Kidney Stones and Subclinical Atherosclerosis in Young Adults: The CARDIA Study

Alexander P. Reiner, Arnold Kahn, Brian H. Eisner,* Mark J. Pletcher, Natalia Sadetsky, O. Dale Williams, Joseph F. Polak, David R. Jacobs, Jr. and Marshall L. Stoller†

From the Departments of Epidemiology, University of Washington (APR) and Division of Public Health Sciences, Fred Hutchinson Cancer Research Center (APR), Seattle, Washington, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota (DRJ), Department of Radiology, Tufts-New England Medical Center (JFP) and Department of Urology, Massachusetts General Hospital (BHE), Boston, Massachusetts, Departments of Urology and Medicine, University of California–San Francisco (NS, MLS, MJP) and California Pacific Medical Center Research Institute (AK), San Francisco, California, and Department of Medicine, University of Alabama, Birmingham, Alabama (ODW)

Abbreviations and Acronyms

BMI = body mass index

BP = blood pressure

CARDIA = Coronary Artery Risk Development in Young Adults

CVD = cardiovascular disease

eGFR = estimated glomerular filtration rate

GFR = glomerular filtration rate

HDL = high-density lipoprotein

HOMA = homeostasis model assessment

ICA = internal carotid artery

IMT = intimal-medial wall thickness

LDL = low-density lipoprotein

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† Correspondence: Department of Urology, Box 0738, San Francisco, California 94143-0738 (telephone: 415-476-1611; FAX: 415-476-8849; e-mail: mstoller@urology.ucsf.edu).

Purpose: Recent reports suggest that nephrolithiasis and atherosclerosis share a number of risk factors. To our knowledge there has been no previous examination of the relationship between kidney stones and subclinical atherosclerotic disease. We studied the relationship between nephrolithiasis, and carotid wall thickness and carotid stenosis assessed by B-mode ultrasound in the general community using data from the CARDIA study.

Materials and Methods: The CARDIA study is a United States, population based, observational study of 5,115 white and African-American men and women between the ages of 18 and 30 years at recruitment in 1985 to 1986.

Results: By the year 20 examination 200 (3.9%) CARDIA participants had reported ever having kidney stones. Symptomatic kidney stones were associated with greater carotid wall thickness measured at the year 20 examination, particularly of the internal carotid/bulb region. Using a composite dichotomous end point of carotid stenosis and/or the upper quartile of internal carotid/bulb wall thickness, the association of kidney stones with carotid atherosclerosis was significant (OR 1.6, 95% CI 1.1–2.3, p = 0.01), even after adjusting for major atherosclerotic risk factors.

Conclusions: The association between a history of kidney stones and subclinical carotid atherosclerosis in young adults adds further support to the notion that nephrolithiasis and atherosclerosis share common systemic risk factors and/or pathophysiology.

Key Words: urolithiasis, atherosclerosis

Kidney stones are a common cause of morbidity in the United States.[1] Their prevalence in young to middle-aged adults is approximately 5% to 10%.[2] While the focus of nephrolithiasis research has been on biochemical alterations in local urinary constituents leading to stone formation, abnormalities in urine chemistry alone do not explain many aspects of urinary stone disease. Epidemiological studies have linked nephrolithiasis to vascular risk factors such as hypertension, obesity and diabetes mellitus,[3–5] suggesting that systemic metabolic conditions in addition to urine composition strongly influence the pathophysiology of stone formation.[6]

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Given the association between nephrolithiasis and risk factors for atherosclerotic disease, our hypothesis is that patients with urinary stone disease should be at greater risk for other vascular complications. While clinical cardiovascular events are rare in a younger population, subclinical carotid disease is not uncommon. The relationship between kidney stones and subclinical vascular disease has not been previously assessed in young, community dwelling adults. Therefore, we examined the association between urinary stone disease and subclinical carotid atherosclerosis to better understand the possible relationship between these 2 disorders.

METHODS

CARDIA Study Participants and Measurements

The CARDIA study was designed as a longitudinal cohort study of the development and evolution of cardiovascular risk factors in young white and African-American adults.[7] In 1985 to 1986, 5,115 participants 18 to 30 years old were recruited from 4 clinical sites in Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota and Oakland, California. CARDIA participants were selected to have approximately the same number of people in subgroups of race, gender, education (high school or less, and more than high school) and age (18 to 24 and 25 to 30). Participants were reexamined at 6 followup examinations with overall retention rates among those surviving of 91% at year 2, 86% at year 5, 81% at year 7, 79% at year 10, 74% at year 15 and 72% at year 20. Data were collected on a variety of medical conditions, lifestyle and dietary factors, as well as blood measurements believed to be related to CVD. Of the 3,549 participants who attended the year 20 examination 3,258 underwent carotid artery ultrasound examination. The study was approved by an institutional review board at all CARDIA sites.

At each examination cycle the history of kidney stones was assessed by self-report, which has been shown to be highly accurate.[8] We created a variable based on whether individuals ever reported at any of the examinations in which they participated that a doctor or nurse had ever said that the individual had kidney stones, and 189 participants reported kidney stones ever. From a review of hospitalization records obtained during CARDIA followup we identified an additional 11 cases for a total of 200 participants with kidney stones. Of the 153 participants who had at least 1 subsequent visit after stones were reported 115 replicated their report at least once. Therefore, the reliability rate was 115 of 153 (75.2%).

For the current analysis we used cardiovascular risk factor measurements made at the year 0 (baseline) and the year 20 followup examination.[7] Smoking status was assessed using a standardized questionnaire. BMI (kg/m^2) was calculated from measurements obtained during the physical examination. Standard methods for measuring blood pressure, fasting total cholesterol, HDL cholesterol, triglycerides, glucose, insulin, uric acid and creatinine were used.[9–12] LDL cholesterol was estimated by the Friedewald equation. The presence of diabetes was defined as fasting blood glucose 126 mg/dl or greater, or taking insulin and/or oral hypoglycemic agents. Insulin resistance was calculated using the homeostasis model assessment (HOMA = fasting plasma insulin [μU/l] $\times$ fasting plasma glucose [mmol/l]/22.5). Serum creatinine was used to estimate GFR and was calculated using the 4-variable Modification of Diet in Renal Disease method.[13] Only a small proportion of participants reported diuretic use at the year 0 (32) and year 20 (120) examinations.

Carotid IMT was determined by B-mode ultrasound (GE LOGIQ 700) at the year 20 examination using standard procedures.[14] The maximum IMT of the common carotid, internal carotid and the bulb was defined as the mean of the maximal intima-media thickness of the near and far wall on the left and right sides. A combined ICA/bulb variable was created consisting of the arithmetic mean of all ICA and bulb measurements. The IMT included the thickness of any atherosclerotic plaque that might be present at the measurement site. Plaque is well-known to be more likely present in the bulb/ICA than in the common carotid, so the common carotid IMT is closer to a pure measure of wall thickness. The presence of any stenosis (mostly 1% to 24% of the lumen) anywhere in the left or right carotid artery was noted separately. We defined the presence of carotid atherosclerosis as any stenosis and/or bulb/ICA in the upper quartile distribution (greater than 1.02 mm).

Statistical Analysis

Clinical and sociodemographic characteristics of the study population were evaluated by chi-square analysis for categorical variables and ANOVA analysis for continuous variables. Associations between ever reporting kidney stones by the year 20 examination and baseline cardiovascular risk factors were evaluated by logistic regression, controlling for other baseline clinical and sociodemographic characteristics. Risk estimates were reported as odds ratios for ever having reported kidney stones by the year 20 examination per indicated unit (SD for continuous variables or category for discrete variables). Multiple linear regression or logistic regression models were performed to evaluate the association between ever reported kidney stones and several dependent variables at year 20, adjusted for other baseline or year 20 participant characteristics and risk factors, including 1) mean common carotid IMT, 2) mean bulb/ICA IMT, 3) presence of carotid stenosis, and 4) presence of carotid atherosclerosis defined by any stenosis and/or bulb/ICA in the upper quartile distribution. We also analyzed quartiles of common or bulb/ICA carotid IMT as a categorical variable using polychotomous ordinal logistic regression. All regression analyses were performed using the statistical package Stata®/SE11 with p less than 0.05 statistically significant. In addition, we considered the relationship of kidney stones that occurred at year 15 or earlier (before carotid ultrasound) to carotid atherosclerosis at year 20.

RESULTS

Descriptive Characteristics of CARDIA Participants

Overall mean age at study entry was 25 years and 55% of participants were women. Current smoking, BMI,

blood pressure and insulin resistance were higher among African-American than among white participants (all $p < 0.001$, table 1). By the year 20 examination 200 (3.9%) participants had reported ever having kidney stones and the prevalence was 2.6-fold higher among white participants (5.7%) than among African-American participants (2.3%, $p < 0.0001$).

Carotid IMT was greater in African-American than in white participants ($p < 0.01$) but the prevalence of carotid stenosis at year 20 was similar in each population (18%, $p = 0.82$). The prevalence of the composite carotid atherosclerosis outcome of the upper quartile of internal carotid/bulb IMT and/or carotid stenosis was 35% among African-American participants and 32% among white participants ($p < 0.05$).

CARDIA Participant Characteristics and Kidney Stones

The association between ever reported kidney stones, and various baseline demographic, lifestyle and clinical characteristics at the baseline (year 0) CARDIA examination is shown in table 2. In a minimally adjusted model age, male gender, white race, clinic site, BMI, LDL cholesterol, uric acid and fasting insulin or HOMA index were positively associated with ever reporting kidney stones, and baseline HDL cholesterol negatively predicted ever reporting kidney stones. In a multivariable adjusted regression model only age and race remained significantly associated with kidney stones. Similar associations with ever reporting kidney stones were obtained when using participant characteristics determined at year 20, with the exception of insulin resistance, which remained significantly associated with kidney stones in the fully adjusted multivariable model ($p = 0.01$).

Kidney Stones and Subclinical Atherosclerosis at Year 20

When minimally adjusted for age, gender, race and clinic, greater carotid wall thickness, particularly of the internal carotid/bulb region, was associated with a reported history of symptomatic kidney stones (table 3, model A). When additional atherosclerotic risk factors (hypertension, blood pressure, cholesterol, insulin resistance, renal function) ascertained at baseline (model B) or year 20 (model C) were

Table 1. *CARDIA participant characteristics at study entry and at most recent followup*

	Yr 0 Examination		Yr 20 Examination	
	White Participants	African-American Participants	White Participants	African-American Participants
No.	2,478	2,637	1,898	1,651
Mean age (range)	25.4 (17–32)	24.3 (17–35)	45.6 (37–52)	44.5 (37–54)
No. female gender (%)	1,307 (53)	1,480 (56)	1,009 (53)	1,005 (61)
Mean ± SD yrs education	14.6 ± 2.4	13.0 ± 1.8	15.8 ± 2.6	14.0 ± 2.2
No. clinic (%):				
Birmingham	529 (21)	649 (24)	379 (20)	440 (27)
Chicago	557 (22)	552 (21)	430 (23)	363 (22)
Minneapolis	783 (32)	619 (23)	603 (32)	322 (20)
Oakland	609 (25)	817 (31)	486 (26)	526 (32)
No. smokers (%):	554 (26)	689 (33)	274 (15)	399 (25)
Former	443 (18)	233 (9)	461 (25)	218 (13)
Current	662 (27)	884 (34)	276 (15)	405 (25)
Mean ± SD ml/wk alcohol consumption	13.6 ± 21.0	10.7 ± 22.7	12.4 ± 20.8	9.0 ± 23.7
Mean ± SD kg/m^2 BMI	23.6 ± 4.1	25.3 ± 5.7	27.9 ± 6.5	31.3 ± 7.6
Mean ± SD mm Hg BP:				
Systolic	109 ± 11	111 ± 11	113 ± 13	121 ± 16
Diastolic	68 ± 9	69 ± 10	70 ± 11	77 ± 12
Mean ± SD mg/dl cholesterol:				
Total	176 ± 32	177 ± 35	187 ± 34	184 ± 36
LDL	108 ± 30	110 ± 32	110 ± 31	110 ± 34
HDL	52 ± 13	54 ± 13	54 ± 17	54 ± 16
Mean ± SD mg/dl triglycerides	79 ± 57	67 ± 38	119 ± 88	98 ± 68
Mean ± SD mg/dl glucose	83 ± 12	82 ± 19	96 ± 22	100 ± 31
Mean ± SD mg/dl insulin	9.3 ± 6.4	12.3 ± 9.0	15.0 ± 10.1	18.4 ± 12.2
Mean ± SD mg/dl uric acid	5.35 ± 1.37	5.14 ± 1.37	5.67 ± 1.43	5.80 ± 1.56
No. diabetes (%)	24 (1.0)	25 (1.0)	108 (6)	167 (10)
Mean ± SD ml/min/1.73 m^2 eGFR	110.8 ± 17.9	130.6 ± 21.0	90.9 ± 19.3	104.7 ± 24.7
No. kidney stones by self-report or hospitalization (%)	27 (1.1)	5 (0.2)	140 (5.7)	60 (2.3)
Mean ± SD mm common carotid IMT	Not determined		0.66 ± 0.11	0.71 ± 0.12
Mean ± SD mm bulb/internal carotid IMT	Not determined		0.72 ± 0.18	0.74 ± 0.18
No./total No. carotid stenosis (%)*	Not determined		319/1,760 (18)	263/1,484 (18)
No./total No. carotid stenosis and/or upper quartile of bulb/internal carotid IMT (%)*	Not determined		546/1,751 (32)	5,033/1,458 (35)

* Number of participants available for each subclinical atherosclerosis outcome is given in the denominator.

Table 2. *Associations between ever having kidney stones through year 20, and demographic characteristics and cardiovascular risk factors at year 0*

Risk Factor	Comparison Unit or SD	Adjusted for Age, Gender, Race			Multivariable Adjusted*		
		OR	SE	*p* Value	OR	SE	*p* Value
Age	Per additional yr	1.06	0.02	0.006	1.06	0.02	0.005
Male gender	vs Female gender	1.48	0.22	0.007	1.39	0.27	0.10
Self-reported white race	vs African-American	2.39	0.38	<0.001	2.75	0.47	<0.001
Clinic:				0.08			0.12
Chicago	vs Birmingham	0.73	0.15	0.13	0.74	0.15	0.20
Minneapolis	vs Birmingham	0.62	0.12	0.02	0.60	0.12	0.02
Oakland	vs Birmingham	0.67	0.13	0.05	0.72	0.14	0.14
Educational attainment	Per additional yr	1.01	0.03	0.79			
Current smokers	vs Never smokers	1.09	0.18	0.59			
Former smokers	vs Never smokers	0.71	0.17	0.15			
Alcohol consumption (ml/day)	21.9	0.92	0.08	0.31			
BMI (kg/m^2)	5.0	1.24	0.09	0.002	1.08	0.10	0.37
Systolic BP (mm Hg)	10.9	1.02	0.08	0.75			
Diastolic BP (mm Hg)	9.6	1.06	0.08	0.44			
LDL cholesterol (mg/dl)	31.2	1.16	0.08	0.03	1.11	0.08	0.18
HDL cholesterol (mg/dl)	13.2	0.85	0.07	0.04	0.95	0.08	0.55
Triglycerides (mg/dl)	48.4	1.02	0.06	0.72			
Fasting blood glucose (mg/dl)	16.3	0.99	0.08	0.92			
Fasting insulin (mg/dl)	8.0	1.18	0.08	0.01			
Uric acid (mg/dl)	1.38	1.19	0.11	0.06	1.04	0.10	0.70
Log (HOMA)	0.62	1.26	0.09	0.002	1.16	0.10	0.09
eGFR (ml/min/1.73 m^2)	18.6	0.96	0.12	0.77			

* Odds ratios were derived from a single multivariable logistic regression model, with all variables listed in the column adjusted for each other. Only variables associated with the outcome at $p < 0.10$ in the minimal model were included in the multivariable model. For the multivariable model the total number of participants with nonmissing values for all baseline covariates was 4,959, of whom 186 ever reported having kidney stones by year 20.

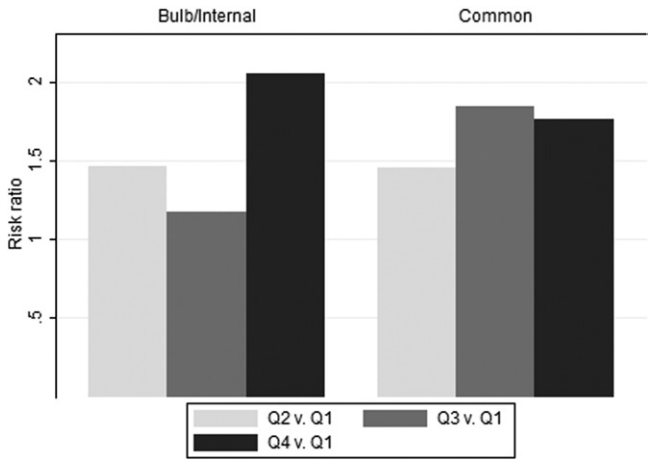
added as covariates to the regression model, there was some attenuation of the apparent relationship between kidney stones and common and internal/bulb IMT, but the association with internal/bulb IMT remained significant. Similar results were obtained when carotid IMT was analyzed according to quartiles using polychotomous logistic regression (see figure). There were no significant differences in the carotid IMT-symptomatic stone disease association according to race or gender for common carotid thickness or bulb/internal carotid thickness (data not shown).

Table 3. *Association between history of kidney stones ever by year 20 and continuous carotid wall thickness measures at year 20 examination*

Atherosclerosis Outcome	Regression Coefficient ± SE		
	Model A*	Model B†	Model C‡
Bulb/internal carotid IMT	0.054 ± 0.018	0.048 ± 0.018	0.041 ± 0.019
p Value	0.003	0.007	0.02
Common carotid IMT	0.028 ± 0.009	0.019 ± 0.009	0.014 ± 0.009
p Value	0.003	0.04	0.16

* Adjusted for age, gender, race and clinic.
† Adjusted for age, gender, race, clinic, smoking, treated hypertension, systolic BP, BMI, LDL cholesterol, HDL cholesterol, eGFR, uric acid and HOMA index, with covariates assessed at year 0.
‡ Adjusted for age, gender, race, clinic, smoking, treated hypertension, systolic BP, BMI, LDL cholesterol, HDL cholesterol, eGFR, uric acid and HOMA index, with covariates assessed at year 20.

Kidney stones were associated with a nonsignificant increased risk of carotid stenosis (table 4). When a composite binary outcome of carotid atherosclerosis was defined as the presence of stenosis and/or upper quartile of bulb/internal IMT, a history of kidney stones was associated with a significantly increased 1.6-fold increased risk of carotid atherosclerosis. The association between kidney stones and the composite outcome of carotid atherosclerosis remained significant even after adjusting for all ma-



Carotid IMT was analyzed according to quartiles using polychotomous logistic regression.

Table 4. *Association between history of kidney stones ever by year 20 and dichotomous carotid atherosclerosis measures at year 20 examination*

Atherosclerosis Outcome	OR (95% CI)		
	Model A*	Model B†	Model C‡
Presence of carotid stenosis	1.37 (0.92–2.04)	1.35 (0.90–2.04)	1.29 (0.84–1.98)
p Value	0.12	0.14	0.24
Presence of carotid stenosis and/or upper quartile of bulb/internal carotid IMT	1.67 (1.17–2.36)	1.58 (1.11–2.27)	1.56 (1.06–2.28)
p Value	0.004	0.01	0.02

* Adjusted for age, gender, race and clinic.
† Adjusted for age, gender, race, clinic, smoking, treated hypertension, systolic BP, BMI, LDL cholesterol, HDL cholesterol, eGFR, uric acid and HOMA index, with covariates assessed at year 0.
‡ Adjusted for age, gender, race, clinic, smoking, treated hypertension, systolic BP, BMI, LDL cholesterol, HDL cholesterol, eGFR, uric acid and HOMA index, with covariates assessed at year 20.

jor atherosclerotic risk factors. In a prospective analysis considering the relationship between kidney stones that occurred at year 15 or earlier (in 153 patients) and the occurrence or progression of carotid atherosclerosis at year 20, the association findings were similar to those presented in tables 3 and 4 (data not shown).

DISCUSSION

In a community based study of young to middle-aged white and African-American adults, a history of kidney stones was associated with carotid wall thickness, particularly of the internal carotid/bulb region, and also with a composite measure of carotid stenosis and internal carotid wall thickness. The association between kidney stones and subclinical vascular disease in community dwelling younger adults from the CARDIA study adds further support to the notion that nephrolithiasis and atherosclerosis share common systemic risk factors and/or pathophysiology. We also found that white participants had a several-fold higher rate of kidney stone formation than African-American participants, consistent with other reports.[2,15,16]

The partial attenuation of the association between kidney stones and subclinical atherosclerosis after adjustment for the full set of vascular risk factors suggests that atherosclerosis and nephrolithiasis may operate in part through multiple, shared pathogenic mechanisms. These may include vascular endothelial injury, and altered calcium, cholesterol and/or glucose metabolism. In young adults from the CARDIA study age, male gender, dyslipidemia, uric acid and insulin resistance at the baseline or year 20 examination were associated with a history of kidney stones by year 20. These findings are consistent with those of recent studies reporting associations between kidney stones and traditional atherosclerotic risk factors including hypertension, diabetes mellitus, dyslipidemia and obesity.[3–5,17,18] Taken together these observations further strengthen the evidence of a link between nephrolithiasis and systemic atherosclerosis and its risk factors.

The apparently stronger association between kidney stones and internal carotid vs common carotid wall thickness noted in the CARDIA study may be noteworthy. Common carotid IMT is a relatively pure measurement of wall thickness and is less indicative of stenosis than internal/bulb IMT. Thus, kidney stones may be specifically or preferentially associated with raised atherosclerotic lesions as opposed to wall thickening. Confirmation of these findings through additional studies involving a larger number of individuals with subclinical measures of carotid disease is required.

On the basis of several lines of evidence, including kidney stone cholesterol content, histological examination of points of attachment for stones in the renal papilla and renal blood flow changes based on sleep position which appear to effect the laterality of stone disease, it has been hypothesized that the precipitating factor may be vascular in origin, and is localized to the vasa recta of the urinary papilla.[6] However, controversy exists whether the collecting ducts rather than the vasa recta represent the true anatomical point of attachment for forming stones.[19] Therefore, additional study is required to clarify whether the pathogenic similarities between an atherosclerotic plaque and nephrolithiasis suggest a vascular origin of kidney stone formation as an alternative to the shared risk factor model.

Strengths of our study include the large sample size, population based sampling of young adults without a significant burden of clinical CVD and the availability of several subclinical disease measures as atherosclerotic outcomes. However, several possible limitations should also be noted. Kidney stones were ascertained by self-report and, therefore, may be subject to measurement error or recall bias. However, self-report of stones has been reported to be more than 95% accurate in other studies.[8] Moreover

because of the longitudinal nature of the CARDIA study we were able to confirm a high rate of reproducibility of self-reported kidney stones among participants who had an opportunity for a second confirmatory report.

Another potential limitation of our study is that our ability to detect associations with coronary atherosclerosis may be limited due to the extent of atherosclerosis present in younger to middle-aged adults. It should also be noted that the presence of subclinical atherosclerosis was not assessed at baseline in the CARDIA study. Thus, it is difficult to draw conclusions on the temporal association between kidney stones and atherosclerosis. Nonetheless we were able to perform a prospective analysis by restricting the number of kidney stone cases to those that occurred or were reported before the measurement of carotid and coronary atherosclerosis. Although the prospective analysis was limited by the smaller number of kidney stone cases, the qualitative similarity of the results to the full cross-sectional year 20 analysis is consistent with kidney stones appearing before atherosclerosis or at least concurrently with atherosclerosis.

While adjustment was performed for major cardiovascular risk factors, residual confounding may account for some of the observed associations between kidney stones and atherosclerosis. Therefore, additional studies are warranted. These studies should include not only more detailed longitudinal assessment of the occurrence of kidney stones, vascular risk factors and atherosclerotic disease, but also analysis of population based samples of older adults with greater atherosclerotic disease burden, and large numbers of clinical end points such as myocardial infarction and stroke.

CONCLUSIONS

We demonstrated that kidney stones are associated with subclinical atherosclerotic disease in young to middle-aged adults. We hypothesize that kidney stones and atherosclerosis tend to occur together because of shared pathogenic mechanisms (vascular injury and inflammation, calcification) and risk factors (hypertension, altered cholesterol and/or glucose metabolism). Further study of the link between nephrolithiasis, and subclinical and clinical CVD, as well as their associated metabolic risk factors, could shed further light on the etiology of kidney stone formation and systemic disorders of calcium metabolism, and future novel therapeutic interventions for both disorders. In addition, there could be important public health implications for patients with kidney stones with respect to cardiovascular risk assessment.

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