Risk Factors for Coronary Artery Calcium Among Patients With Chronic Kidney Disease (from the Chronic Renal Insufficiency Cohort Study)

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Cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD). We examined the cross-sectional association between novel risk factors and coronary artery calcium (CAC) measured using electron beam computed tomography or multidetector computed tomography among 2,018 patients with CKD. Using the total Agatston scores, the participants were classified as having no (0), moderate (>0–100), or high (>100) CAC. After adjustment for age, gender, race, study sites, cigarette smoking, previous cardiovascular disease, hypertension, and diabetes, the use of lipid-lowering drugs, body mass index, waist circumference, and cystatin C, several novel risk factors were significantly associated with high CAC. For example, the odds ratios of high CAC associated with 1 SD greater level of risk factors were 1.20 (95% confidence interval 1.04 to 1.38) for serum calcium, 1.21 (95% confidence interval 1.04 to 1.41) for serum phosphate, 0.83 (95% confidence interval 0.71 to 0.97) for log (total parathyroid hormone), 1.21 (95% confidence interval 1.03 to 1.43) for log (homeostasis model assessment–insulin resistance), and 1.23 (95% confidence interval 1.04 to 1.45) for hemoglobin A1c. Additionally, the multivariate-adjusted odds ratio for 1 SD greater level of cystatin C was 1.31 (95% confidence interval 1.14 to 1.50). Serum high-sensitive C-reactive protein, interleukin-6, tumor necrosis factor-α, and homocysteine were not statistically significantly associated with high CAC. In conclusion, these data indicate that abnormal calcium and phosphate metabolism, insulin resistance, and declining kidney function are associated with the prevalence of high CAC, independent of the traditional risk factors in patients with CKD. Additional studies are warranted to examine the causal effect of these risk factors on CAC in patients with CKD. **(Am J Cardiol 2012;110:1735–1741)**

Prospective cohort studies have documented that cardiovascular disease (CVD) is the major cause of premature death in patients with chronic kidney disease (CKD).[1–3] Coronary arterial calcium (CAC) independently predicts the risk of CVD over and above the traditional risk factors in the general population.[4] CAC is more common and severe in patients with CKD[5,6] and is more strongly associated with an increased risk of CVD in patients with end-stage renal disease compared to the general population.[7,8] In a meta-analysis of 30 cohort studies with 218,080 subjects, the presence of CAC was associated with a three- to fourfold greater risk of CVD in the overall population and more than sixfold greater risk among patients with end-stage renal disease.[8] In the general population, cigarette smoking, obesity, dyslipidemia, hypertension, diabetes, and inflammation are all associated with an increased risk of CAC.[9–11] These risk factors are common in those with CKD and might partially contribute to increased risk of CAC.[12,13] However, data are sparse on novel risk factors for CAC in patients with predialysis CKD.[14] The Chronic Renal Insufficiency Cohort (CRIC) study included a large group of patients with CKD with a broad spectrum of renal function and co-morbid conditions. More than ½ of CRIC participants underwent electron beam computed tomography (CT) or multidetector CT, which provided an exceptional opportunity to examine the traditional and novel risk factors for CAC in patients with CKD.

Methods

The CRIC study included a racially and ethnically diverse group of men and women aged 21 to 74 years with mild-to-moderate CKD (age-based estimated glomerular fil-

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tration rate entry criteria 20 to 70 mL/min/1.73 m^2); approximately ½ of the cohort had diabetes. A total of 3,612 CRIC participants were recruited from May 2003 to August 2008 from 7 clinical centers in the United States.[15] Patients with cirrhosis, human immunodeficiency virus infection, polycystic kidney disease, or renal cell carcinoma, those requiring dialysis or who had received a kidney transplant, and those taking immunosuppressant drugs were excluded from the CRIC study. Additionally, patients with a history of coronary artery revascularization were excluded from electron beam CT/multidetector CT. Of the CRIC study participants, 1,142 were randomly selected from the entire cohort and stratified by age, gender, race/ethnicity, diabetes status, and estimated glomerular filtration rate for electron beam CT/multidetector CT. In addition, electron beam CT/multidetector CT was performed on all eligible CRIC participants from 3 clinical centers for an ancillary study. A total of 2,018 CRIC participants had CAC data and were included in the present analysis.

The CRIC study was approved by the institutional review boards from each of the participating clinical centers and the scientific and data coordinating center. All participants provided written informed consent. The present study also conformed to the Health Insurance Portability and Accountability Act guidelines.

All CRIC study data were collected by trained study staff during the baseline and annual clinical visits. All data collection procedures and equipment were standardized across study sites. A baseline medical history questionnaire was administered to obtain information on demographic characteristics, lifestyle risk factors, history of CVD, and the use of medications. Cigarette smokers were defined as participants who had smoked >100 cigarettes in their lifetime. Alcohol drinkers were defined as participants who had a drink of any kind of alcoholic beverage in the previous 12 months. Body weight and height were measured, and the body mass index was calculated as an index for obesity. The waist circumference was measured at the uppermost lateral border of the iliac crest using a Gulick II tape measure. Three seated blood pressure measurements were obtained by trained and certified staff after ≥5 minutes of quiet rest. These measurements were performed according to a standard protocol using an aneroid sphygmomanometer, and the average of 3 measurements was used for analysis.[16] Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the current use of antihypertensive medications.

Glucose, cholesterol, triglycerides, glycated hemoglobin, phosphate, calcium, total parathyroid hormone, uric acid, hemoglobin, and alkaline phosphatase were measured using standard laboratory methods. High-sensitive C-reactive protein, interleukin-6, tumor necrosis factor-α, homocysteine, and cystatin C were measured using the particle enhanced immunonephelometry method. Fibrinogen was measured using the immunochemical reaction method. Urinary albumin was measured by radioimmunoassay. Diabetes was defined as a fasting glucose of ≥126 mg/dl, random glucose of ≥200 mg/dl, and/or the use of insulin or other antidiabetic medication. Estimated glomerular filtration rate was calculated using the 4-variable Modification of Diet in Renal Disease equation after calibrating the serum creatinine measurements to the Cleveland Clinic Foundation reference values.[17] Homeostasis model of assessment (HOMA) was calculated to evaluate insulin resistance using the following formula: (fasting serum insulin [μU/ml] × fasting plasma glucose [mmol/L])/22.5.[18] All laboratory measurements were performed in a centralized laboratory at the University of Pennsylvania.

As a part of the CRIC protocol, a subcohort of participants underwent measurement of CAC with either electron beam CT or multidetector CT at the year 1 visit. Trained and certified technologists scanned all participants twice over phantoms of known physical calcium concentrations. A cardiologist read all computed tomographic scans at a central reading center (Los Angeles Biomedical Research Institute, Harbor UCLA Medical Center, Torrance, California). The total Agatston score, which is a pseudocontinuous variable derived from the plaque densities and their areas in all coronary arteries, was computed.[19] We used the average Agatston score from the 2 scans in all analyses. From the distribution of the Agatston score in our study participants, we divided the CRIC participants into no (0), moderate (>0–100), or high (>100) CAC.

The baseline characteristics of the participants were summarized as the mean ± SD for continuous variables and percentages for categorical variables by CAC status. Statistical significance was tested using analysis of variance for continuous variables and chi-square tests for categorical variables. Logarithmic transformation was performed for severely skewed variables to stabilize variances and normalize distributions.

The adjusted odds ratios (ORs) of moderate and high CAC associated with the risk factors were estimated using a multinomial logistic regression model. For the multivariate analysis of traditional risk factors, the backward elimination method was used, and only covariates that were significant ($p < 0.05$) were retained in the final model. For the multivariate analysis of novel risk factors, age, gender, race, and significant covariates (cigarette smoking, history of hypertension, diabetes, and the use of lipid-lowering drugs, body mass index, and waist circumference) from the final traditional risk factor model, and previous CVD, were adjusted for each novel risk factor in separate models. Furthermore, the serum cystatin C level was adjusted in the multivariate model to control for the confounding effect of kidney function. ORs and 95% confidence intervals (CIs) of moderate and high CAC associated with categorical variables or 1 SD increase in continuous variables are presented. In a sensitivity analysis, the 2-part model, in which binary CAC (0 vs >0) was modeled using Poisson regression with robust variance estimation and log (CAC + 1) was modeled using linear regression among those with CAC >0, was used.[20] All analyses were conducted using SAS, version 9.1 (SAS Institute, Cary, North Carolina). All p values were 2-sided, and statistical significance was defined as $p < 0.05$.

Results

Compared to those without CAC, the participants with moderate or high CAC were more likely to be older, male, and current or former smokers and to have a history of

Table 1
Baseline characteristics of study participants stratified coronary artery calcium (CAC) score

Variable	Total Agatston Score			p Value
	0 (n = 689)	>0–100 (n = 578)	>100 (n = 751)	
Age (years)	51.9 ± 12.3	59.1 ± 10.2	63.9 ± 8.1	<0.0001
Men	41.9%	53.3%	63.6%	<0.0001
Race				0.10
White	47.2%	45.2%	51.3%	
Black	37.4%	36.3%	32.1%	
Other	15.4%	18.5%	16.6%	
High school graduation	83.7%	78.7%	80.4%	0.06
Physical activity (MET/wk)	6.2 ± 22.0	5.0 ± 19.2	3.6 ± 16.3	0.04
Cigarette smoking				<0.0001
Current	9.0%	10.4%	10.5%	
Former	31.8%	37.7%	49.1%	
Never	59.2%	51.9%	40.3%	
Alcohol consumption	65.0%	62.2%	59.2%	0.08
Previous cardiovascular disease	11.8%	21.6%	40.9%	<0.0001
Previous peripheral arterial disease	2.3%	2.2%	10.1%	<0.0001
Previous congestive heart failure	3.3%	5.5%	10.7%	<0.0001
Previous stroke	4.5%	9.3%	13.4%	<0.0001
Previous myocardial infarction	4.5%	8.7%	25.3%	<0.0001
Hypertension	76.4%	89.1%	94.3%	<0.0001
Diabetes mellitus	29.6%	46.2%	62.5%	<0.0001
Use of lipid-lowering drugs	43.4%	60.2%	77.0%	<0.0001
Systolic blood pressure (mm Hg)	122.4 ± 20.1	127.0 ± 21.4	129.4 ± 21.2	<0.0001
Body mass index (kg/m^2)	30.4 ± 6.9	31.5 ± 6.7	31.5 ± 6.5	0.002
Waist circumference (cm)	99.9 ± 16.1	104.3 ± 15.7	106.7 ± 15.1	<0.0001
High-density lipoprotein cholesterol (mg/dl)	51.9 ± 17.3	47.9 ± 15.0	47.0 ± 14.5	<0.0001
Low-density lipoprotein cholesterol (mg/dl)	109.8 ± 36.5	104.6 ± 34.4	95.8 ± 32.2	<0.0001
Calcium (mg/dl)	9.3 ± 0.5	9.3 ± 0.5	9.3 ± 0.5	0.96
Phosphate (mg/dl)	3.6 ± 0.7	3.7 ± 0.7	3.8 ± 0.7	0.002
Alkaline phosphatase (U/L)	89.2 ± 32.2	93.1 ± 33.7	92.9 ± 37.5	0.07
Total parathyroid hormone (pg/ml)	66.9 ± 64.5	67.0 ± 57.9	72.1 ± 81.8	0.28
Log (total parathyroid hormone) (pg/ml)	4.0 ± 0.7	4.0 ± 0.7	4.0 ± 0.7	0.3439
HOMA-insulin resistance*	5.0 ± 6.4	6.1 ± 7.4	6.8 ± 7.7	<0.0001
Log (HOMA-insulin resistance)	1.5 ± 0.6	1.7 ± 0.6	1.8 ± 0.7	<0.0001
Hemoglobin A1c (%)	6.2 ± 1.5	6.5 ± 1.5	6.8 ± 1.5	<0.0001
Uric acid (mg/dl)	6.9 ± 1.9	7.2 ± 1.8	7.4 ± 1.9	<0.0001
Homocysteine (μmol/L)	13.2 ± 5.3	14.3 ± 6.5	15.5 ± 6.0	<0.0001
Fibrinogen (mg/dl)	3.9 ± 1.1	4.1 ± 1.2	4.2 ± 1.1	<0.0001
High-sensitive C-reactive protein (mg/L)	4.7 ± 7.8	5.0 ± 9.3	4.6 ± 6.9	0.57
Log (high sensitive C-reactive protein) (mg/L)	1.3 ± 0.8	1.3 ± 0.9	1.3 ± 0.8	0.78
Interleukin-6 (mg/dl)	2.9 ± 12.5	4.8 ± 21.8	4.0 ± 15.7	0.13
Log (interleukin-6) (mg/dl)	1.0 ± 0.6	1.1 ± 0.7	1.2 ± 0.6	<0.0001
Tumor necrosis factor-α (mg/dl)	3.5 ± 15.1	3.2 ± 6.5	2.8 ± 2.4	0.40
Log (tumor necrosis factor-α) (mg/dl)	1.2 ± 0.6	1.2 ± 0.5	1.2 ± 0.4	0.06
Estimated glomerular filtration rate (ml/min/1.73 m^2)	44.4 ± 16.5	42.5 ± 14.7	39.2 ± 13.5	<0.0001
Cystatin C (mg/L)	1.4 ± 0.5	1.5 ± 0.5	1.6 ± 0.5	<0.0001
24-Hour urine albumin (g/24 hours)	0.6 ± 1.4	0.8 ± 2.0	0.7 ± 1.8	0.28
Log (24-hour urine albumin) (g/24 hours)	0.3 ± 0.5	0.3 ± 0.6	0.3 ± 0.5	0.61

Data are presented as mean ± standard deviation or percentages.
* HOMA–insulin resistance = (fasting serum insulin [μU/ml] × fasting plasma glucose [mmol/L])/22.

clinical CVD, hypertension, diabetes, or the use of lipid-lowering medications, and were less likely to be physically active (Table 1). On average, participants with CAC had greater systolic blood pressure levels, body mass index, and waist circumference and lower levels of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and estimated glomerular filtration rate. In addition, participants with CAC had greater than average levels of serum phosphate, HOMA-insulin resistance, glycated hemoglobin, uric acid, homocysteine, fibrinogen, log (interleukin-6), and cystatin C.

In the age-, gender-, race-adjusted model, current and former cigarette smoking, a history of hypertension, diabetes, and the use of lipid-lowering medication, systolic blood pressure, body mass index, and waist circumference were positively associated with the odds of CAC, and high-density lipoprotein cholesterol, low-density lipoprotein cho-

Table 2
Multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs)* of moderate (>0–100) and severe (>100) coronary artery calcium (CAC) associated with traditional risk factors

Variable	Age-, Gender-, Race-Adjusted OR (95% CI)			Multivariate-Adjusted OR (95% CI)†		
	Moderate (>0–100)	High (>100)	p Value for Trend	Moderate (>0–100)	High (>100)	p Value for Trend
High school graduation	0.86 (0.62–1.17)	0.94 (0.68–1.30)	0.61			
Physical activity (19.2 MET/wk)	1.00 (0.89–1.11)	0.95 (0.84–1.09)	0.74			
Smoking			0.006			0.004
Current	1.37 (0.91–2.06)	1.98 (1.30–3.01)		1.51 (0.97–2.34)	2.31 (1.45–3.70)	
Former	0.98 (0.76–1.27)	1.34 (1.04–1.74)		0.97 (0.74–1.27)	1.31 (0.98–1.74)	
Alcohol consumption	0.95 (0.74–1.22)	0.77 (0.60–1.00)	0.11			
Hypertension	2.11 (1.50–2.97)	4.06 (2.70–6.11)	<0.0001	1.77 (1.22–2.57)	2.24 (1.43–3.51)	0.0004
Diabetes mellitus	2.10 (1.64–2.68)	4.60 (3.55–5.95)	<0.0001	1.65 (1.26–2.16)	3.25 (2.44–4.34)	<0.0001
Use of lipid-lowering drugs	1.66 (1.31–2.11)	3.37 (2.60–4.35)	<0.0001	1.37 (1.06–1.78)	2.56 (1.92–3.40)	<0.0001
Systolic blood pressure (21.1 mm Hg)	1.15 (1.02–1.31)	1.30 (1.15–1.48)	0.0002			
Body mass index (6.7 kg/m^2)	1.21 (1.07–1.36)	1.32 (1.17–1.49)	<0.0001	0.89 (0.69–1.14)	0.69 (0.53–0.90)	0.02
Waist circumference (15.9 cm)	1.26 (1.11–1.42)	1.49 (1.31–1.68)	<0.0001	1.29 (1.00–1.66)	1.66 (1.27–2.17)	0.001
High-density lipoprotein cholesterol (15.8 mg/dl)	0.80 (0.70–0.91)	0.79 (0.69–0.90)	0.0002			
Low-density lipoprotein cholesterol (34.9 mg/dl)	0.93 (0.83–1.04)	0.75 (0.66–0.85)	<0.0001			
Estimated glomerular filtration rate (15.1 ml/min/1.73 m^2)	0.90 (0.80–1.01)	0.70 (0.62–0.79)	<0.0001			

* OR were calculated using multinomial logistic regression models.
† Variables with p <0.05 were kept in final model using backward selection.

lesterol, and estimated glomerular filtration rate had an inverse association (Table 2). In the final model selected by backward elimination, cigarette smoking, history of hypertension, diabetes, and lipid-lowering medications, and waist circumference were positively and significantly associated with the odds of CAC, and body mass index was inversely and significantly associated with the odds of CAC.

The age-, gender-, race-adjusted and multivariate-adjusted ORs of CAC associated with novel risk factors are listed in Table 3. After adjusting for age, gender, and race, greater levels of serum phosphate, log (HOMA-insulin resistance), glycated hemoglobin, uric acid, homocysteine, fibrinogen, log (interleukin-6), log (tumor necrosis factor-α), cystatin C, and 24-hour urinary excretion of albumin were all significantly associated with greater odds of CAC. In addition, serum alkaline phosphatase was significantly associated with greater odds of high CAC. After adjusting for multiple traditional risk factors, serum phosphate and cystatin C remained significantly associated with overall odds of CAC. In addition, log (HOMA-insulin resistance), glycated hemoglobin, homocysteine, and fibrinogen were significantly associated with greater odds of high CAC. In the multivariate model, including cystatin C, greater levels of calcium, phosphate, log (HOMA-insulin resistance), and glycated hemoglobin were positively, and log (parathyroid hormone) was inversely, associated with greater odds of high CAC.

In the sensitivity analysis using the 2-part model, the presence of CAC (total Agatston score >0) was positively and significantly associated with 1 SD greater levels of phosphate (OR 1.05, 95% CI 1.02 to 1.08; p = 0.001), log (HOMA-insulin resistance) (OR 1.05, 95% CI 1.01 to 1.08, p = 0.004), glycated hemoglobin (OR 1.05, 95% CI 1.02 to 1.09; p = 0.001), fibrinogen (OR 1.03, 95% CI 1.00 to 1.06; p = 0.03), and cystatin C (OR 1.04; 95% CI 1.01 to 1.07; p = 0.01) after adjusting for multiple covariables in Poisson regression. Log (CAC + 1) was positively and significantly associated with 1 SD greater levels of phosphate (β = 0.19; 95% CI 0.07 to 0.30; p = 0.001), homocysteine (β = 0.13; 95% CI 0.02 to 0.24; p = 0.02), and cystatin C (β = 0.21; 95% CI 0.11 to 0.30; p <0.0001) among participants with CAC >0 after adjustment for multiple covariables in linear regression.

Discussion

The present study has contributed to our understanding of the etiology of CAC among patients CKD in several ways. First, the findings from the present study indicate that, just as in the general population, cigarette smoking, hypertension, diabetes mellitus, dyslipidemia, and obesity are related to an increased risk of CAC among patients with CKD. Second, the results from the present study have shown that calcium and phosphate metabolism might play an important etiologic role in CAC among patients with CKD. Furthermore, the present study has revealed that elevated levels of insulin resistance and glycated hemoglobin are associated with an increased risk of CAC. Finally, the present study found that cystatin C, a measure of kidney function, is independently associated with elevated CAC.

Our study findings are worthwhile because they are based on data from a large sample of patients with CKD. The study outcome (CAC) and numerous traditional and novel CVD risk factors were carefully measured with rigorous quality control. Therefore, our study should provide an accurate estimate of the association between risk factors and CAC. A major limitation of the present analysis was its cross-sectional nature; therefore, the temporal relationship between risk factors and CAC could not be established. The

Table 3
Multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs)* of moderate (>0–100) and severe (>100) coronary artery calcium (CAC) associated with novel risk factors

Variable	Age-, Gender-, Race-Adjusted			Multivariate-Adjusted†			Multivariate-Adjusted‡		
	Moderate (>0–100)	High (>100)	p Value for Trend	Moderate (>0–100)	High (>100)	p Value for Trend	Moderate (>0–100)	High (>100)	p value for trends
Calcium (0.54 mg/dl)	0.99 (0.87–1.11)	0.97 (0.86–1.10)	0.89	1.05 (0.92–1.19)	1.13 (0.98–1.29)	0.23	1.07 (0.94–1.22)	1.20 (1.04–1.38)	0.04
Phosphate (0.67 mg/dl)	1.26 (1.11–1.43)	1.66 (1.45–1.90)	<0.0001	1.11 (0.97–1.27)	1.30 (1.13–1.50)	0.001	1.09 (0.94–1.25)	1.21 (1.04–1.41)	0.04
Alkaline phosphatase (34.7 U/L)	1.11 (0.98–1.25)	1.15 (1.02–1.30)	0.07	1.01 (0.89–1.15)	1.01 (0.88–1.15)	0.99	0.99 (0.86–1.13)	0.94 (0.82–1.08)	0.67
Log (total parathyroid hormone, 0.68 pg/ml)	1.03 (0.92–1.17)	1.11 (0.98–1.26)	0.24	0.96 (0.85–1.09)	1.00 (0.87–1.14)	0.78	0.90 (0.77–1.05)	0.83 (0.71–0.97)	0.07
Log (homeostasis model of assessment–insulin resistance, 0.65)	1.37 (1.20–1.56)	1.69 (1.48–1.93)	<0.0001	1.13 (0.96–1.31)	1.20 (1.03–1.41)	0.08	1.13 (0.96–1.31)	1.21 (1.03–1.43)	0.06
Hemoglobin A1c (1.54%)	1.36 (1.20–1.55)	1.82 (1.59–2.08)	<0.0001	1.10 (0.93–1.29)	1.22 (1.03–1.44)	0.07	1.10 (0.93–1.30)	1.23 (1.04–1.45)	0.05
Uric acid (1.88 mg/dl)	1.09 (0.96–1.23)	1.19 (1.05–1.35)	0.02	0.98 (0.86–1.12)	1.03 (0.89–1.18)	0.80	0.95 (0.82–1.09)	0.94 (0.81–1.09)	0.66
Homocysteine (5.96 μmol/L)	1.14 (0.99–1.32)	1.32 (1.14–1.52)	0.0006	1.03 (0.90–1.19)	1.14 (1.00–1.31)	0.15	1.01 (0.87–1.16)	1.03 (0.89–1.20)	0.90
Fibrinogen (1.14 mg/dl)	1.25 (1.10–1.41)	1.43 (1.26–1.63)	<0.0001	1.11 (0.97–1.26)	1.17 (1.01–1.34)	0.09	1.09 (0.95–1.25)	1.09 (0.94–1.26)	0.41
Log (high-sensitivity C-reactive protein, 0.83 mg/L)	1.05 (0.93–1.18)	1.06 (0.93–1.19)	0.63	1.01 (0.89–1.15)	1.01 (0.88–1.17)	0.98	1.00 (0.88–1.14)	0.99 (0.86,1.14)	0.97
Log (interleukin-6, 0.63 mg/dl)	1.20 (1.06–1.37)	1.29 (1.13–1.48)	0.0006	1.11 (0.97–1.26)	1.12 (0.97–1.29)	0.23	1.09 (0.95–1.25)	1.06 (0.91–1.22)	0.45
Log (tumor necrosis factor-α, 0.51 mg/dl)	1.14 (1.00–1.28)	1.17 (1.03–1.33)	0.04	1.07 (0.94–1.21)	1.04 (0.91–1.19)	0.59	1.04 (0.91–1.18)	0.94 (0.81–1.08)	0.30
Cystatin C (0.53 mg/L)	1.24 (1.10–1.41)	1.62 (1.43–1.84)	<0.0001	1.10 (0.97–1.26)	1.31 (1.14–1.50)	0.0005			
24-Hour urine albumin (1.72 g/24 hours)	1.26 (1.10–1.45)	1.35 (1.17–1.56)	0.0002	1.12 (0.98–1.28)	1.08 (0.93–1.26)	0.27	1.10 (0.96–1.27)	1.01 (0.86–1.18)	0.25

* ORs were calculated using multinomial logistic regression models.
† Adjusted for age, gender, race, cigarette smoking, previous clinical CVD, hypertension, and diabetes, use of lipid-lowering drugs, body mass index, and waist circumference.
‡ Adjusted for age, gender, race, cigarette smoking, previous CVD, hypertension, and diabetes, use of lipid-lowering drugs, body mass index, waist circumference, and cystatin C.

use of a subclinical measurement (CAC) in our study, however, should have minimized the cross-sectional bias owing to the change in risk factors because of the diagnosis of clinical disease. Furthermore, it is unlikely that CAC caused the elevated traditional CVD risk factors, serum calcium and phosphate levels, insulin resistance, or serum cystatin C levels, in patients with CKD and CAC.

Patients with advanced CKD usually develop hyperphosphatemia owing to impaired renal phosphate excretion.[14] Elevated serum levels of calcium, phosphate, and calcium phosphate product were associated with greater CAC in patients with end-stage renal disease receiving hemodialysis[7] and patients with predialysis CKD.[21,22] Garland et al[21] reported that the serum calcium level correlated with the CAC scores in 119 patients with CKD. Adeney et al[22] reported that the serum phosphate concentration was associated with a 21% greater prevalence of CAC in 439 patients with CKD from the Multi-Ethnic Study of Atherosclerosis. Our study, with a large sample size, documented the positive and independent associations of serum calcium and phosphate levels with CAC. In addition, we found an inverse and independent association between serum total parathyroid hormone, an important hormone regulating calcium-phosphate metabolism, and CAC. Tsuchihashi et al[23] reported that hypoparathyroidism was associated with a greater serum calcium level and coronary artery disease among 48 patients with end-stage renal disease. The findings from our study, and others, have provided strong evidence that abnormal calcium-phosphate metabolism is probably the most important pathogenetic factor in vascular calcification among patients with CKD.[13,22]

Insulin resistance and hemoglobin A1c are associated with greater CAC in the general population and in patients with diabetes.[24,25] In a small clinical study, Kobayashi et al[26] reported that HOMA-insulin resistance was greater in 17 patients with CKD with total Agatston scores >600 compared to those with a score <600. In that large study of patients with CKD, we found that HOMA-insulin resistance and hemoglobin A1c were positively and independently associated with greater CAC. These findings support the notion that insulin resistance and hyperglycemia are important risk factors for coronary artery disease in patients with CKD.

Recent investigations have suggested that cystatin C might be a better filtration marker than creatinine, especially at greater glomerular filtration rates.[27] Serum cystatin C has been associated with an increased risk of CVD.[28] Maahs et al[29] reported that cystatin C was modestly predictive of CAC progression in 509 adults with type 1 diabetes. However, Ix et al[30] reported that cystatin C was not independently associated with CAC in 6,749 participants in the Multi-Ethnic Study of Atherosclerosis. We identified a strong, independent, and dose–response association between cystatin C and CAC in this CKD patient population. These findings suggest that kidney function, as measured by cystatin C, is an independent risk factor for CAC.

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