Association between Chronic Kidney Disease and Coronary Artery Calcification: The Dallas Heart Study

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The hypothesis that chronic kidney disease (CKD) is associated with increased coronary artery calcification (CAC) was tested using data from the Dallas Heart Study, a representative sample of Dallas County residents aged 30 to 65 yr. CKD was defined as presence of microalbuminuria and GFR >60 ml/min per 1.73 m² (stage 1 to 2), or GFR <60 ml/min per 1.73 m² (stage 3 to 5), excluding end-stage kidney disease. Logistic regression was used to examine the association between stages of CKD and CAC scores >10, >100, and >400 versus scores ≤10 compared with no CKD while adjusting for covariates. Analyses were repeated after stratifying by presence of diabetes. The mean age was 43.9 yr, and hypertension and diabetes were noted in 31.0 and 9.8%, respectively. No association was noted between stage 1 to 2 CKD and increased CAC scores. Compared with no CKD, stage 3 to 5 CKD was associated with CAC scores >100 (odds ratio, 2.85; 95% confidence interval, 0.92 to 8.80) and >400 (odds ratio, 8.35; 95% confidence interval, 1.94 to 35.95) in the total population after adjustment for covariates, but these associations were substantially reduced after exclusion of participants with diabetes. Participants with diabetes and stage 3 to 5 CKD had a ninefold increased odds of CAC scores >10 versus scores ≤10 compared with participants with diabetes and without CKD, whereas no association was noted between stage 3 to 5 CKD and CAC scores >10 in the nondiabetic population. In conclusion, stage 3 to 5 CKD is associated with increased CAC scores, but this association may be substantially stronger among adults with diabetes. These findings need to be confirmed in study populations that include adults >65 yr of age and a larger number of CKD cases.


Approximately 20 million adults in the United States have early chronic kidney disease (CKD), defined as the presence of increased urine albumin excretion and/or a GFR <60 ml/min per 1.73 m² body surface area (BSA). CKD increases the risk for end-stage kidney disease and future need for renal replacement therapy such as dialysis or kidney transplantation. However, patients with CKD are more likely to succumb to cardiovascular disease (CVD) before ever reaching end-stage kidney disease. For example, 50% of the Hypertension Detection and Follow-Up Program participants with a baseline serum creatinine ≥2.5 mg/dl died during the 8-yr study follow-up, and a baseline serum creatinine ≥1.7 mg/dl was associated with a twofold increased mortality risk after adjustment for multiple cardiovascular risk factors (1).

Increased coronary artery calcification (CAC), measured by electron-beam computed tomography, confirms the presence of atherosclerotic plaque (2) and has >90% sensitivity for detecting atherosclerotic lesions with ≥50% stenosis (3). Although the amount of CAC correlates with overall atherosclerotic burden, the utility of measuring CAC, even in high-risk groups, remains uncertain (2). Extensive CAC has been noted in patients who have end-stage kidney disease and receive dialysis (4–6) with some investigators reporting 10-fold higher calcium scores than the 95th age and gender percentiles for young adults without kidney disease (6). However, data on subclinical coronary artery disease in adults with CKD are currently limited. We tested the hypothesis that CKD is associated with increased CAC scores by examining the association between CKD and CAC in a representative sample of Dallas County residents using data from the Dallas Heart Study. Because diabetes is strongly linked with both kidney disease and cardiovascular risk, we examined this association after stratifying the study population by presence of diabetes.

Materials and Methods

The Dallas Heart Study was a multistage probability sample whose target population was the estimated 1.42 million civilian, noninstitutionalized English- or Spanish-speaking adults who maintained a primary residence in Dallas County, TX, between July 2000 and January 2002. This included an estimated 124,156 black men, 154,761 black women, 601,867 nonblack men, and 551,946 nonblack women. The study was designed so that inferences could be extrapolated to the Dallas County population. All participants were between the ages of 30 and 65 yr, and the upper age limit was set at 65 because excess cardiovascular mortality among blacks occurs mainly before the age of 65. The sample allocation was heavily weighted to census tracts with large concentrations of blacks to ensure adequate representation. Sampling and recruitment procedures have been described previously in detail (7). The University of Texas Southwestern and the Research Triangle Institute developed the sampling frame and oversaw all field
staff operations. Institutional review boards at both institutions approved the study.

The study consisted of a household survey (visit 1), an in-home blood and urine specimen collection (visit 2), and noninvasive cardiac imaging during a clinic visit (visit 3). Overall, 3556 Dallas County residents completed the household survey during visit 1, 3398 (96%) provided blood and urine specimens during visit 2, and 2971 (84%) returned for noninvasive cardiac imaging during a clinic visit (visit 3). All three visits were completed within an 11-mo period. End-stage kidney disease that required dialysis was reported by 10 patients, and these study participants were excluded from all analyses. This study was limited to the 2961 study participants who did not have end-stage kidney disease and who completed visit 3. We excluded 110 (3.7%) participants because of missing data on urine albumin excretion (n = 109) and GFR (n = 1). Among the 2851 study participants with complete information on urine albumin excretion and estimated GFR, 191 (6.5%) were excluded because of missing data on CAC.

Measures of Kidney Function

An overnight first void urine sample and fasting venous blood was collected during the home visit. Urine albumin and creatinine were measured in the first morning void urine samples, and the albumin/creatinine ratio (ACR) was calculated in mg/g for each participant. A Beckman Coulter analyzer (Beckman Coulter, Fullerton, CA) was used for all biochemical measurements. Urine albumin was quantified by a turbidimetric method, and the coefficient of variation ranged from 2.6 to 4.4%. Both serum and urine creatinine concentrations were determined by the alkaline picrate method. The coefficient of variation for urine creatinine ranged from 2.8 to 3.7%, whereas the coefficient of variation for serum creatinine ranged from 1.5 to 5.0%. GFR (ml/min per 1.73 m² BSA) was estimated with the modified Modification of Diet in Renal Disease Study formula using the serum creatinine measurement: GFR = 186 × (serum creatinine⁻¹·134) × (age⁻⁰·²⁰³) × (0.742 if female) × (1.21 if black) (8).

CKD was defined as an ACR (mg/g) ≥17 in men and ≥25 in women (9) and a GFR ≥60 ml/min per 1.73 m² BSA consistent with the National Kidney Foundation Guidelines CKD stage 1 to 2 (10). Stage 3 to 5 CKD was defined as an estimated GFR <60 ml/min per 1.73 m² BSA among study participants who did not receive dialysis. This level of GFR was chosen by the National Kidney Foundation because it represents a 50% loss of the adult normal level of kidney function (11).

CAC

Electron beam computed tomography was performed on an Imatron C-150 coronary scanner using a standard protocol (7). The method of Arad et al. (12) was used to determine the calcium score in each of the three major vessels and total coronary calcium score. Forty contiguous 3-mm slices were obtained during nonforceful held exhalations, and an overlap protocol was used to ensure that small gaps between the 3-mm slices were examined.

Covariates

All Dallas Heart Study participants completed a computerized questionnaire during a home visit. The questionnaire consisted of 27 modules that were administered in either Spanish or English and queried medical history, use of medications, and use of tobacco. Race (white, black, or other) and presence of Hispanic ethnicity were self-reported. BP was measured after the 60-min interview with the participant in a seated position using an automatic oscillometric device (Welch Allyn) and appropriately sized cuffs. Five consecutive BP readings were recorded at 1-min intervals, and the average of the third, fourth, and fifth BP measurements was used for this analysis. Diagnosis of hypertension was defined as self-reported diagnosis or treatment for hypertension, a systolic BP (SBP) ≥140 mmHg, or a diastolic BP ≥90 mmHg. Presence of diabetes was based on self-reported physician diagnosis of diabetes (other than during pregnancy), use of insulin or an oral hypoglycemic agent, or a fasting glucose value of ≥126 mg/dl. Use of prescribed cholesterol-lowering medication and current smoking status were based on self-report. Height was measured to the nearest 0.1 cm with the participant in stocking feet, and weight was measured to the nearest pound with the participant in light clothing using a balanced scale and converted to kilograms. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Statistical Analyses

The Dallas Heart Study data are weighted to account for the probability of selection and to adjust for nonresponse. All statistical analyses were completed with SAS-callable SUDAAN (Research Triangle Institute) to incorporate sample weights and adjust for the strata of the complex sample design. The inclusion of sample weights in the statistical analysis incorporates the differential probability of selection for each sample person and allows the calculation of prevalence estimates for the entire Dallas County population. Thus, the actual percentage of study participants in a particular sampled group may not equal the projected Dallas County population prevalence when using the sample weights. Categorical variables were compared using the Wald χ² test, and mean values of continuous variables were compared between groups using the unpaired t test.

 Logistic regression was used to calculate the odds of having mild (CAC score >10), moderate (CAC score >100), or severe (CAC score >400) CAC versus having a CAC score ≤10 by presence of stage 1 to 2 and stage 3 to 5 CKD compared with no CKD. Thus, separate regression models were created to calculate the odds of mild, moderate, and severe CAC scores among participants with stage 1 to 2 CKD compared with participants with no CKD and among participants with stage 3 to 5 CKD compared with participants with no CKD. All regression models were performed using the sample weights and adjusted for the following covariates: age, gender, race, SBP, BMI, serum cholesterol level, current smoking, presence of diabetes, and use of antihypertensive and lipid-lowering medication. Age, BMI, SBP, and serum cholesterol levels were fitted as continuous variables. Race was categorized as white, black or other (American Indian, Alaska Native, Asian, Pacific Islander, East Indian, or other) with white race as the reference group. Current smoking, presence of diabetes, and use of antihypertensive medication and lipid-lowering medication were categorized as yes/no. Because diabetes is strongly associated with both CKD and CAC, all logistic regression analyses were repeated after stratifying the Dallas Heart Study participants by presence of diabetes.

Results

The characteristics of the weighted study samples are shown in Table 1. The weighted size of the 2660 study participants who completed visit 3 was approximately 884,000. In the weighted sample, race was reported as white in 67.8%, black in 19.5%, and other in 12.7%; Hispanic ethnicity was reported by 25.9%. The mean age of the weighted sample was 43.9 yr, ranging from 30 to 65 yr, and 49.5% of the participants were male. One third were obese, and hypertension and diabetes were noted in 31.0 and 9.8%, respectively. Mean serum creatinine was 0.9 mg/dl, ranging from 0.3 to 9.5 mg/dl, and mean ACR was 10.0 mg/g, ranging from 0 to 2829 mg/g.
The weighted prevalence of CKD (stage 1 to 5) among the 2660 Dallas Heart Study participants who completed all three examinations was 5.9% (95% confidence interval [CI], 4.7 to 67.1%; sample size \( n = 211 \)). Stage 1 to 2 CKD was noted in 4.9% (95% CI, 3.7 to 6.1%; sample size \( n = 170 \)), and stage 3 to 5 CKD was noted in 1.0% (95% CI, 0.6 to 1.5%; sample size \( n = 41 \)). Compared with study participants without CKD, study participants with CKD (stage 1 to 5) were more likely to have hypertension (50.1 versus 29.7%; \( P = 0.0006 \)), diabetes (27.3 versus 8.7%; \( P = 0.002 \)), and higher SBP and diastolic BP (Table 2). Black race was also more frequent among study participants with CKD compared with participants without CKD (35.1 versus 18.5%; \( P = 0.002 \)). There was, however, no significant difference in age, smoking status, or serum lipid levels between participants with and without CKD.

CAC scores ranged from 0 to 7601.2, and the majority of CAC scores in the weighted sample were \( \leq 10 \) (82.1%) and only 1.9% had CAC scores \( >400 \) (95% CI, 1.3 to 2.5%). The weighted prevalence of increased CAC scores in the total study population and in the nondiabetic and diabetic population by presence of CKD are shown in Figure 1. Among the total Dallas Heart Study population without CKD, CAC scores \( 0 \) to 10, 11 to 100, 101 to 400, and \( >400 \) were noted in 82.8, 10.1, 5.4, and 1.7%, respectively. The prevalence of CAC scores \( >400 \) was twofold higher among participants with stage 1 to 2 CKD (3.5%) and more than ninefold higher among participants with stage 3 to 5 CKD (16.5%) compared with participants without CKD (1.7%). In the nondiabetic population, the frequency of CAC scores \( >400 \) was noted in 1.4% without CKD, 1.1% with stage 1 to 2 CKD, and 3.5% with stage 3 to 5 CKD. Among participants with diabetes, CAC scores \( >400 \) were noted in 4.7% in those without CKD, 9.5% with stage 1 to 2 CKD, and 55.7% with stage 3 to 5 CKD.

Table 3 shows the association between stages of CKD (1 to 2 and 3 to 5) and increased CAC scores, compared with...
participants without CKD, in the total and nondiabetic Dallas Heart Study population (data on participants with diabetes not shown). In the total population, we noted no significant association between stage 1 to 2 CKD and increased CAC scores compared with participants without CKD in the age-, gender-, and race-adjusted or multivariate-adjusted models among participants without CKD in the age-, gender-, and race-adjusted or multivariate-adjusted models.

Similar results were noted after stratification by presence of diabetes. No significant association was noted between stage 1 to 2 CKD and increased CAC scores compared with participants without CKD in the age-, gender-, and race-adjusted or multivariate-adjusted models among participants with and without diabetes.

In contrast, stage 3 to 5 CKD was significantly associated with CAC scores >10 versus ≤10 (OR, 2.75; 95% CI, 1.07 to 7.10), >100 versus ≤10 (OR, 5.27; 95% CI, 1.23 to 22.48), and >400 versus ≤10 (OR, 10.69; 95% CI, 1.16 to 88.15) compared with no CKD after adjustment for age, gender, and race. In the multivariate-adjusted model, stage 3 to 5 CKD remained significantly associated with CAC scores >400 versus ≤10 (OR, 8.35; 95% CI, 1.94 to 35.95) compared with no CKD but not with CAC scores >10 or >100. After participants with diabetes were excluded, the multivariate-adjusted association between stage 3 to 5 CKD and CAC scores >400 versus ≤10 compared with no CKD was reduced to 2.14, and the 95% CI included 1. The number of participants with diabetes and stage 3 to 5 CKD and CAC scores >100 or >400 was too small to calculate stable adjusted estimates. However, stage 3 to 5 CKD was associated with a ninefold increased odds of CAC scores >10 versus ≤10 compared with those without CKD (95% CI, 1.16 to 70.05) after adjustment for all covariates in the diabetic study population.

In contrast, no association was noted between stage 3 to 5 CKD and CAC scores >10 in the nondiabetic study population (OR, 1.18; 95% CI, 0.47 to 3.00).

**Discussion**

In a representative sample of adults who lived in Dallas County, we noted no independent association between mild CKD (stage 1 to 2), defined as the presence of increased urine albumin excretion and a GFR ≥60 ml/min, and increased CAC scores. However, more advanced CKD (stage 3 to 5), defined as a GFR <60 ml/min, was associated with an eightfold increased odds of CAC scores >400 versus scores ≤10 compared with no CKD after adjustment for all covariates. Extensive CAC was demonstrated previously in patients with end-stage kidney disease (4–6), but to our knowledge, this is the first study to examine the association between CKD and CAC in a general population.

The association between stage 3 to 5 CKD and increased CAC scores differed substantially by presence of diabetes. The strong association between decreased GFR and increased CAC scores in adults with diabetes may simply reflect end-organ damage after years of exposure to multiple metabolic derangements. It is also possible that decreased GFR leads to changes in levels of calcium-regulating glycoproteins and/or cytokines that interact with elevated serum glucose levels and accelerate the development and/or progression of atherosclerosis in patients with diabetes. Calcium actively precipitates in coronary atherosclerotic lesions in a mechanism mediated by glycoproteins involved in bone formation (2). Decreased serum levels of extracellular calcium-regulatory proteins such as fetuin-A (α2-Heremans Schmid glycoprotein) and Matrix GLA protein, have been implicated as risk factors for excess vascular calcification in dialysis patients (13,14) and may be operative in patients who have diabetes and decreased GFR.

Multiple studies have demonstrated an increased risk for cardiovascular events and mortality in adults with increased urine albumin excretion. For example, the presence of albuminuria (spot urine ACR approximately 17 mg/g) for both men and women) in the Heart Outcomes and Prevention and Evaluation Study increased the risk for major cardiovascular events (myocardial infarction, stroke, or cardiovascular death) by 61% among nondiabetic individuals who were ≥55 yr of age and had a history of CVD (15). The association between increased urine albumin excretion and cardiovascular events and mortality has also been reported in other high-risk groups, such as patients with diabetes (16), hypertension, (17), and established CVD (18–20) and the elderly (21). Although we noted no association between stage 1 to 2 CKD and increased CAC scores in the Dallas Heart Study population, other measures of subclinical CVD such as left ventricular hypertrophy may also mediate the increased risk for cardiovascular events noted in adults with stage 1 to 2 CKD (22–25). CKD is a very strong predictor of CVD, and a low CAC score should not warrant the withholding of long-term preventive interventions (26).

The strengths of this study include the use of a representative sample of the Dallas County community that experiences very high rates of both CVD and kidney disease. In addition, blacks were oversampled to ensure that the black population was well

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**Figure 1.** Prevalence of increased coronary artery calcification scores by presence of chronic kidney disease (CKD) and diabetes mellitus in the Dallas Heart Study Population. No CKD = spot urine albumin/creatinine ratio (mg/g) <17 in men and <25 in women and GFR ≥60 ml/min per 1.73 m² body surface area. Stage 1–2 CKD = a spot urine albumin/creatinine ratio (mg/g) ≥17 in men and ≥25 in women and a GFR ≥60 ml/min per 1.73 m² body surface area. Stage 3–5 CKD = GFR <60 in ml/min per 1.73 m² body surface area. + Data are weighted.
represented. The main objective of the Dallas Heart Study was to investigate the cause of racial disparities in CVD in the Dallas community. Patient recruitment was limited to men and women who were between the ages of 30 and 65 because most of the excess CVD among blacks occurs before the age of 65 (27,28). Therefore, this study may not be applicable to men and women who are 65 yr of age. According to the National Kidney Foundation, CKD may be defined by persistent increased urine albumin excretion, abnormalities in urine sediment or imaging studies, and/or a GFR <60 ml/min per 1.73 m² body surface. The Dallas Heart Study did not collect information on urine sediment or image the kidneys and may have underestimated the true prevalence of CKD. Although the prevalence of stage 3 to 5 CKD in the Dallas Heart Study population was similar to the prevalence reported in the general U.S. population (29), the small number of stage 3 to 5 CKD cases limited the power of the study to examine the association between this level of CKD and CAC scores, especially among elderly adults, who may have a higher prevalence of CKD. The prevalence of stage 1 to 2 CKD among the Dallas Heart Study participants was lower than previous reports in the U.S. population (29), which may have been due to variations in urine albumin measurements between laboratories and the exclusion of participants who could not undergo the electron beam computed tomography examination. Moreover, the modified MDRD formula for estimation of GFR used in this study was based on serum creatinine values measured at the Cleveland Clinic laboratory, and serum creatinine values may also vary between laboratories. These findings need to be confirmed in study populations with larger number of CKD cases, such as the ongoing Chronic Renal Insufficiency Cohort Study (30). However, this investigation provides useful and provocative information that may help guide future studies that investigate the excess cardiovascular risk associated with CKD.

In conclusion, we noted an association between stage 3 to 5 CKD (GFR <60 ml/min) and increased CAC scores, which was most notable in participants with diabetes. These findings suggest a potential interaction between CKD and metabolic abnormalities associated with diabetes on the development and/or progression of atherosclerosis.

Acknowledgments

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Table 3. Adjusted odds ratios for coronary artery calcification by presence of CKD in the total and nondiabetic Dallas Heart Study population

<table>
<thead>
<tr>
<th>No CKD Referent/CKD Stage 1–2 CKD</th>
<th>Stage 3–5 CKD</th>
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<tbody>
<tr>
<td>Total Dallas Heart Study population (n = 2660)</td>
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</tr>
<tr>
<td>CAC &gt; 10 ( \text{versus} \leq 10 )</td>
<td>1.00</td>
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<tr>
<td>age, gender, and race adjusted</td>
<td>1.00</td>
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<tr>
<td>multivariate adjusted</td>
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<tr>
<td>CAC &gt; 100 ( \text{versus} \leq 10 )</td>
<td>1.00</td>
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<tr>
<td>age, gender, and race adjusted</td>
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<tr>
<td>multivariate adjusted</td>
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<tr>
<td>CAC &gt; 400 ( \text{versus} \leq 10 )</td>
<td>1.00</td>
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<tr>
<td>age, gender, and race adjusted</td>
<td>1.00</td>
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<tr>
<td>multivariate adjusted</td>
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<tr>
<td>Nondiabetic Dallas Heart Study population (n = 2318)</td>
<td></td>
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<tr>
<td>CAC &gt; 10 ( \text{versus} \leq 10 )</td>
<td>1.00</td>
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<td>age, gender, and race adjusted</td>
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<tr>
<td>CAC &gt; 400 ( \text{versus} \leq 10 )</td>
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<td>multivariate adjusted</td>
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</table>

aCAC, coronary artery calcification. All logistic regression models were performed using the sample weights. No CKD = urine albumin/creatinine ratio (mg/g) <17 in men and <25 in women and a GFR ≥60 ml/min per 1.73 m² body surface area. Stage 1–2 CKD = spot urine albumin/creatinine ratio (mg/g) ≥17 in men and ≥25 in women and a GFR ≥60 ml/min per 1.73 m² body surface. Stage ≥3 CKD = GFR <60 ml/min per 1.73 m² body surface area. bAdjusted for age, gender, race, systolic BP, body mass index, serum cholesterol level, current smoking, presence of diabetes, and use of antihypertensive and lipid-lowering medication.
The data in this article were presented at the American Heart Association Epidemiology Council Meeting, Washington, D.C.; March 3–5, 2004.

References


