidney stone formation is associated with subclinical coronary atherosclerosis. This association appeared stronger with coronary artery calcification severity than with coronary artery calcification presence.

Key Words: kidney, urolithiasis, coronary artery disease, arteriosclerosis, recurrence

Abbreviations and Acronyms

CAC = coronary artery calcification

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KIDNEY stone disease is linked to systemic conditions, including chronic kidney disease,[1] hypertension,[2] obesity[3] and diabetes mellitus.[4] Recent longitudinal studies have also shown an association of kidney stone disease with coronary heart disease.[5,6] Therefore, biological pathways that result in CAC may also lead to the development of nephrolithiasis.

CAC, which is present only in atherosclerotic arteries, is a marker of subclinical atherosclerosis.[7] CAC is quantified noninvasively by computerized tomography and the calculated CAC score reflects the presence and extent of atherosclerotic disease. In 2010 ACC (American College of Cardiology) and AHA (American Heart Association) guidelines indicated that measuring CAC for cardiovascular risk assessment in asymptomatic adults may be reasonable in those at intermediate risk, defined as a 10% to 20% 10-year risk of cardiovascular events.[8] Adding CAC to the Framingham Risk Score improves disease prediction and it is considered an independent predictor of cardiovascular events.[7,9,10]

While atherosclerotic disease and nephrolithiasis have shared risk factors, to our knowledge the relationship between CAC and kidney stone disease has not been previously examined. The purpose of this study was to evaluate our hypothesis that participants reporting a history of kidney stones have a greater prevalence and extent of coronary artery calcification.

MATERIALS AND METHODS

Data Source and Study Population

MESA is a cohort study of 6,814 men and women designed to evaluate the prevalence of and risk factors for subclinical cardiovascular disease.[11] Participants who were free of clinical cardiovascular disease at the time of study entry (2000 to 2002) were recruited from 6 communities in the United States, including Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan, New York; and St. Paul, Minnesota. Specific details about sampling, recruitment and data collection were reported previously.[11] The study included a racial/ethnic distribution of 38% Caucasian, 28% African-American, 22% Hispanic and 12% Chinese-American participants. Of the original participants 4,716 attended Exam 5 in 2010 to 2012, when they were queried about kidney stone history and evaluated for interval development of cardiovascular disease. Institutional review boards at each site approved the study and all participants provided written informed consent.

Assessment

Kidney Stones. Participants were asked whether their doctor or health care provider had ever told them that they had a kidney stone. Participants who answered yes were also asked the number of kidney stones. Participants were categorized into those who had previously had 0, 1, or 2 or more stones and were termed never, single and recurrent, respectively.

Coronary Artery Calcification. Multidetector row computerized tomography using a standardized protocol was performed in 3,305 of the participants followed through Exam 5 to evaluate for CAC.[12] The Agatston scoring method was used to evaluate calcium levels, normalized to a calcium phantom with 4 bars of known calcium density that were scanned along with the participant. The Agatston score is based on the area of calcification and weighted by the highest density of calcification in each plaque.[13] The phantom adjustment method serves to calibrate results across sites and evaluators.

Covariates

Exam 5 covariates included age (continuous), gender, race/ethnicity, diabetes status (normal, impaired fasting glucose, or untreated or treated diabetes) and body mass index (weight in kg/height in m^2, continuous). Dietary variables were treated continuously and derived from a validated food frequency questionnaire administered at Exam 5.[14] Dietary covariates selected as plausibly related to kidney stone formation included energy intake in kcal per day, animal protein consumption level in gm per day, calcium intake level in mg per day and sodium intake level in mg per day.

Statistical Analysis

We included in analysis 3,282 participants who attended Exam 5, responded to the kidney stone questionnaire, underwent computerized tomography and had no missing covariates. Of these participants 69.4% had detectable coronary calcium and 3.3% had previously experienced myocardial infarction or stroke, indicating that the majority had subclinical atherosclerosis. When comparing the baseline characteristics of those with vs without CAC among the original MESA cohort, there were no appreciable differences in the baseline characteristics measured at Exam 5.

To evaluate the relationship of kidney stones to CAC prevalence 4 models were performed, adjusting first for age, gender and race/ethnicity category, and then additionally adjusting for the nutrition and health related variables. Post hoc adjustment was done to account for smoking status, hypertension status, education level and health insurance status.

In the first model logistic regression was performed with the presence of CAC (CAC score greater than 0) as the outcome and with kidney stone history (0, 1, or 2 or greater stones) as the potential predictor of interest. In the second model linear regression was performed with log-transformed CAC score as the outcome and kidney stone history (0, 1, or 2 or greater) as the predictor of interest. Only participants with detectable CAC (greater than 0) were included in this model. Coefficients of interest were exponentiated and, thus, are interpretable as ratios of geometric means between the kidney stone groups. In the third model logistic regression was performed with a CAC score less than 100 vs 100 or greater as the outcome and kidney stone history (0, 1, or 2 or greater) as the predictor of interest. An Agatston score threshold of 100 defines medium to high levels of coronary

calcium, representing a greater risk of coronary heart disease events.[7] In the fourth model CAC score was categorized into 4 groups (0, 1 to 99, 100 to 399 and 400 or greater) based on risk categories indicated in previous studies.[7] The advantage of this model was to better address the nonlinear distribution of CAC scores in the study population. Ordinal logistic regression analysis was performed with CAC category as the outcome and kidney stone category (0, 1, or 2 or greater) as the predictor of interest.

CIs were generated using robust SEs to allow for unequal variance across observations. Significance was determined at 2-sided $\alpha = 0.05$. For all models complete case analysis was performed. Missing data due to missing covariates were uncommon.

RESULTS

Table 1 shows descriptive distribution statistics of variables of interest by kidney stone status. The prevalence of kidney stone disease in this population was 9.0%. Overall mean ± SD participant age was 69.5 ± 9.3 years, 39% of participants were Caucasian and 47% were men. Of the 289 stone formers 129 (44.6%) had formed 2 or more stones in the past. Of stone formers 65% were men and 52% were Caucasian. The mean ± SD CAC score among nonstone formers and stone formers was 279 ± 595 and 380 ± 602, respectively. There were 1,006, 982, 640 and 648 participants in the 0, 1 to 99, 100 to 399 and 400 or greater CAC score categories, respectively. The figure shows the proportion of participants among the 4 CAC risk categories by stone history status. Higher proportions of single and recurrent stone formers were in higher CAC score categories than participants who had never had a kidney stone.

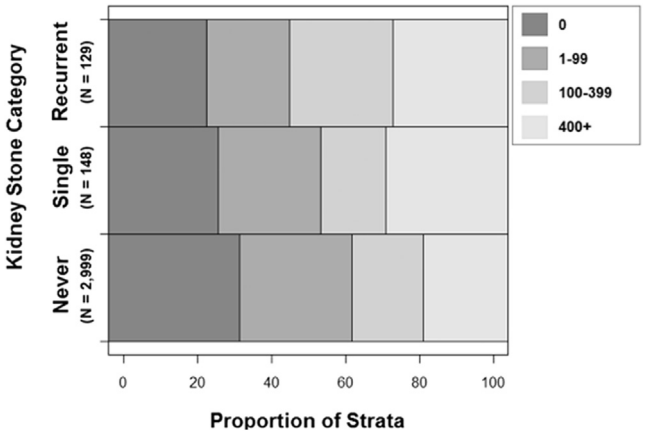
Table 2 shows the results of regression analyses. When evaluating the association between the presence of CAC and stone history in the first model, there was a significant association among recurrent stone formers only compared to nonstone formers on univariate analysis (OR 1.57, 95% CI 1.03–2.39). However, this association among recurrent stone formers was not statistically significant after adjustment.

When evaluating the association between CAC score among those with detectable CAC and stone history in the second model, there was a significant association among recurrent stone formers with an estimated 58% higher CAC score (95% CI 15–118 higher) compared to nonstone formers on univariate analysis. After adjustment for age, gender and race/ethnicity recurrent stone formers were observed to have an estimated 40% higher CAC score (95% CI 3–89 higher). However, this association was not significant on multivariable analysis when additionally adjusted for nutritional and health related variables ($p = 0.09$).

In contrast in the third model the association between CAC score in those with medium and high CAC scores (100 or greater) and recurrent stone formers was significant after adjustment for age, gender and race/ethnicity (OR 1.77, 95% CI 1.21–2.59). After adding nutritional and health related variables the association remained significant (OR 1.80, 95% CI 1.22–2.67).

Table 1. *MESA Exam 5 demographics and descriptive statistics*

	No Kidney Stone	Single Kidney Stone	Recurrent Kidney Stone
No. pts	2,999	148	129
Mean ± SD age	69.4 ± 9.3	71.1 ± 8.67	68.9 ± 8.84
No. male (%)	1,376 (46)	90 (61)	91 (71)
No. female (%)	1,623 (54)	58 (39)	38 (29)
No. race (%):			
Caucasian	1,147 (38)	80 (54)	61 (47)
African-American	822 (27)	31 (21)	23 (18)
Hispanic	669 (22)	21 (14)	37 (29)
Chinese-American	361 (12)	16 (11)	8 (6)
No. diabetes (%):			
Normal	1,762 (59)	85 (57)	66 (51)
Impaired fasting glucose	635 (21)	34 (23)	29 (22)
Untreated	49 (2)	2 (1)	3 (2)
Treated	539 (18)	26 (18)	30 (23)
Missing	14 (0.5)	1 (0.7)	1 (0.8)
Mean ± SD body mass index (kg/m^2)	28.6 ± 5.6	28.0 ± 4.7	29.7 ± 5.3
Mean ± SD serum creatinine (mg/dl)	0.92 ± 0.44	0.93 ± 0.28	0.96 ± 0.29
Mean ± SD caloric intake (kcal)	1,628 ± 1,052	1,595 ± 751	1,720 ± 822
Mean ± SD animal protein intake (gm)	39.7 ± 33.7	37.8 ± 22.3	40.3 ± 24.0
Mean ± SD calcium intake (mg)	804 ± 703	779 ± 568	755 ± 495
Mean ± SD sodium intake (mg)	2,451 ± 1,763	2,359 ± 1,175	2,583 ± 1,331
Mean ± SD CAC score	279 ± 595	382 ± 626	359 ± 531



CAC score categories by kidney stone history (0, 1, or 2 or more)

In the fourth model the association between CAC score category (0, 1 to 99, 100 to 399 and 400 or greater) and recurrent stone formers was significant in the full model on multivariate analyses (OR 1.44, 95% CI 1.03–2.01). In other words a participant with recurrent stones was found to have an estimated 44% higher adjusted odds of being in 1 CAC category higher than a participant with no history of stones.

Furthermore, the results did not appreciably change when additional adjustment to the full model was performed with serum creatinine, smoking status, hypertension status, education level and health insurance status.

DISCUSSION

Our study shows an independent association between a history of recurrent kidney stone formation and coronary artery calcium, specifically in participants with medium or high CAC scores. A recurrent stone former was found to have an estimated 80% higher adjusted odds of a CAC score greater than 100 than a nonstone former. The relationship was similar when 4 categories of CAC score were used and this association appeared stronger for CAC severity than for CAC presence. While this relationship was not seen when comparing patients without vs all those with detectable coronary calcium, a larger sample size may be needed to detect a difference in stone risk in those with smaller amounts of coronary calcium. The clinical significance of these findings is that a recurrent stone former with no prior cardiac history who is otherwise asymptomatic may have higher levels of coronary calcification and be at risk for future cardiovascular events. The presence of calcium in the coronary vasculature provides objective evidence of subclinical atherosclerosis before a major cardiovascular event such as myocardial infarction or stroke.

A shared origin of kidney stone formation and CAC is biologically plausible since they share a common pathophysiological mechanism through ectopic calcification. As a marker of atherosclerotic disease CAC marks the propensity of atherosclerotic plaque in the coronary artery to calcify. Nephrolithiasis has been theorized to result from vascular injury at the tip of the renal papillae, leading to repair and atherosclerosis-like calcification of the vessel wall that erodes into the interstitium and papillary ducts of Bellini.[15,16] These calcifications erode onto the papillary surface and are now referred to as Randall plaques. In the presence of supersaturated urine these calcifications develop

Table 2. *Regression analysis of association between CAC and kidney stone history*

Kidney Stone History Model	Unadjusted OR (95% CI)	Adjusted Model 1 OR (95% CI)*	Adjusted Model 2 OR (95% CI)†
Detectable CAC vs stone history (log regression analysis):‡			
Never	Referent	Referent	Referent
Single	1.32 (0.91–1.92)	0.96 (0.63–1.44)	0.94 (0.61–1.43)
Recurrent	1.57 (1.03–2.39)	1.32 (0.84–2.10)	1.40 (0.87–2.24)
Log CAC score vs stone history (linear regression analysis):§			
Never	Referent	Referent	Referent
Single (geometric mean ratio)	1.29 (0.89–1.88)	1.03 (0.73–1.46)	0.94 (0.67–1.33)
Recurrent (geometric mean ratio)	1.58 (1.15–2.18)	1.40 (1.03–1.89)	1.30 (0.96–1.76)
CAC score greater than 100 vs stone history (logistic regression analysis):			
Never	Referent	Referent	Referent
Single	1.41 (1.01–1.96)	1.04 (0.71–1.51)	0.95 (0.64–1.41)
Recurrent	1.97 (1.38–2.81)	1.77 (1.21–2.59)	1.80 (1.22–2.67)
CAC score (0, 1–99, 100–399 + 400 or greater) vs stone history:			
Never	Referent	Referent	Referent
Single	1.47 (1.09–1.99)	1.12 (0.82–1.53)	1.03 (0.75–1.42)
Recurrent	1.72 (1.26–2.36)	1.46 (1.05–2.02)	1.44 (1.03–2.01)

* Adjusted for age, gender and race/ethnicity.
† Adjusted for age, gender, race/ethnicity, diabetes status, daily energy intake, body mass index, animal protein consumption, calcium intake and sodium intake.
‡ Detectable CAC considered CAC score greater than 0.
§ Limited to 2,271 participants with CAC greater than 0.

into a calculus in the collecting system. It has also been proposed that collecting ducts and not the renal microvasculature are the starting point of stone attachment and development.[17] Further studies are needed to elucidate the mechanisms of stone formation in the papillae.

Epidemiological evidence links nephrolithiasis to a cluster of systemic diseases that also comprise metabolic syndrome.[2–6] Recent data further support the association between kidney stone formation and subclinical markers of atherosclerotic disease. Reiner et al evaluated the relationship between stone formation and carotid wall thickness in the CARDIA (Coronary Artery Risk Development in Young Adults) study.[18] With a composite end point of carotid stenosis and/or the upper quartile of internal carotid/bulb wall thickness a history of kidney stones was associated with a 1.6-fold increased risk of carotid atherosclerosis after adjusting for major atherosclerotic risk factors (95% CI 1.05–2.28).

Furthermore, Fabris et al reported that compared to age and gender matched controls idiopathic calcium stone formers had significantly increased arterial stiffness after adjustment for confounders.[19] Arterial stiffness, which was assessed by carotid-radial pulse wave velocity, carotid-femoral pulse wave velocity and the augmentation index, has been associated with early atherosclerosis.[20] The group noted that such a process also occurs elsewhere, eg in central elastic arteries and peripheral muscular arteries, adding support to the view that this is a systemic phenomenon.

Shavit et al reported that abdominal aortic calcification in patients with recurrent calcium nephrolithiasis was more severe compared to that in age and gender matched nonstone formers, although the prevalence of abdominal aortic calcification was similar.[21] These investigators also noted lower vertebral bone mineral density in kidney stone formers compared to the control group, suggesting that nephrolithiasis is linked to systemic calcium homeostasis.

In our study the association with CAC was seen in recurrent stone formers but not in single stone formers. Additional studies in a larger number of single stone formers and with greater power may be able to detect an association in this population. It is known that single stone formers are at high risk of a second event with a risk of stone recurrence of approximately 50% in the subsequent 10 years.[22,23] Furthermore the rates of metabolic derangements in first time and recurrent stone formers have been shown to be similar.[24,25] Alternatively the timing of the first stone event may indeed represent a different phenotype of stone former and this population may be less inclined to future cardiovascular events. Additional studies are needed to distinguish cardiovascular risk among first time and recurrent stone formers.

Strengths of this study include the large sample size, the racial/ethnic distribution of the MESA participants and the availability of coronary calcium as a marker of subclinical atherosclerosis. However, the findings of this study must be interpreted within the context of the study limitations. Because of the cross-sectional design, temporal associations between kidney stone formation and CAC could not be evaluated. There is potential selection and survival bias in this study population as approximately half of original MESA participants were present at Exam 5 and also met inclusion criteria for our analysis. The history of kidney stones was determined by self-report, was not adjudicated and was subject to recall bias. However, in a prior study self-report of kidney stones has been shown to be highly reliable compared to chart review.[3] Residual confounding may account in part for the observed association between CAC and stones. The profile of confounders may have also changed after individuals experienced kidney stone episodes. For example a participant with newly diagnosed kidney stones may have reduced the salt and animal protein intake. Therefore, further studies are needed to validate the findings of this study, including longitudinal studies that detail vascular risk factors and the development of kidney stones.

CONCLUSIONS

This study demonstrates an association between a history of kidney stone formation and CAC category among recurrent kidney stone formers after adjustment for demographic and known dietary factors known to contribute to stone formation. These findings suggest that greater severity of coronary calcium is more strongly linked to recurrent stone history than to the presence of detectable coronary calcium. This association was not seen in nonstone formers or in single stone formers. These findings provide additional support for a common pathophysiology between kidney stone disease and atherosclerotic disease. Additional prospective and longitudinal studies are needed to confirm the link between stone disease and subclinical atherosclerosis.

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