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Urine Calcium Excretion, Cardiovascular Events and Mortality in Outpatients with Stable Coronary Artery Disease (From the Heart and Soul Study)

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Abstract

We sought to evaluate the association of urine calcium excretion (UCaE), which reflects systemic calcium absorption, with CV events and mortality in outpatients with prevalent coronary heart disease (CHD). Calcium supplementation is associated with vascular calcification and adverse cardiovascular (CV) outcomes in patients with end-stage renal disease. Recent studies have raised concern that this phenomenon may also extend to the general population. However, prior studies assessed oral calcium intake, which correlates poorly with systemic calcium absorption. We measured UCaE from 24 hour urine collections provided by 903 outpatients who were recruited from 2000 to 2002. We used Cox proportional hazard models to evaluate the association of baseline UCaE with a primary endpoint of any CV event (myocardial infarction, heart failure, stroke, or CV mortality). During a mean follow-up of 6±3 years, 287 subjects (32%) had a CV event. Following multivariate adjustment for demographics, traditional CV risk factors, and kidney function, there was no association between UCaE and the primary endpoint of any CV event (per 10 mg/day greater UCaE: HR 1.00 95% CI 0.98–1.02). Evaluation of individual CV outcomes revealed a lower rate of MI with higher UCaE (HR 0.97, 95% CI 0.94–1.00). Greater UCaE is not associated with higher overall CV event rates or mortality in outpatients with stable CHD. In contrast, greater UCaE is associated with a modestly lower rate of MI. These findings suggest that greater systemic calcium absorption does not confer CV harm in outpatients with prevalent CHD.

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Keywords

Calcium; Calcium Supplements; Cardiovascular Events; Coronary Artery Disease; Urine Calcium Excretion; Vascular Calcification

Introduction

Urine calcium excretion (UCaE) provides an estimate of the amount of calcium that is systemically absorbed, and overcomes limitations of recall bias and differences in intestinal absorption. Therefore, in a well characterized cohort of participants with known stable coronary disease, we sought to determine the association between UCaE and cardiovascular (CV) events.

Methods

The Heart and Soul Study is a prospective cohort study originally designed to investigate psychosocial factors and health outcomes in subjects with stable coronary heart disease (CHD). Details regarding recruitment methods and study design have been published previously.[1] In brief, 1,024 outpatients with stable CHD were recruited from two Veterans Administration Medical Centers, one university medical center, and nine public health clinics in the San Francisco Bay Area. Eligible participants met one or more of the following criteria: (1) history of MI; (2) evidence of at least 50% stenosis in one or more coronary vessels on cardiac catheterization; (3) evidence of exercise-induced ischemia by treadmill electrocardiogram or nuclear perfusion stress imaging; or (4) a history of coronary revascularization. Subjects were excluded if they had a history of MI in the previous 6 months, were unable to walk 1 block, or were planning to move out of the local area within 3 years. The study was approved by the institutional review board and all participants provided written informed consent.

Between September 2000 and December 2002, all participants underwent a baseline study appointment which included a medical history, physical examination, and comprehensive health status questionnaire. Outpatient 24-hour timed urine collections and fasting (12-hour) morning venous blood samples were obtained. Of the 1,024 original study subjects, we excluded 121 subjects with missing covariate data. Participants were followed for CV events through April 12, 2012. The remaining 903 participants are the subjects of this analysis.

The protocol used for collection of the 24-hour timed urine specimens has been previously described in detail.[2] In brief, participants were given detailed instructions regarding accurate timing of the urine collection and appropriate refrigeration of the specimens. Subjects were asked to void at the end of their study appointment and to begin the collection from that point forward. Research personnel retrieved the urine 24 hours after the collection was initiated to avoid over- or under-collection. If participants were unable to collect all urine for any reason or if collections were <1 or >3 L, the protocol was repeated. Urine volume was recorded. The 24-hour urine collections were originally collected at the time of the baseline examination and stored for future analyses of the associations between urine metabolites and CV events. The collections were stored frozen at 80 degrees Celsius until the time of analysis in 2009, when specimens were thawed and treated with 1 mol/L hydrochloric acid. Urine calcium was measured using a Cobas 6000 clinical analyzer (Roche Diagnositics, www.roche.com). The lower limit of detection was 0.6 mg/dL, and coefficients of variation were <2.0%.

The primary outcome was any CV event, which was defined as a composite of hospitalization for MI, stroke, heart failure, or CV death. Between the baseline examination

and April 12, 2012, we conducted annual follow-up interviews with participants or their proxy to inquire about interval death or hospitalization for “heart trouble”. For any reported event, we retrieved medical records, which two independent and blinded physician adjudicators reviewed. If the adjudicators agreed on the outcome classification, their classification was binding. In the event of a disagreement, a third blinded adjudicator was consulted.

All-cause mortality was determined by review of death certificates. MI was defined using the American Heart Association diagnostic criteria. A heart-disease-related death was defined as a death occurring during the same hospitalization in which an acute MI, congestive heart failure, severe cardiac dysrhythmia, or coronary artery bypass surgery was documented, or a death occurring within 1 hour of the onset of terminal symptoms not explained by other etiologies. Stroke was defined as a new neurological deficit not known to be secondary to brain trauma, tumor, infection, or other cause. Heart failure was defined as hospitalization for a clinical syndrome based on the Framingham congestive heart failure criteria, which require validation of 2 major or 1 major plus 2 minor criteria. (Major criteria: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, third heart sound, cardiomegaly on chest radiograph, pulmonary edema on chest radiograph, weight loss ≥ 4.5 kg in 5 days in response to HF therapy. Minor criteria: peripheral edema, night cough, dyspnea on exertion, hepatomegaly, pleural effusion, heart rate > 120/min).[3]

Age, sex, race, medical history, and smoking status were determined by self-reported questionnaire. Alcohol use was measured by use of the AUDIT-C questionnaire, with a score of ≥4 used to define regular alcohol use. Weight and height were measured, and body mass index was calculated as weight (in kilograms) divided by height (in meters) squared. Systolic and diastolic blood pressures were measured in the supine position after five minutes of rest.

Serum cystatin C concentrations were measured with a particle-enhanced immunonephelometric assay[4] (N Latex Cystatin-C, Dade Behring, Inc, Deerfield, IL) and used to calculate estimated GFR ($eGFR_{cys}$) with the following formula: $eGFR_{cys} = 76.7 \times \text{cystatin C}^{-1.19}$. This formula has been validated by comparison with iothalamate-measured GFR in a pooled cohort of kidney disease studies.[5] Total cholesterol and high-density lipoprotein cholesterol, were measured from fasting (12-hour overnight) blood samples drawn at the baseline study appointment and low density lipoprotein cholesterol was calculated using the Friedewald equation. High-sensitivity C-reactive protein was measured with Roche (Indianapolis, IA) or Beckman Extended Range (Galway, Ireland) assays. Parathyroid hormone (PTH) was measured using the Roche PTH immunoassay on an Elecsys E170 automated analyzer (Indianapolis, IN). Resting echocardiograms were performed on all participants using a standardized protocol by one of two trained and experienced technicians. A single experienced reader blinded to clinical information interpreted all studies as described previously.[1]

In the absence of clear cut points and after confirming linearity of the measure, we analyzed UCaE levels by tertiles. Differences in participant characteristics by tertiles of baseline UCaE were compared using chi-square tests for dichotomous variables and one-way analysis of variance for continuous variables. To determine the unadjusted association of UCaE with CV events, we measured cumulative event-free survival by the method of Kaplan-Meier, and compared unadjusted differences using the log-rank test. Next, we used Cox proportional hazards models to evaluate the association of UCaE with the composite outcome in multivariable models by tertiles. The lowest tertile served as the reference

category. We also evaluated UCaE as a continuous predictor (per 10 mg/day higher) in companion analyses.

We developed sequential models: model 1 was adjusted for demographics (age, sex, and race); model 2 was adjusted for model 1 variables plus traditional CV risk factors (body mass index, myocardial infarction, stroke, hypertension, systolic blood pressure), medications (angiotensin receptor antagonists, loop diuretics, thiazide diuretics) and C-reactive protein. C-reactive protein was log-transformed to normalize the distribution. Model 3 was adjusted for model 2 variables plus $eGFR_{cys}$. We assessed proportional hazards assumptions by visual inspection of Schoenfeld residuals, log-minus-log plots, and use of time-varying covariates to assess for heterogeneity of effects across follow-up, and found no evidence of violation.

To determine whether any association between UCaE and CV events could have been due to incomplete urine collections in subjects with low UCaE, we performed a sensitivity analysis excluding participants whose measured creatinine clearance on 24 hour urine collections was discrepant from $eGFR_{cys}$ by >30%, as previously described by Ix et al.[6] Because diuretics influence urine calcium excretion, we also performed a subgroup analysis restricted to subjects not receiving diuretics.

We then tested for interaction to determine whether the association between UCaE and the primary endpoint differed by sex, race, presence of moderate CKD (defined as eGFR>60 mL/min/1.73 m^2), or use of calcium supplements, with a p-value of <0.10 considered statistically significant for interaction terms, and $p<0.05$ considered significant for all other analyses. All analyses were conducted using STATA version 11.0 (College Station, TX).

Results

The mean age of the 903 study participants was 67±11 years; 82% were men, reflecting heavy recruitment from VA medical centers; and 30% had moderate CKD. The median UCaE was 72.5 mg/day (intertertile range, 50–109 mg/day). Compared with participants who had UCaE in the lowest tertile, those in the highest tertile were younger, more likely to be of Caucasian race, and had higher body mass indices. Participants in the lowest tertile had a greater prevalence of myocardial infarction, stroke, and hypertension. They were more likely to be taking cardiac medications, had higher systolic blood pressures, lower eGFRs, higher C-reactive protein levels, and higher parathyroid hormone (PTH) levels (Table 1).

During 6.2 years (mean) follow-up, there were 287 CV events. Greater UCaE was associated with a lower rate of the primary endpoint of any CV event in unadjusted analysis. Following multivariate adjustment for demographics, CV risk factors, cardiac medications, and eGFR, the association was no longer present. In fully adjusted models evaluating UCaE as a continuous variable (per 10 mg/day greater), the confidence intervals around the point estimate were narrow (Table 2). Examination of individual CV outcomes revealed no significant associations between UCaE and heart failure, stroke, CV mortality, or all-cause mortality. Higher UCaE was associated with a modestly lower rate of MI, which remained statistically significant in the fully adjusted model(Table 3). We found no effect modification by sex, race, presence of moderate CKD, or use of calcium supplements (p for interaction all > 0.10).

To determine whether any bias might be present due to incomplete urine collection, we performed a sensitivity analysis excluding participants whose measured 24 hour urine creatinine clearance and $eGFR_{cys}$ differed by >30% (n=290). Among those excluded, creatinine clearance overestimated $eGFR_{cys}$ in 247 subjects and underestimated $eGFR_{cys}$ in 43 subjects. After excluding these subjects, results were unchanged and point estimates for

the analyses performed in the remaining 613 individuals were comparable to those observed in the entire sample. The subgroup analysis restricted to subjects not receiving diuretics showed somewhat lower rates of myocardial infarction and all-cause mortality (Table 4).

Discussion

In the present study, we demonstrate that UCaE, which reflects systemic calcium absorption, is not associated with higher overall CV event or mortality rates among outpatients with coronary artery disease. These results were similar irrespective of sex, race, CKD status, and use of calcium supplements. To the degree that calcium is systemically absorbed, we found no evidence that it adversely affected CV outcomes. On the contrary, greater UCaE was associated with a modestly lower rate of myocardial infarction.

The concern for CV harm was first raised by Bolland and colleagues, who analyzed data from a trial of calcium supplementation in postmenopausal women. Initially hypothesizing benefit of calcium based on prior literature, they found the opposite - an elevated risk of CV events in those receiving supplementation.[7] The same investigators subsequently performed a re-analysis of the Women's Health Initiative, which demonstrated higher CV event rates in subjects receiving calcium supplementation, regardless of vitamin D co-administration.[8] Although others have raised concerns regarding methodologic limitations of these studies; [9–11] they nevertheless generated public health concern. Given the high prevalence of calcium supplement use in the population, even modest increases in CHD risk could have important public health implications.

Our observations of no harm and potential benefit of greater urinary calcium are concordant with the results of two recent meta-analyses. An analysis from the AHRQ showed no significant associations between calcium intake (with or without vitamin D) and CV events, death, or myocardial infarction.[12] A meta-analysis by Wang and colleagues also showed no association between calcium supplementation (without vitamin D) and CV events, but demonstrated a trend toward reduction in CV events with combined calcium and vitamin D supplementation.[13]

Our results are also in keeping with the results of the recent trial by Lewis et al, in which subjects were randomized to calcium or placebo, and followed for the combined endpoint of atherosclerotic vascular mortality or first hospitalization. The results of the trial revealed that the intervention group did not have a higher rate of the primary endpoint; moreover, calcium supplementation appeared to reduce the risk of hospitalization and mortality in those with preexisting coronary heart disease[14]. Similarly, a recent analysis of fifteen common vitamin and mineral supplements found calcium to be the only supplement associated with a reduction in mortality.[15]

It is now well established that greater calcium intake is associated with more extensive vascular calcification in subjects with end stage renal disease.[16–18] Furthermore, this is one mechanism which has been proposed to mediate CV risk in persons receiving calcium supplements.[19] Therefore, we tested for interaction by presence of CKD to determine whether subjects with CKD might have increased risk of CV events. However, we observed no heterogeneity, suggesting that the relationship of UCaE with CV events is similar in persons with or without CKD.

Diuretics influence urine calcium excretion; therefore, we also performed a subgroup analysis restricted to subjects not receiving diuretics. We observed a lower rate of myocardial infarction and all-cause mortality in subjects who were not taking diuretics, which could indicate a protective effect of greater calcium absorption, or may simply indicate selection of healthier individuals. Regardless, CV harm was not observed.

We also found that PTH levels were higher in subjects with low urine calcium compared to subjects with high urine calcium. This effect is consistent with prior balance studies demonstrating higher PTH levels in subjects with low calcium intake, which mediates higher fractional intestinal calcium absorption.[20, 21] PTH converts 25-hydroxy-vitamin D to 1,25-hydroxy-vitamin D, which stimulates intestinal absorption of calcium.[22]

The findings of the present study are in concordance with the majority of the evidence to date, which suggests no harm and potential cardiovascular benefit of calcium. Calcium supplementation if needed to meet daily requirements, in combination with vitamin D, is recommended by current society guidelines[23, 24] based on data demonstrating increased bone mineral density[25, 26] and reduction in fracture risk.[27] A recent commission of the Institute of Medicine[28] and a position statement by the American Society for Bone and Mineral Research[29] upheld these recommendations, finding that the weight of the evidence favors the safety of calcium supplementation. Our results of no cardiovascular harm and potential benefit of greater systemic calcium absorption are in agreement with these recommendations.

Despite the advantages of UCaE by 24-hour urine collection described previously, this method also has limitations. First, precision of UCaE depends upon accurate collection. If accurately collected, measured creatinine clearance using the 24-hour urine collections and estimated creatinine clearance using serum creatinine based equations (and thus entirely independent of the accuracy of the timed urine collection) should be similar. To evaluate this, we performed a sensitivity analysis of subjects with concordant measured and estimated creatinine clearance, which yielded similar results. Second, dietary sodium, potassium, and alkali intake may influence UCaE, and persons with history of nephrolithiasis often have higher UCaE. These factors were not measured in our study. Third, low vitamin D has itself been associated with adverse CV events,[30] which was not measured in this study. Future studies are required to determine if the association of low UCaE with higher risk of MI observed here can be confirmed in other settings, and if so, whether it may reflect vitamin D deficiency.

Our study had other limitations. The study participants were mostly men, and all had stable CHD. Generalizability to other settings is unknown. Last, as with all null studies, we cannot exclude that a true association was missed, and results should be interpreted within the confines of the 95% confidence intervals. However, in continuous analyses, our confidence intervals were narrow, suggesting that any missed association would likely be very modest in strength, at best.

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Table 1

Baseline Characteristics of 903 Participants with Stable Coronary Heart Disease, by Tertiles of Urinary Calcium Excretion

	Urinary Calcium Excretion (mg/day)			
Variable	**I (≤50)**	**II (50–109)**	**III (109–490)**	**p-value**
Age (years)	70±11	67±11	63±10	<0.001
Male	81%	83%	83%	0.83
Race				
White	55%	63%	64%	<0.001
Black	23%	14%	10%	
Other	22%	24%	26%	
Current Smoker	20%	17%	22%	0.24
Regular Alcohol Use	26%	27%	32%	0.24
Body Mass Index (kg/m^2)	28±6	28±5	29±5	0.008
Ejection Fraction (%)	61±10	62±10	62±9	0.40
Myocardial Infarction	61%	52%	50%	0.01
Stroke/Transient Ischemic Attack	18%	13%	11%	0.05
Heart Failure	21%	15%	16%	0.08
Diabetes	30%	24%	24%	0.13
Hypertension	80%	65%	68%	<0.001
Revascularization	64%	57%	58%	0.12
Aspirin	76%	76%	80%	0.37
Beta-blocker	63%	55%	55%	0.07
Angiotensin inhibitor	57%	51%	47%	0.05
Thiazide diuretic	23%	13%	8%	<0.001
Loop diuretic	20%	15%	12%	0.03
Statin	65%	63%	65%	0.86
Calcium supplements	12%	17%	13%	0.21
Systolic Blood Pressure (mmHg)	136±22	131±21	132±19	0.002
Cholesterol (mg/dL)				
Total	176±41	178±43	178±43	0.82
High Density Lipoprotein	45±15	46±13	45±14	0.58
Low Density Lipoprotein	104±33	106±35	103±31	0.61
Estimated Glomerular Filtration Rate, by cystatin, (mL/min/1.73 m^2)	61±23	72±22	81±18	<0.001
ln-CRP (mg/L)	0.9±1.3	0.8±1.3	0.5±1.4	0.002
ln-PTH (mg/L)	4.1±0.5	4.0±0.4	3.9±0.4	<0.001

All values are expressed as mean ± standard deviation or percentage

Table 2

Association of 24-hour Urinary Calcium Excretion with the Composite Outcome of Any Cardiovascular Event*

	Hazard Ratio (95% CI)			HR (95% CI), as a Continuous Variable	
	Tertile I (≤50 mg/day)	**Tertile II (50–109 mg/day)**	**Tertile III (≥109 mg/day)**	**Per 10 mg/day Greater Urine Calcium**	**p-value**
Proportion with Events	40% (121/301)	30% (89/301)	26% (77/301)		
Model 1	1.00	0.70 (0.53–0.93)	0.67 (0.50–0.91)	0.98 (0.96–1.00)	0.02
Model 2	1.00	0.74 (0.56–0.99)	0.75 (0.55–1.03)	0.98 (0.97–1.00)	0.07
Model 3	1.00	0.86 (0.64–1.15)	1.00 (0.71–1.40)	1.00 (0.98–1.02)	0.96

Model 1 = Adjusted for demographics (age, sex, race)

Model 2 = Adjusted for above plus traditional cardiovascular risk factors (BMI, MI, stroke, HTN, systolic blood pressure, C-reactive protein) and medications (angiotensin receptor antagonists, loop diuretics, thiazide diuretics)

Model 3 = Adjusted for above plus estimated glomerular filtration rate

SD = Standard Deviation CI = Confidence Interval

*Any Cardiovascular Event was defined as myocardial infarction, heart failure, stroke/transient ischemic attack, or cardiovascular death

Table 3

Association of Urine Calcium Excretion with Individual Outcomes in 903 Subjects with Stable Coronary Heart Disease

	HR (95% CI), per 10 mg/day Greater Urine Calcium Excretion					
	Myocardial Infarction (n=117)	**Heart Failure (n=155)**	**Stroke/TIA (n=41)**	**Any CV Event* (n=287)**	**CV Mortality (n=113)**	**All-Cause Mortality (n=341)**
Model 1	0.95 (0.92–0.98)	0.99 (0.97–1.01)	0.97 (0.93–1.02)	0.98 (0.96–1.00)	0.97 (0.94–1.00)	0.97 (0.96–0.99)
Model 2	0.96 (0.93–0.99)	0.99 (0.97–1.02)	0.99 (0.94–1.03)	0.98 (0.97–1.00)	0.97 (0.95–1.00)	0.98 (0.96–0.99)
Model 3	0.97 (0.94–1.00)	1.01 (0.99–1.04)	0.99 (0.95–1.04)	1.00 (0.98–1.02)	0.98 (0.95–1.01)	0.99 (0.97–1.00)

HR = hazard ratio; CI = confidence interval; CV = cardiovascular

* Any event or CV mortality is defined as myocardial infarction, heart failure, stroke, or death from cardiovascular causes

Model 1 = Adjusted for demographics (age, sex, race)

Model 2 = Adjusted for above plus cardiovascular risk factors (body mass index, myocardial infarction, prior stroke, hypertension, systolic blood pressure), C-reactive protein, and medications (angiotensin receptor antagonists, loop diuretics, thiazide diuretics)

Model 3 = Adjusted for above plus estimated glomerular filtration rate

Table 4

Association of Urine Calcium Excretion with Individual Outcomes, by Subgroups*

	HR (95% CI), per 10 mg/day Greater Urine Calcium Excretion					
	Myocardial Infarction	**Heart Failure**	**Stroke/TIA**	**Any CV Event†**	**CV Mortality**	**All-Cause Mortality**
Entire Cohort (n=903)	0.97 (0.94–1.00)	1.01 (0.99–1.04)	0.99 (0.95–1.04)	1.00 (0.98–1.02)	0.98 (0.95–1.01)	0.99 (0.97–1.00)
Subgroup not on diuretic therapy (n=634)	0.95 (0.92–0.99)	0.99 (0.95–1.03)	0.98 (0.91–1.05)	0.98 (0.96–1.01)	0.97 (0.93–1.01)	0.97 (0.95–1.00)
Subgroup with ideal urine collections (n=613)‡	0.96 (0.92–1.00)	1.01 (0.97–1.04)	1.00 (0.94–1.07)	1.00 (0.97–1.02)	0.98 (0.94–1.03)	0.99 (0.96–1.01)

HR = hazard ratio; CI = confidence interval; CV = cardiovascular; TIA = transient ischemic attack

*All models are adjusted for demographics (age, sex, race), cardiovascular risk factors (body mass index, myocardial infarction, prior stroke, hypertension, systolic blood pressure), C-reactive protein, and medications (angiotensin receptor antagonists, loop diuretics, thiazide diuretics), and estimated glomerular filtration rate, by cystatin

†Any event or CV mortality is defined as myocardial infarction, heart failure, stroke, or death from cardiovascular causes

‡Ideal urine collections were defined as those for which measured 24 hour urine creatinine clearance and estimated glomerular filtration rate differed by <30%