Ethnic Differences in the Relationship Between Albuminuria and Calcified Atherosclerotic Plaque

The African American-Diabetes Heart Study

JASMIN DIVERS, PHD[1]
LYNNE E. WAGENKNECHT, DRPH[1]
DONALD W. BOWDEN, PHD[2,3,4]
J. JEFFREY CARR, MD[1,5]
R. CARESSE HIGHTOWER, BS[5]
JIANZHAO XU, BS[4]
CARL D. LANGEFELD, PHD[1]
BARRY I. FREEDMAN, MD[6]

OBJECTIVE — Despite higher rates of nephropathy, calcified atherosclerotic plaque is less prevalent in African Americans with diabetes relative to European Americans. We explored ethnicity-specific relationships between albuminuria and calcified plaque involving the infrarenal aorta, coronary artery, and carotid artery in 835 European American and 393 African American subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Generalized estimating equations with exchangeable correlation and the sandwich estimator of the variance were used to test for association between the principal component of calcified plaque in the three vascular beds and urine albumin-to-creatinine ratio (ACR).

RESULTS — Mean ± SD ages of African American and European American participants were 56.7 ± 9.6 and 61.7 ± 9.1 years, respectively, with diabetes duration of 10.4 ± 7.4 and 10.0 ± 7.3 years and median urine ACR of 17.5 and 13.4 mg/g. In African American and European American participants, respectively, median calcified plaque mass scores were 53.5 and 291 for coronary artery, 3 and 35.5 for carotid artery, and 761 and 3,237 for aorta. With adjustment for age, sex, glomerular filtration rate, and BMI, albuminuria was significantly associated with calcified plaque in European Americans ($P = 3.4 \times 10^{-8}$) but not in African Americans ($P = 0.33$), with significant ethnic interaction ($P = 0.01$). Ethnic differences in this relationship persisted after adjustment for blood pressure, smoking, lipids, and use of ACE inhibitors or angiotensin receptor blockers.

CONCLUSIONS — Albuminuria is strongly associated with severity of calcified plaque in European Americans with diabetes but not in African Americans. Disparities in this relationship may contribute to ethnic differences in the rates of cardiovascular disease that are observed in subjects with type 2 diabetes.

Diabetes Care **33:131–138, 2010**

African Americans have overall higher rates of type 2 diabetes (1) and greater risk for diabetes-associated renal and cardiovascular complications relative to European Americans (2,3). In contrast, reports from the Veterans Administration and Kaiser Permanente reveal that when given access to equivalent medical care, African Americans with diabetes had approximately half the rate of myocardial infarctions as that seen in European Americans (4,5). In accordance with this observation, computed tomography (CT)-derived coronary artery calcified plaque (CP) is markedly lower in African Americans with and without diabetes relative to European Americans (6–10). Coronary CP correlates with the extent of atherosclerosis and subsequent risk for cardiovascular disease (CVD) events (11). Coronary artery CP scores also predict the risk for CVD events in individuals of all ethnic groups (12) and are higher among patients with renal disease relative to individuals without kidney disease who have known coronary artery disease (13).

CVD remains the major cause of morbidity and mortality in patients with chronic kidney disease (CKD) and end-stage renal disease (2). Among incident dialysis patients, African Americans had fewer myocardial infarctions and improved survival relative to European Americans (14). As individuals with diabetes and nephropathy approach end-stage renal disease, they typically have albuminuria with falling glomerular filtration rates (GFRs) over several years. Associations between albuminuria and coronary artery CP are robust in European Americans and seem to be at least equivalent to the risk that is associated with other established CVD risk factors (15). We hypothesized that ethnic differences in the relationship between albuminuria and atherosclerosis might contribute to the lower levels of CP that are widely observed in African Americans with diabetes.

The African American-Diabetes Heart Study (AA-DHS) is assessing ethnic differences and inherited factors that contribute to the development of CP. Herein, we compare the relationship between albuminuria (urine albumin-to-creatinine ratio [ACR]) and CP in the coronary (Cor) and carotid (Car) arteries and infrarenal aorta (Aor) in African American and European American subjects with type 2 diabetes. We made use of a principal

From the [1]Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina; the [2]Department of Endocrinology, Wake Forest University School of Medicine, Winston-Salem, North Carolina; the [3]Department of Biochemistry, Wake Forest University School of Medicine, Winston-Salem, North Carolina; the [4]Centers for Diabetes Research and Human Genomics, Wake Forest University School of Medicine, Winston-Salem, North Carolina; the [5]Division of Radiologic Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina; and the [6]Department of Nephrology, Wake Forest University School of Medicine, Winston-Salem, North Carolina.
Corresponding author: Barry I. Freedman, bfreedma@wfubmc.edu.
Received 9 July 2009 and accepted 27 September 2009. Published ahead of print at http://care.diabetesjournals.org on 13 October 2009. DOI: 10.2337/dc09-1253.

component that encompasses the burden of calcified atherosclerotic plaque in all three vascular beds. The majority of AA-DHS participants have preserved renal function, allowing for separation of the effects of hyperphosphatemia, uremia, and ingestion of phosphate binders on vascular calcification.

RESEARCH DESIGN AND METHODS

— Siblings concordant for type 2 diabetes were recruited from internal medicine clinics and community advertising in the Diabetes Heart Study (DHS) (8). Diabetes was diagnosed after the age of 34 years in the absence of historical evidence of ketoacidosis. In addition, 213 unrelated African American subjects were subsequently recruited in the AA-DHS using these same diagnostic criteria, except that type 2 diabetes was diagnosed after the age of 30 years. Subjects who underwent prior coronary artery bypass surgery or carotid endarterectomy were excluded from this analysis because it was felt that the CP mass score in relevant arteries would be affected by these procedures; those with prior myocardial infarction or stroke were included. The study was approved by the institutional review board at the Wake Forest University School of Medicine, and all participants provided written informed consent.

Participant examinations were conducted in the General Clinical Research Center of the Wake Forest University School of Medicine and included interviews for medical history, current medications and health behaviors, measurements of body size, resting blood pressure, 12-lead electrocardiogram, fasting blood sample, and morning spot urine collection. Laboratory assays included urine albumin and creatinine for ACR, total cholesterol, LDL, HDL, triglycerides, A1C, and fasting serum glucose. Renal function was assessed using serum creatinine concentration and Modification of Diet in Renal Disease estimation of GFR. History of CVD was provided by self-report and chart review. Hypertension was defined as self-report of a physician's diagnosis, blood pressure >140/90 mmHg, or use of antihypertensive medications. Antihypertensive medications were grouped into drug classes, particularly ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), medicines known to reduce urine ACR.

Vascular imaging

CP was measured in the coronary and carotid arteries and infrarenal abdominal aorta using single and multidetector CT systems incorporating a standardized scanning protocol based on those currently implemented in the National Heart, Lung, and Blood Institute's Multi-Ethnic Study of Atherosclerosis studies, and these methods have been reported previously (8,16). Traditionally, the Agatston score, also called the calcium score, has been used to report results. However, the nature of this scoring system adds noise to the CT measurement of CP compared with CP volume–based measures (17). In this report, we used the calcium mass score (SmartScore; GE Healthcare, Waukesha, WI), which is derived from the volume score but in addition accounts for the density of CP on a pixel-by-pixel basis. Additional scoring parameters included a 90-Hounsefield unit threshold and two adjacent pixels to define the maximum calcified lesion size, and the program accounted for slice thickness.

Statistical methods

A series of generalized estimating equations assuming exchangeable correlation and using the empirical estimate of the variance to adjust for familial correlation was computed to test for associations between urine ACR and CP (18). The natural log of (urine ACR + 1) was calculated to minimize the influence of extremely large covariate values on parameter estimates in these models. The Box-Cox method was applied to identify the appropriate transformation of each outcome variable that would best approximate the distributional assumptions of conditional normality and homogeneity of variance of the residuals (19). The natural logs of (CorCP + 1), (CarCP + 1), and (AorCP + 1) were analyzed. We applied principal component analysis (PCA) to compute a linear combination of CorCP, CarCP, and AorCP that we used as the primary outcome variable. The principle component encompasses the burden of calcified atherosclerotic plaque in these three vascular beds. There is a strong correlation between the amount of CP in the coronary arteries, carotid arteries, and aorta of individuals with diabetes (20). PCA was conducted using the correlation matrix instead of the covariance matrix to account for the differences in measurement scales between the three variables. The first principal component explained ~70% of the total variation observed in these three variables and is computed as

$$\text{PCA1\_CP} = 0.6 \times \text{CarCP} + 0.5 \times \text{CorCP} + 0.6 \times \text{AorCP}$$

The variable PCA1_CP was computed using the standardized values of CarCP, CorCP, and AorCP. The Box-Cox transformation that best approximated the distributional assumptions of the model was the inverse PCA1_CP, i.e., $(\text{PCA1\_CP})^{-1}$. For PCA1_CP, models were adjusted for age, sex, BMI, and GFR. Subsequent analyses were further adjusted for use of ACEIs or ARBs, blood pressure, lipid levels, A1C, and smoking. Standard regression diagnostics for collinearity and influence were computed for each model reported.

RESULTS

— A total of 1,427 individuals with type 2 diabetes had complete data for analysis. Of these, 1,008 were European Americans from 445 families and 419 were African Americans from 297 families. Coronary artery bypass grafting or carotid endarterectomy was performed in 173 European American and 26 African American participants, and these individuals were excluded. Tables 1 and 2 contain demographic and clinical information in study participants. Urine ACR was <30 mg/g in 60.3% of African American and 71.0% of European American participants, 30–299 mg/g in 29.0% of African American and 23.5% of European American participants, and ≥300 mg/g in 10.7% of African American and 5.5% of European American participants (Table 1). Median Modification of Diet in Renal Disease estimated GFR was 1.34 ml/s in African American and 1.09 ml/s in European American participants (*P* value for ethnic difference 6.3×10^{-22}), with graded reductions in GFR from normoalbuminuric to overt proteinuric participants in both ethnic groups (Table 2).

Coronary CP was detectable in 81.7 and 93.3% of African American and European American participants, respectively (*P* value for ethnic difference 1×10^{-9}). Because distributions of CP mass scores are highly skewed, mean scores should be interpreted cautiously and median values are more reflective of central tendency. In African American subjects, the median CorCP mass score was 53.5 (mean 697), median CarCP mass score was 3 (mean 170), median AorCP mass score was 761 (mean 4,934),

Table 1—*Demographic characteristics of the study population by ethnicity*

	European American urine ACR				African American urine ACR			
	<30 mg/g	30–299 mg/g	≥300 mg/g	Total	<30 mg/g	30–299 mg/g	≥300 mg/g	Total
n	593	196	46	835	237	114	42	393
Age (years)								
Mean ± SD	61.2 ± 8.9	62.4 ± 9.7	65.4 ± 8.3	61.7 ± 9.1	56.5 ± 9.3	56.9 ± 10.3	56.8 ± 9.7	56.7 ± 9.6
Median	61	62	65	61.9	57	56	58	57.0
P value*	1.34×10^{-10}	1.05×10^{-5}	1.55×10^{-4}	8.1×10^{-17}				
Diabetes duration (years)								
Mean ± SD	9.2 ± 6.6	11.2 ± 8.2	14.7 ± 8.7	10.0 ± 7.3	9.2 ± 6.9	11.9 ± 8.0	13 ± 7.4	10.4 ± 7.4
Median	7	9	14	8	7	10	13	8
P value	0.7	0.4	0.6	0.43				
BMI (kg/m^2)								
Mean ± SD	32.7 ± 6.6	32.9 ± 7.3	31.6 ± 6.4	32.7 ± 6.7	35.3 ± 7.8	34.7 ± 8.1	34 ± 9.5	35 ± 8.1
Median	31.4	32.2	30.5	31.5	34.1	32.6	33.5	33.7
P value	8.6×10^{-6}	0.09	3.05×10^{-6}	3.8×10^{-6}				
Systolic blood pressure (mmHg)								
Mean ± SD	137.7 ± 17.4	143.4 ± 18.3	158.7 ± 20.0	140.2 ± 18.4	132.5 ± 17.7	139.5 ± 21.4	154.7 ± 20.1	136.9 ± 20.2
Median	136	141	158	139	131.0	137.5	151.0	135.0
P value	1.08×10^{-4}	0.04	0.03	0.002				
Diastolic blood pressure (mmHg)								
Mean ± SD	73 ± 9.6	73.8 ± 11.2	74 ± 10.0	74 ± 10.0	75.2 ± 11.2	76.9 ± 12.8	82.7 ± 10.9	76.5 ± 11.9
Median	72.5	73.0	74.5	72.5	74	77	82	76
P value†	0.02	0.04	3.29×10^{-4}	7.1×10^{-6}				
ACEIs or ARBs								
n (%)	266 (44.9)	103 (52.6)	30 (65.2)	399 (47.8)	120 (50.6)	53 (46.5)	26 (61.9)	199 (50.6)
P value‡	(0.71)	(0.85)	(0.21)	(0.72)				
Lipid medications								
n (%)	244 (41.5)	89 (45.6)	24 (53.3)	357 (43.1)	112 (47.7)	52 (45.6)	24 (58.5)	188 (48.2)
P value‡	(0.74)	(0.70)	(0.48)	(0.57)				
Insulin								
n (%)	126 (21.3)	60 (30.6)	17 (37.0)	203 (24.3)	95 (40.3)	49 (43.0)	25 (59.5)	169 (43.1)
P value‡	(2.3×10^{-8})	(0.03)	(0.03)	(2.3×10^{-11})				
Smoking, *n* (%)								
Former	210 (42.5)	57 (35.2)	16 (41.1)	283 (40.7)	81 (38)	29 (28.2)	14 (34.2)	124 (34.7)
Current	72 (14.6)	27 (16.7)	10 (25.6)	109 (15.7)	52 (24.4)	22 (21.3)	12 (29.3)	86 (24.1)
Never	212 (42.9)	78 (48.1)	13 (33.3)	303 (43.6)	80 (37.6)	52 (50.5)	15 (36.6)	147 (41.2)
P value§	0.01	0.72	0.96	0.02				

**P* value for the Wilcoxon rank statistic testing for equality of the median of each variable between European Americans and African Americans at each level of ACR. †(%) for each variable reflects the available sample size. ‡*P* value for the association between each categorical variable and race. §*P* value for the Armitage trend test for association between smoking status and race.

Table 2—*Laboratory characteristics of the study population by ethnicity*

	European American urine ACR				African American urine ACR			
	<30 mg/g	30–299 mg/g	≥300 mg/g	Total	<30 mg/g	30–299 mg/g	≥300 mg/g	Total
n	593	196	46	835	237	114	42	393
Estimated GFR (ml/s)								
Mean ± SD	1.16 ± 0.30	1.11 ± 0.33	0.95 ± 0.38	1.14 ± 0.32	1.45 ± 0.46	1.44 ± 0.44	1.06 ± 0.45	1.40 ± 0.47
Median	1.11	1.07	0.84	1.09	1.38	1.31	1.01	1.34
P value*	2.8×10^{-18}	5.3×10^{-9}	0.16	6.3×10^{-22}				
Serum creatinine (μmol/l)								
Mean ± SD	92.8 ± 22.1	97.2 ± 23.9	118.5 ± 41.6	94.6 ± 24.8	89.3 ± 28.3	88.4 ± 24.8	124.6 ± 64.5	92.8 ± 34.5
Median	88.4	97.2	114.9	88.4	88.4	88.4	106.1	88.4
P value*	0.02	0.003	0.64	0.003				
Fasting blood sugar (mmol/l)								
Mean ± SD	7.96 ± 2.9	8.71 ± 3.4	9.76 ± 4.2	8.24 ± 3.1	7.83 ± 3.0	10.0 ± 4.7	11.27 ± 5.1	8.82 ± 4.0
Median	7.33	7.96	8.80	7.49	7.27	9.05	10.55	7.94
P value*	0.42	0.01	0.11	0.05				
A1C (proportion of total)								
Mean ± SD	0.075 ± 0.02	0.078 ± 0.02	0.085 ± 0.02	0.076 ± 0.02	0.081 ± 0.02	0.090 ± 0.03	0.094 ± 0.02	0.085 ± 0.02
Median	0.071	0.074	0.082	0.072	0.076	0.084	0.093	0.080
P value*	9.1×10^{-6}	1.8×10^{-5}	0.02	1.2×10^{-12}				
Serum calcium (mmol/l)								
Mean ± SD	2.33 ± 0.1	2.33 ± 0.1	2.33 ± 0.1	2.33 ± 0.1	2.35 ± 0.1	2.38 ± 0.1	2.30 ± 0.1	2.35 ± 0.1
Median	2.33	2.30	2.30	2.33	2.38	2.40	2.30	2.38
P value*	1.6×10^{-4}	5×10^{-5}	0.55	1.4×10^{-6}				
Serum phosphorus (mmol/l)								
Mean ± SD	1.07 ± 0.2	1.07 ± 0.2	1.10 ± 0.2	1.07 ± 0.2	1.10 ± 0.2	1.10 ± 0.2	1.16 ± 0.3	1.10 ± 0.2
Median	1.07	1.07	1.07	1.07	1.10	1.10	1.13	1.10
P value*	0.003	0.26	0.20	7.5×10^{-4}				
Coronary CP								
Mean ± SD	1,165 ± 2,378	1,511 ± 2,813	1,686 ± 2,111	1,277 ± 2,479	603 ± 1,507	771 ± 1,678	1,028 ± 2,244	697 ± 1,649
Median	213	411	884	291	37.8	62.5	219.5	53.5
P value*	2.5×10^{-10}	5.4×10^{-5}	0.001	2.39×10^{-14}				
Coronary CP >0%								
n (%)†	519 (93.2)	174 (92.1)	44 (100)	737 (93.3)	187 (79.9)	92 (82.1)	37 (90.2)	316 (81.7)
P value‡	3.8×10^{-8}	0.009	0.03	1.0×10^{-9}				
Carotid CP								
Mean ± SD	244 ± 627	334 ± 660	407 ± 524	275 ± 631	138 ± 463	211 ± 749	236 ± 550	170 ± 569
Median	23.5	78.5	202	35.5	0.5	8.5	48	3
P value*	7.7×10^{-8}	7.2×10^{-5}	0.002	8.2×10^{-11}				

Table 2—*Continued*

	European American urine ACR				African American urine ACR			
	<30 mg/g	30–299 mg/g	≥300 mg/g	Total	<30 mg/g	30–299 mg/g	≥300 mg/g	Total
Carotid CP >0%								
n (%)	395 (72)	148 (78.7)	41 (93.2)	584 (74.8)	118 (50.6)	70 (63.1)	30 (73.2)	218 (56.6)
P value‡	9.7×10^{-9}	0.003	0.01	3.1×10^{-10}				
Aorta CP								
Mean ± SD	8,478 ± 13,192	12,383 ± 16,691	14,201 ± 13,692	9,803 ± 14,339	4,009 ± 7,509	6,355 ± 13,422	6,105 ± 8,593	4,934 ± 9,856
Median	2,751	4,470	10194	3,237	713	742	2053	761
P value*	7.7×10^{-8}	7.06×10^{-5}	0.002	1.03×10^{-14}				
Aorta CP >0%								
n (%)	388 (95.1)	148 (95.5)	32 (100)	568 (95.5)	170 (80.6)	95 (86.4)	29 (87.9)	294 (83.1)
P value‡	9.0×10^{-9}	0.008	0.04	1.5×10^{-11}				
HDL (mmol/l)								
Mean ± SD	1.10 ± 0.3	1.11 ± 0.3	1.14 ± 0.3	1.11 ± 0.3	1.26 ± 0.4	1.19 ± 0.4	1.33 ± 0.4	1.25 ± 0.4
Median	1.06	1.04	1.11	1.06	1.19	1.17	1.35	1.19
P value*	5.2×10^{-9}	0.03	0.01	1.9×10^{-11}				
LDL (mmol/l)								
Mean ± SD	2.70 ± 0.8	2.78 ± 0.9	2.78 ± 0.9	2.72 ± 0.8	2.81 ± 0.9	2.86 ± 1.0	3.26 ± 1.3	2.87 ± 1.0
Median	2.64	2.72	2.69	2.64	2.82	2.72	3.06	2.80
P value*	0.12	0.65	0.09	0.03				
Triglycerides (mmol/l)								
Mean ± SD	2.34 ± 1.5	2.47 ± 1.7	2.82 ± 2.0	2.40 ± 1.6	1.28 ± 0.7	1.81 ± 2.1	1.88 ± 1.4	1.50 ± 1.4
Median	1.99	2.05	2.31	2.00	1.07	1.32	1.62	1.14
P value*	6.3×10^{-34}	1.8×10^{-8}	0.002	2.4×10^{-40}				

*P value for the Wilcoxon rank statistic testing for equality of the median of each variable between European Americans and African Americans at each level of ACR. †(%) for each variable reflects the available sample size. ‡P value for the association between each categorical variable and race.

and median ACR was 17.5 mg/g (mean ± SD 230 ± 758). In European American subjects, the median CorCP mass score was 291 (mean 1,277), median CarCP mass score was 35.5 (mean 275), median AorCP mass score was 3,237 (mean 9,803), and median ACR was 13.4 mg/g (110 ± 531); these ethnic differences were highly significant ($P = 8.2 \times 10^{-11}$ to 2.39×10^{-14}). Statistically significant and graded increases in median vascular CP mass score were observed with increasing levels of ACR in European Americans with *P* values = 1.6×10^{-4}, 2.7×10^{-4}, and 1.0×10^{-6}, respectively, for AorCP, CorCP, and CarCP using traditional ACR cut points <30, 30–299, and >300 mg/g to stratify the sample. When stratification was done using quartiles of urine ACR, *P* values improved to 4.7×10^{-7} and 1.2×10^{-8} for AorCP and CorCP but decreased to 4.8×10^{-5} for CarCP. In African Americans, only CarCP had a significant positive relationship with urine ACR ($P = 9.6 \times 10^{-3}$ using ACR quartiles, $P = 5.8 \times 10^{-3}$ using traditional ACR cutoff values) (Table 2 and supplementary Table 1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-1253/DC1).

Table 3 focuses on the relationship between urine ACR and CP, separately in each vascular distribution and for the first principal component of CP. In age-, sex-, BMI- and GFR-adjusted analyses, significant associations were seen between urine ACR with each vascular bed as well as for the principal component in European Americans, whereas significant relationships were not present in African Americans. In addition, significant ethnic differences were observed in the relationship between urine ACR and the principal component for CP ($P = 0.01$) and a trend for urine ACR with CarCP ($P = 0.06$).

Table 4 reveals the parameter estimate for the relationship between log urine ACR and the first principal component for CP across the three vascular beds, adjusted for additional covariates including ACEIs or ARBs. The log urine ACR was significantly associated with the first principal component for CP in European Americans (parameter estimate ± SEM −0.0387 ± 0.008; $P = 8.34 \times 10^{-7}$), whereas a significant relationship was not observed in African Americans (parameter estimate −0.0068 ± 0.011; $P = 0.54$), and there was a significant ethnic interaction ($P = 0.01$). The Box-Cox transformation suggested using a decreasing

Table 3—*Relationship between albuminuria and calcified atherosclerotic plaque*

		Adjusted for age and sex				Adjusted for age, sex, BMI, and GFR			
		Main effect		Ethnic interaction		Main effect		Ethnic interaction	
Vascular bed	Ethnicity	Estimate	*P*	Estimate	*P*	Estimate	*P*	Estimate	*P*
Aorta	African American	0.17	5.1×10^{-2}	−0.08	0.42	0.13	1.9×10^{-1}	−0.11	0.34
	European American	0.26	7.3×10^{-6}			0.28	3.5×10^{-6}		
Carotid artery	African American	0.18	6.0×10^{-3}	−0.13	0.12	0.14	7×10^{-2}	−0.13	0.06
	European American	0.31	1.0×10^{-9}			0.33	1.0×10^{-10}		
Coronary artery	African American	0.16	1.1×10^{-2}	−0.02	0.84	0.11	1.4×10^{-1}	−0.05	0.53
	European American	0.18	1.0×10^{-4}			0.19	4.7×10^{-5}		
First principal component for aorta, carotid artery, and coronary artery CP*	African American	−0.02	5.8×10^{-2}	0.03	0.03	−0.01	3.3×10^{-1}	0.03	0.01
	European American	−0.04	4.3×10^{-8}			−0.04	3.4×10^{-8}		

*Box-Cox transformation suggested using a decreasing function of the principal component. Therefore, direction indicated by the sign of the parameter estimate for relationships between parameters and CP should be inverted when reverting to the original scale.

function of the principal component; therefore, the direction indicated for the sign of the parameter estimate should be inverted when one reverts to the original scale. Ethnic differences in the relationship between sex and CP were also detected ($P = 0.0001$). Although there was no association between sex and the first principal component for CP in African Americans ($P = 0.37$), sex was strongly associated with CP in European Americans, with men having greater CP than women ($P = 6.4 \times 10^{-7}$).

CONCLUSIONS — This report characterized ethnic differences in the relationship between calcified atherosclerotic plaque and albuminuria in African Americans and European Americans with type 2 diabetes and without advanced renal dysfunction. Albuminuria and kidney disease are important risk factors for the development of atherosclerosis (21). After adjustment for the covariates of age, sex, BMI, and GFR, a significant and positive relationship was observed between albuminuria and CP in European Americans but not in African Americans. Consequently, the ethnic difference in this relationship suggests that lower amounts of CP in African Americans with diabetes, with attendant reduced risk for myocardial infarction relative to that in European Americans, could be related in part to a differential effect of albuminuria. Myocardial infarctions occur significantly less often in African American patients receiving renal replacement therapy compared with European American patients, and CVD is the leading cause of death in subjects with nephropathy (2,14). Our report intentionally examined European American and African American subjects with diabetes and relatively preserved kidney function, thereby minimizing the potential effects of exogenous vitamin D and vitamin D analogs, phosphate binders, and calcimimetic agents on CP. These

Table 4—*Generalized estimating equation for the first principal component of aorta, carotid artery, and coronary artery CP*

	African American	*P*	European American	*P*	Ethnic interaction (African American: European American)*	*P*
Intercept	1.8343 ± 0.2499	2.15E−13	1.5561 ± 0.2234	3.31E−12	—	—
Log ACR	−0.0068 ± 0.0110	0.54	−0.0387 ± 0.0079	8.34E−07	0.03 ± 0.01	0.01
Age	−0.0165 ± 0.0024	0.00	−0.0142 ± 0.0018	1.55E−15	−0.002 ± 0.00	0.54
Female sex	−0.0339 ± 0.0379	0.37	0.1460 ± 0.0293	6.4E−07	−0.18 ± 0.05	0.0001
BMI	0.0019 ± 0.0022	0.37	−0.0016 ± 0.0021	0.45	0.0035 ± 0.0029	0.22
Diastolic blood pressure	−0.0012 ± 0.0022	0.59	0.0040 ± 0.0017	0.02	−0.0039 ± 0.0027	0.14
Systolic blood pressure	0.0006 ± 0.0013	0.63	−0.0005 ± 0.0010	0.58	0.0008 ± 0.0015	0.58
Estimated GFR	0.0004 ± 0.0007	0.61	−0.0003 ± 0.0008	0.73	−0.001 ± 0.0010	0.29
ACEIs or ARBs	−0.0921 ± 0.0534	0.08	−0.0396 ± 0.0366	0.28	−0.005 ± 0.04	0.90
LDL	−0.0007 ± 0.0005	0.11	0.0000 ± 0.0004	0.97	−0.0005 ± 0.0006	0.38
HDL	0.0009 ± 0.0013	0.49	0.0004 ± 0.0012	0.75	0.001 ± 0.0017	0.49
A1C	0.0016 ± 0.0055	0.77	−0.0122 ± 0.0086	0.16	0.008 ± 0.01	0.24
Smoking						
Never	0.2050 ± 0.0418	4.69E−07	0.1860 ± 0.0369	2.31E−07	−0.0064 ± 0.0571	0.91
Former	0.1001 ± 0.0473	0.03	0.1250 ± 0.0341	1.23E−04	−0.0397 ± 0.0605	0.51

Data are estimates ± SEM. Box-Cox transformation suggested using a decreasing function of the principal component. Therefore, direction indicated by the sign of the parameter estimate for relationships between parameters and CP should be inverted when reverting to the original scale. *Except sex comparison, which tests the interaction between African American women vs. others.

medications and associated hyperphosphatemia may have an impact on risk for development of subclinical CVD in patients with advanced nephropathy (22).

A recent report confirmed the lower risk of CVD in African Americans with advanced stages of CKD, relative to European Americans (23). There is mounting evidence that biological differences may contribute to ethnic differences in risk for CVD and development of CP with subsequent CVD (6–10). Given equal access to health care, African Americans with type 2 diabetes and CKD face lower risks for CVD events than European Americans (4,5,14,23). In the current report, ACEIs, ARBs, and lipid-lowering medications were prescribed nearly equally in African American and European American participants. Previously, biological factors have been implicated in ethnic disparities in the development of kidney failure (24). Ethnic differences in *MYH9* risk allele distribution reveal that inherited factors are capable of causing ethnic differences in the incidence of common diseases. It remains possible that other inherited factors contribute to the ethnic differences in the development of CP relating to albuminuria.

Markedly lower levels of CP are observed in African American subjects relative to those in European American subjects with and without diabetes (6–10). Although ethnic differences exist in the presence of CP, the severity of CP is strongly associated with risk for coronary events among individuals of all ethnic groups. In the Multi-Ethnic Study of Atherosclerosis (MESA), Americans of European, African, Hispanic, and Chinese descent demonstrated equivalent risk for CVD events based on level of CP (12). Conventional CVD risk factors may have ethnic-specific effects on risk for CP (20). Therefore, it is important to assess whether ethnic differences in the relationship between albuminuria and CP exist because African Americans are known to develop type 2 diabetes-associated nephropathy with resultant albuminuria more often than European Americans (2). In addition, calcium metabolism clearly differs between African Americans and European Americans. Although African Americans typically ingest less dietary calcium than European Americans, they have denser bone with lower rates of osteoporosis and skeletal resistance to the effects of parathyroid hormone (25). Related phenomena may prove to be important in the development of CP because vascular endothelial cells assume osteoblastic phenotypes and deposit bone matrix in blood vessels.

Albuminuria markedly increases the risk for CVD in European Americans with type 2 diabetes (15). The current analyses emphasize the importance of ethnic differences in the effect of albuminuria on risk for CVD. We studied a population of subjects with median 8-year durations of diabetes, and diabetes would be expected to magnify atherosclerotic vascular disease. However, there is no a priori reason to suspect that the relationship between albuminuria and CP would be different in African Americans and European Americans without diabetes. Studies in these individuals remain to be performed. It is possible that the lower levels of CP in African Americans despite the presence of similar or more severe conventional CVD risk factors, as well as the differential effects of atherosclerotic risk factors on the amounts of CP, relate to inherited factors because CorCP is a heritable trait. The AA-DHS will soon perform mapping by admixture linkage disequilibrium in an attempt to detect genes underlying development of CP.

Potential weaknesses of this report are reliance on cross-sectional data, a single measurement of albuminuria, and inclusion of only subjects with diabetes. Equivalent diabetes durations and similar prescription of lipid-lowering and proteinuria-reducing medications in African American and European American participants, as well as consistency of CorCP scores when contrasted with other reports, suggest the lack of bias. Albuminuria is both a marker of renal impairment and a sign of systemic endothelial dysfunction. It seems likely that the balance between these relationships may differ between African Americans and European Americans. In the future, it will be important that longitudinal studies clarify the relationship between classic and novel CVD risk factors on ethnic differences in susceptibility to CP. These analyses need to be performed in subjects with and without diabetes.

In summary, albuminuria is strongly associated with CP in European Americans with type 2 diabetes but not in African Americans with type 2 diabetes. Ethnic differences in the relationship between CP and albuminuria may contribute to the lower levels of CP and reduced risk for myocardial infarction in African Americans with diabetes. It remains to be determined whether interventions that reduce albuminuria and preserve renal function will prevent the development of calcified atherosclerotic plaque and reduce CVD rates equally in African Americans and European Americans with type 2 diabetes.

Acknowledgments— This study was supported in part by the General Clinical Research Center of the Wake Forest University School of Medicine (Grant M01-RR-07122), National Institute of Diabetes and Digestive and Kidney Diseases (Grant R01-DK-071891) (B.I.F.), National Institute of Arthritis and Musculoskeletal and Skin Diseases (Grant R01-AR-048797) (J.J.C.), and National Heart, Lung, and Blood Institute (Grant R01-HL-67348) (D.W.B.).

No potential conflicts of interest relevant to this article were reported.

We acknowledge the cooperation of our participants and study recruiters Carrie Smith and Cassandra Bethea.

References

1. Cowie CC, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C, Williams DE, Gregg EW, Bainbridge KE, Saydah SH, Geiss LS. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988–1994 and 2005–2006. Diabetes Care 2009;32:287–294
2. U.S. Renal Data System. *USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. Bethesda, MD, U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2009
3. Manolio TA, Burke GL, Psaty BM, Newman AB, Haan M, Powe N, Tracy RP, O'Leary DH. Black-white differences in subclinical cardiovascular disease among older adults: the Cardiovascular Health Study. CHS Collaborative Research Group. J Clin Epidemiol 1995;48:1141–1152
4. Young BA, Maynard C, Boyko EJ. Racial differences in diabetic nephropathy, cardiovascular disease, and mortality in a national population of veterans. Diabetes Care 2003;26:2392–2399
5. Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV. Ethnic disparities in diabetic complications in an insured population. JAMA 2002;287:2519–2527
6. Bild DE, Detrano R, Peterson D, Guerci A, Liu K, Shahar E, Ouyang P, Jackson S, Saad MF. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2005;111:1313–1320
7. Newman AB, Naydeck BL, Whittle J, Sutton-Tyrrell K, Edmundowicz D, Kuller LH. Racial differences in coronary artery calcification in older adults. Arterioscler Thromb Vasc Biol 2002;22:424–430

8. Freedman BI, Hsu FC, Langefeld CD, Rich SS, Herrington DM, Carr JJ, Xu J, Bowden DW, Wagenknecht LE. The impact of ethnicity and sex on subclinical cardiovascular disease: the Diabetes Heart Study. Diabetologia 2005;48: 2511–2518
9. Budoff MJ, Nasir K, Mao S, Tseng PH, Chau A, Liu ST, Flores F, Blumenthal RS. Ethnic differences of the presence and severity of coronary atherosclerosis. Atherosclerosis 2006;187:343–350
10. Carnethon MR, Bertoni AG, Shea S, Greenland P, Ni H, Jacobs DR Jr, Saad M, Liu K. Racial/ethnic differences in subclinical atherosclerosis among adults with diabetes: the Multiethnic Study of Atherosclerosis. Diabetes Care 2005;28:2768–2770
11. Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, Guerci AD, Lima JA, Rader DJ, Rubin GD, Shaw LJ, Wiegers SE; American Heart Association Committee on Cardiovascular Imaging and Intervention; American Heart Association Council on Cardiovascular Radiology and Intervention; American Heart Association Committee on Cardiac Imaging; Council on Clinical Cardiology. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation 2006; 114:1761–1791
12. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–1345
13. Russo D, Palmiero G, De Blasio AP, Balletta MM, Andreucci VE. Coronary artery calcification in patients with CRF not undergoing dialysis. Am J Kidney Dis 2004; 44:1024–1030
14. Young BA, Rudser K, Kestenbaum B, Seliger SL, Andress D, Boyko EJ. Racial and ethnic differences in incident myocardial infarction in end-stage renal disease patients: the USRDS. Kidney Int 2006;69: 1691–1698
15. Freedman BI, Langefeld CD, Lohman KK, Bowden DW, Carr JJ, Rich SS, Wagenknecht LE. Relationship between albuminuria and cardiovascular disease in type 2 diabetes. J Am Soc Nephrol 2005; 16:2156–2161
16. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR Jr, Sidney S, Bild DE, Williams OD, Detrano RC. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. Radiology 2005;234:35–43
17. Budoff MJ, McClelland RL, Chung H, Wong ND, Carr JJ, McNitt-Gray M, Blumenthal RS, Detrano RC. Reproducibility of coronary artery calcified plaque with cardiac 64-MDCT: the Multi-Ethnic Study of Atherosclerosis. AJR Am J Roentgenol 2009;192:613–617
18. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986;42:121–130
19. Box GEP, Cox DR. An analysis of transformations. J R Stat Soc Ser B 1964;26:211–246
20. Wagenknecht LE, Langefeld CD, Carr JJ, Riley W, Freedman BI, Moossavi S, Bowden DW. Race-specific relationships between coronary and carotid artery calcification and carotid intimal medial thickness. Stroke 2004;35:e97–e99
21. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension 2003;42:1050–1065
22. Mathew S, Tustison KS, Sugatani T, Chaudhary LR, Rifas L, Hruska KA. The mechanism of phosphorus as a cardiovascular risk factor in CKD. J Am Soc Nephrol 2008;19:1092–1105
23. Kovesdy CP, Anderson JE, Derose SF, Kalantar-Zadeh K. Outcomes associated with race in males with nondialysis-dependent chronic kidney disease. Clin J Am Soc Nephrol 2009;4:973–978
24. Kopp JB, Smith MW, Nelson GW, Johnson RC, Freedman BI, Bowden DW, Oleksyk T, McKenzie LM, Kajiyama H, Ahuja TS, Berns JS, Briggs W, Cho ME, Dart RA, Kimmel PL, Korbet SM, Michel DM, Mokrzycki MH, Schelling JR, Simon E, Trachtman H, Vlahov D, Winkler CA. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. Nat Genet 2008;40:1175–1184
25. Acheson LS. Bone density and the risk of fractures: should treatment thresholds vary by race? JAMA 2005;293:2151–2154