Familial Aggregation of Coronary Artery Calcium in Families With Type 2 Diabetes

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Type 2 diabetes is widely recognized as a major risk factor for atherosclerotic cardiovascular disease, including subclinical atherosclerosis as measured by noninvasive procedures. However, the role of genetic factors that contribute to various measures of subclinical atherosclerosis is largely unknown. We hypothesize that subclinical atherosclerosis, measured as coronary artery calcification (CAC), will be extensive in individuals with type 2 diabetes and that its presence depends on both genetic and environmental factors. The genetic factors should result in the familial aggregation of CAC. To determine the extent of familial aggregation of CAC in the presence of type 2 diabetes, we studied 122 individuals with type 2 diabetes (mean age 60 years) and 13 individuals without diabetes in 56 families. CAC was measured by fast-gated helical computed tomography. Other measured factors included blood pressure, body size, lipids, HbA_{1c}, and self-reported medical history. To test for an association between CAC and these factors while accounting for the potential familial correlation of CAC, generalized estimating equations were used. CAC was detectable in 80% of individuals with diabetes (median score 84, range 0–5,776). Extent of CAC, adjusted for age, was positively associated with male sex ($P = 0.0003$), reduced HDL ($P = 0.02$), albumin-to-creatinine ratio ($P = 0.008$), and cigarette pack–years ($P = 0.03$). CAC was also positively associated with a history of angina, myocardial infarction, stroke, and vascular procedures (all $P < 0.01$). HbA_{1c} and fasting glucose were positively, but nonsignificantly, associated with the extent of CAC ($P = 0.14$ and 0.08, respectively). CAC, adjusted for age, sex, race, and diabetes status, was heritable ($h^2 = 0.50$; $P = 0.009$). In multivariate analysis with additional adjustment for HDL, BMI, hypertension, and smoking, $h^2 = 0.40$ ($P = 0.038$). These results suggest that strong (independent) genetic factors as well as environmental factors contribute to the variance of CAC in individuals with type 2 diabetes. In these data, CAC seems heritable and may serve as an important feature in designing studies to map genes contributing to both atherosclerosis and type 2 diabetes. *Diabetes* 50:861–866, 2001

Atherosclerosis is accelerated in type 2 diabetes (1,2). It has been hypothesized that this relationship is due to common genetic factors (pleiotropic genes that mediate the development of both type 2 diabetes and atherosclerosis), common environmental factors, or a combination of environmental and genetic factors.

Significant qualitative evidence suggests that genes play a role in the development of cardiovascular disease (CVD) (3); however, only a few efforts have been made to measure the quantitative component of genetic risk. Duggirala et al. (4) detected high heritabilities (range 0.86–0.92) in measurements of carotid intimal medial thickness in sibships from Mexico City, suggesting a powerful genetic component for atherosclerosis. In contrast, lower heritabilities of intimal medial thickness have been reported ranging from 0.13 to 0.23 in the San Antonio Family Heart Study and the National Heart, Lung, and Blood Institute Family Heart Study, respectively (S. S. Rich, unpublished data) (5). O'Donnell et al. (6) have reported a significant sibling pair correlation (0.35, $P < 0.0001$) for lumbar aortic calcification, a marker of aortic atherosclerosis. None of these studies have directly addressed the heritability of CVD in the atherogenic environment of type 2 diabetes.

Calcium hydroxyapatite is deposited in arterial walls in an active process similar to bone formation. The amount of calcium deposited in the coronary arteries, as measured with computed tomography (CT), correlates with pathological extent of atherosclerosis and presence of stenosis as identified by coronary angiography (7–9). Its ability to predict future CVD events, independent of CVD risk factors, has been reported in short-term studies (10–12). None of these studies have focused on individuals with diabetes per se, whose vessels are often characterized by increased amounts of connective tissue, glycoproteins, and calcium (13,14), nor have any studies reported the extent to which coronary artery calcification (CAC) is under genetic control. This study was designed to investigate the extent and familial aggregation of subclinical atherosclerosis as indexed by CAC in the presence of type 2 diabetes.

RESEARCH DESIGN AND METHODS

Siblings concordant for type 2 diabetes were recruited from internal medicine and endocrinology clinics and through community advertising. Type 2 diabetes was defined as a diagnosis of diabetes after 34 years of age, in the absence

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ACR, albumin-to-creatinine ratio; apoE, apolipoprotein E; CABG, coronary artery bypass graft; CAC, coronary artery calcification; CHD, coronary heart disease; CT, computed tomography; CVD, cardiovascular disease; GEE1, generalized estimating equations; OR, odds ratio; SOLAR, Sequential Oligogenic Linkage Analysis Routines.

of historical evidence of diabetic ketoacidosis. Up to one unaffected sibling per family, similar in age to the siblings with diabetes, was also recruited. Individuals with serious health conditions, e.g., dialysis, were not eligible to participate. The study was approved by the Institutional Review Board. All participants gave informed consent.

The participant examinations were conducted in the General Clinical Research Center of the Wake Forest University Baptist Medical Center and included interviews for medical history and health behaviors, anthropometric measures, resting blood pressure, 12-lead electrocardiography, fasting blood sampling, and spot urine collection. Laboratory assays included urine albumin and creatinine, total cholesterol, LDL, HDL, triglycerides, HbA_{1c}, fasting glucose, and blood chemistries. DNA was isolated from blood samples and stored for later studies.

CAC was measured using fast-gated helical CT. All scans were performed on two single-slice subsecond helical CT scanners equipped for retrospective cardiac gating and capable of 500-ms temporal resolution (HiSpeed LX with the SmartScore Cardiac scan package; General Electric Medical Systems, Milwaukee, WI). Participants were placed in the supine position on the CT couch over a quality-control calibration phantom (Image Analysis, Columbia, KY). After obtaining a scout image of the chest, a helical volume of the entire heart during suspended respiration at end inspiration was obtained with the following parameters: 3-mm slice thickness, 26-cm display field of view, retrospective cardiac gating, 120 kv, 240 mA, and CT scan pitch adjusted to heart rate as previously described (15). To further improve the precision of the calcium score, a replicated scan was performed immediately after the initial scan so that the average of the two scores could be calculated. The reproducibility of the calcium score was high: $r = 0.98$ (Spearman correlation coefficient) between the first and second CAC scores. The amount of coronary calcium was scored using a modified Agatston method with the traditional 130–Henry U threshold and a minimum lesion definition of 0.52 mm^2. In our previously published work, this method has very high correlation with the electron-beam CT–derived measure of coronary calcium ($r = 0.98$) and high agreement when categorizing individuals based on their coronary calcium score (15).

Statistical methods

A two-stage modeling approach was used to investigate the potential relationships between CAC and the above demographic characteristics as well as anthropometric, clinical, and laboratory measures. In the first stage, we modeled the presence or absence of calcium (CAC > 0 or CAC $= 0$) using a generalized estimating equations (GEE1) approach assuming a logit link and allowing for familial correlation in calcium scores (16). In the second stage, we modeled the natural log of CAC for individuals with CAC > 0 using GEE1, assuming an identity link and allowing for familial correlation in CAC. Thus, no assumptions were made regarding common determinants of the presence/absence of measurable calcium and the magnitude of CAC. Due to the limited sample size, extensive multivariable modeling was not appropriate, and only age-adjusted models were computed (sex adjustment was made for race, BMI, and waist-to-hip ratio). We log-transformed HDL, triglycerides, albumin-to-creatinine ratio (ACR), and pack-years of exposure to tobacco.

To determine the contribution of genetic factors to CAC, we analyzed the log-transformed CAC data obtained on family members using the Sequential Oligogenic Linkage Analysis Routines (SOLAR) software package (Southwest Foundation for Biomedical Research) (17). SOLAR performs a variance components analysis of family data that decomposes the total variance of the phenotype (CAC) into components that are due to genetic (polygenic) effects (additive genetic variance), measured covariates, and random environmental effects. The relative contribution of genetic factors to CAC variation is then estimated by the heritability (h^2), defined by the ratio of the genetic variance component to the residual (after removal of covariates) phenotypic variance. A series of models were developed that incorporated an increasing number of covariates related to CAC to determine the extent of genetic factors contributing to the variation in CAC independent of the measured risk factors. The first model included only the effects of age, sex, the interaction of age and sex, and race as covariates (Model 1). Additional models added the effects of diabetes status in the family members (Model 2), HDL and BMI (Model 3), and hypertension and smoking (Model 4). Significance of the estimated heritabilities was determined by likelihood ratio tests, in which the likelihood of the models with the additive genetic variance component and covariates was compared with the model with the likelihood in which the additive genetic variance component was constrained to be 0.

All descriptive and GEE1 analyses were conducted on the subset of 122 individuals with type 2 diabetes. The genetic analysis (variance component analysis) was performed in the overall sample (both affected and unaffected relatives) and then in a restricted sample that excluded individuals with previous coronary artery bypass graft (CABG) surgery.

RESULTS

A total of 56 families participated in the study for a total of 135 family members, 122 of whom had type 2 diabetes. The number of families contributing 1, 2, 3, and 4 siblings with type 2 diabetes was 2, 45, 6, and 3, respectively. Of the participants with diabetes, the average age was 60 years, the duration of diabetes was 10 years, 60% were women, and 19% were African-American (Table 1). Of those participants with diabetes, 30% were currently being treated with insulin, and one-third were taking lipid-lowering medications. The average HbA_{1c} was 8.5%; 15.7% of the participants were microalbuminuric, and 8.3% had overt proteinuria. History of CVD (angina, heart attack, stroke, or vascular procedure) was reported by 30% ($n = 36$) of participants with diabetes, 15 of whom reported previous CABG surgery. None of the siblings were concordant for CABG surgery. Among the 13 siblings without diabetes, the average age was 59 years, 77% ($n = 10$) were women, 8% ($n = 1$) were African-American, and 38% ($n = 5$) reported history of CVD.

Of this sample of individuals with diabetes, 80% ($n = 97$) had detectable CAC (86% of men and 75% of women) and 27% had CAC >400, suggestive of extensive atherosclerotic plaque burden (18). In contrast, among the 13 siblings without diabetes, 31% ($n = 4$) had detectable CAC and 8% ($n = 1$) had CAC >400 ($P = 0.0034$, comparing the distributions). The proportions with detectable CAC across age groups of 40–49 ($n = 13$), 50–59 ($n = 46$), 60–69 ($n = 34$), and 70–79 years ($n = 22$) were 77, 70, 94, and 96%, respectively.

The presence of CAC in individuals with diabetes was strongly and positively associated with age (Table 2; $P < 0.0001$); it was not associated with sex ($P = 0.14$). The odds ratio (OR) (95% CI) for presence of CAC for a change of 10 years of age was 2.75 (1.78, 4.22), and for male sex relative to female sex it was 2.13 (0.79, 5.78). Among those 97 individuals with CAC >0, age ($P = 0.0004$) and male sex ($P = 0.0003$) were positively associated with extent of CAC (Table 3).

In addition to the strong association between age and the presence of CAC, we observed additional associations between other covariates and presence of CAC when we adjusted for age. Specifically, the presence of CAC was positively associated with taking lipid-lowering medications (OR 4.76, 95% CI 1.56–14.52; $P = 0.006$) and a history of vascular procedure (OR 16.53, 95% CI 1.94–140.79; $P = 0.01$). Presence was also weakly associated with white race (OR 3.16, 95% CI 0.90–11.14; $P = 0.073$) and pack-years of exposure to tobacco ($P = 0.059$). The result for vascular procedure is noteworthy, because 23 of the 23 individuals with diabetes and a history of vascular procedures had detectable CAC, whereas only 72 of 97 (74%) individuals without a history of vascular procedures had measurable CAC.

The extent of CAC among 97 individuals with detectable CAC was strongly and positively associated with age and duration of diabetes (Table 2). Adjusting for age, we found that CAC was associated with male sex ($P = 0.0003$), inversely associated with log HDL ($P = 0.017$), and weakly associated with log triglycerides ($P = 0.062$). Extent of CAC was strongly associated with log ACR ($P = 0.0075$). Pack-years among ever smokers was also positively asso-

TABLE 1
Characteristics of individuals with type 2 diabetes

	Mean ± SD or % (*n*)	Median (range)
Age (years)	59.5 ± 10.6	59 (34–80)
Duration of diabetes (years)	9.8 ± 7.8	6.5 (1–40)
Sex (% female)	60 (73)	–
Race (% African-American)	19 (23)	–
Treatment for diabetes		
Insulin (%)	30 (36)	–
Oral hypoglycemic (%)	68 (81)	–
Lipid-lowering medication (%)	32 (39)	–
BMI (kg/m^2)	33.7 ± 7.7	32.0 (20.7–58.0)
Waist-to-hip ratio	0.92 ± 0.09	0.93 (0.52–1.20)
Laboratory		
Total cholesterol (mmol/l)	4.99 ± 0.94	4.89 (3.05–7.58)
HDL (mmol/l)	1.07 ± 0.33	1.03 (0.54–2.35)
LDL (mmol/l)	2.93 ± 0.80	2.91 (1.34–5.09)
Triglycerides (mmol/l)	2.23 ± 1.46	1.92 (0.51–9.75)
Glycated hemoglobin (%)	8.5 ± 2.3	7.9 (4.9–16.4)
Fasting glucose (mmol/l)	8.6 ± 3.2	7.9 (2.6–19.7)
Albumin/creatinine ratio (mg/g)		
<30 (%)	76.0 ± 92	–
30–300 (%)	15.7 ± 19	–
>300 (%)	8.3 ± 10	–
Serum creatinine	0.95 ± 0.55	0.8 (0.4–4.1)
Behaviors		
Smoking		
Current (%)	16 (19)	–
Past (%)	41 (49)	–
Never (%)	43 (52)	–
Pack-years (among ever smokers)	34 ± 31	25 (0.6–135)
Prevalent cardiovascular conditions		
Hypertension (%)*	80 (97)	–
Angina (%)†	23 (25)	–
Heart attack (%)†	16 (19)	–
Stroke (%)†	6 (7)	–
Any vascular procedure (%)‡	19 (23)	–
Any self-reported CVD§	30 (36)	–
CAC score	458 ± 967	84 (0–5,776)
CAC categories (ref. 18)		
0 (%)	20.5 (25)	–
1–10 (%)	13.1 (16)	–
11–100 (%)	18.9 (23)	–
101–400 (%)	20.5 (25)	–
>400 (%)	27.0 (33)	–

Sample size was 122 and varied by no more than 4, except for LDL, which was missing 8 (due to extreme triglyceride values), and angina, which was missing 12. *Hypertension defined as a doctor's diagnosis of hypertension by self-report or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg; †self-reported conditions in response to the question, "Has a doctor ever told you that you have [. . .]?"; ‡any vascular procedure included self-reported CABG surgery, coronary or leg angioplasty, or carotid endarterectomy; §any self-reported CVD included self-report of angina, heart attack, stroke, or vascular procedures.

ciated with CAC ($P = 0.027$). Individuals reporting angina ($P = 0.003$), myocardial infarction ($P < 0.0001$), stroke ($P = 0.0021$), vascular procedures ($P = 0.0003$), and use of lipid-lowering medication ($P = 0.039$) all had higher CAC levels.

The heritability of CAC, adjusted for age, sex, and race, was 0.40 ($P = 0.032$) (Table 3). After further adjustment for diabetes status, $h^2 = 0.50$ ($P = 0.009$). Note that these residual heritabilities are higher than they would be if they were expressed as a proportion of the total phenotypic variance. This occurs because adjustment for other measured covariates, such as diabetes, reduces the remaining unexplained variance, allowing the genetic contribution to become more apparent. In contrast, further adjustment for coronary heart disease (CHD) risk factors, including HDL, BMI, hypertension, and history of smoking, increased the total proportion of explained variance to 0.40, although h^2 declined to 0.40 ($P = 0.038$). This may be a result of adjusting for one or more highly heritable factors that are also strongly associated with CAC. In fact, in our sample, the heritability of HDL was 0.62 ($P < 0.0001$) after adjusting for demographic characteristics and diabetes status (not shown). In the restricted sample, excluding individuals with history of CABG surgery, $h^2 = 0.50$ ($P = 0.017$) for Model 1, $h^2 = 0.57$ ($P = 0.009$) for Model 2, $h^2 = 0.50$ ($P = 0.025$) for Model 3, and $h^2 = 0.50$ ($P = 0.031$) for Model 4.

DISCUSSION

To our knowledge, this is the first report of the familial aggregation of CAC and one of only several to characterize the extent and correlates of calcification in individuals with type 2 diabetes. In this study, our estimate of the heritability of CAC in individuals with type 2 diabetes is at least 40%, providing evidence that a search for CAC-predisposing genes is warranted. As hypothesized, CAC was more extensive in individuals with diabetes than in their unaffected family members; 80 and 31% presented with detectable CAC, respectively. Also, 27% had extensive calcification (i.e., CAC >400). These findings are consistent with the known excess risk of CHD among individuals with type 2 diabetes (1,2).

Although this is the first study to examine the familial aggregation of coronary atherosclerosis as measured by CAC, extensive research has been conducted on the familial nature of early clinical CHD (3), with estimates of the heritability of CHD ranging from 0.13 to 0.61 (19,20). The same is true for the familial nature of CHD risk factors, with heritability estimates of 0.26–0.33 reported for systolic and diastolic blood pressures (21,22), 0.50–0.51 reported for HDL (21–23), 0.11–0.36 reported for fasting insulin (21–24), and 0.42–0.54 reported for BMI (21–23). Our heritability estimate of 0.40 for CAC suggests that both genetic and nongenetic factors play important roles in the deposition of CAC. The limitation of h^2 as an estimate of heritability is that it does not delineate between shared genes and shared environment. Hence, when common environment is a possible risk factor (e.g., childhood diet as a risk factor for atherosclerosis), h^2 may overestimate the genetic contribution. Nevertheless, this estimate of heritability of CAC reaches statistical significance and is of moderate magnitude, thus providing support for further investigations into the genetic basis of CAC in families affected with type 2 diabetes.

Several investigators have examined candidate genes for CAC and have been met with limited success. Pfolhl et al. (25) observed a higher incidence and greater extent of coronary lesion calcification, as determined by intravascular ultrasound, in 46 of 146 patients with the DD genotype of the ACE gene. Kardia et al. (26) did not find that the apolipoprotein E (apoE) genotypes predicted the presence of CAC in a sample of 329 men and women. There was evidence, however, that certain apoE genotypes influence the relationship between CAC and established risk factors,

TABLE 2
Age-adjusted correlates of the presence and extent of CAC in individuals with type 2 diabetes

	Presence		Extent	
	β (SE)	*P* value	β (SE)	*P* value
Age (years)	0.101 (0.022)	<0.0001	0.082 (0.023)	0.0004
Duration of diabetes (years)*	−0.003 (0.027)	0.91	0.047 (0.022)	0.032
Sex (female)	−0.756 (0.509)	0.14	−1.536 (0.422)	0.0003
Race (African-American)†	−1.152 (0.642)	0.073	−0.540 (0.594)	0.36
Treatment (insulin)	−0.627 (0.493)	0.20	0.375 (0.441)	0.40
Treatment (oral hypoglycemic)	0.041 (0.603)	0.95	0.493 (0.456)	0.28
Lipid-lowering medication	1.560 (0.569)	0.006	0.909 (0.441)	0.039
BMI (kg/m^2)†	0.025 (0.047)	0.59	0.012 (0.042)	0.78
Waist-to-hip ratio†	−0.106 (2.766)	0.97	3.089 (2.238)	0.17
Laboratory				
Total cholesterol (mg/dl)	0.005 (0.007)	0.46	−0.006 (0.005)	0.28
log HDL (mg/dl)	−1.210 (0.946)	0.20	−2.034 (0.848)	0.017
LDL (mg/dl)	0.008 (0.009)	0.41	−0.012 (0.007)	0.12
log Triglycerides (mg/dl)	0.091 (0.425)	0.83	0.669 (0.358)	0.062
Glycated hemoglobin (%)	−0.075 (0.091)	0.41	0.121 (0.081)	0.14
Fasting glucose (mg/dl)	0.001 (0.003)	0.77	0.006 (0.003)	0.08
log ACR	−0.267 (0.839)	0.75	1.406 (0.526)	0.0075
Smoking				
Current	0.431 (0.663)	0.52	0.452 (0.661)	0.49
Past	0.271 (0.524)	0.60	0.476 (0.507)	0.35
log Pack-years (among ever smokers)	0.435 (0.230)	0.059	0.458 (0.207)	0.027
Prevalent CVD, procedures				
Hypertension	0.717 (0.494)	0.15	0.646 (0.558)	0.25
Angina	1.118 (0.628)	0.075	1.408 (0.475)	0.003
Myocardial infarction	1.628 (1.088)	0.13	2.000 (0.460)	<0.0001
Stroke	−0.427 (1.088)	0.69	1.435 (0.466)	0.0021
Any vascular procedure	2.805 (1.093)‡	0.01	1.662 (0.465)	0.0003

*Not age-adjusted; †also sex-adjusted; ‡these parameter estimates were computed by adding 0.5 to each cell in the corresponding 2 × 2 table (see text).

such as BMI. Finally, Ellsworth et al. (27) reported a relationship between the E-selectin S128R polymorphism and both the presence and quantity of CAC. This finding was limited to women aged ≤50 years. These studies provide a preliminary indication that certain polymorphisms may be associated with the presence and progression of CAC.

The increased prevalence and extent of CAC in individuals with type 2 diabetes relative to individuals without diabetes is similar to other reports in the literature. Wong et al. (28) observed CAC in 79% of men and 56% of women with diabetes, compared with 56% of men and 43% of women without diabetes. We report a similarly high prevalence of detectable CAC in our sample of subjects with type 2 diabetes. Higher absolute CAC scores were reported by Yoshida et al. (29) in those with type 2 diabetes compared with those without diabetes (248 vs. 149, $P < 0.05$). In a preliminary report, Hsia et al. (30) reported significantly higher CAC scores in 168 individuals with diabetes relative to those without ($n = 2{,}214$) at all decades of age, indicating that diabetes was a potent independent correlate of CAC, second only to age. Another report shows similar differences in the extent of CAC in women with diabetes (31) relative to women without. CAC, a subclinical marker of atherosclerosis, is clearly accelerated in type 2 diabetes. It is noteworthy, however, that 20% of our sample had no detectable calcification, providing further evidence of genetic susceptibility and possible gene-environment interactions.

Few reports of the correlates of CAC among individuals

TABLE 3
Heritability of (log) coronary artery calcium in families with type 2 diabetes

Adjusted for:	Proportion of variance accounted for by demographic, metabolic, and behavioral factors	Heritability (h^2)	SE of h^2	*P* value
Model 1 Age, sex, age*sex, and race	0.310	0.395	0.221	0.032
Model 2 Age, sex, age*sex, race, and diabetes status	0.358	0.495	0.216	0.009
Model 3 Age, sex, age*sex, race, diabetes status, HDL, and BMI	0.386	0.426	0.225	0.026
Model 4 Age, sex, age*sex, race, diabetes status, HDL, BMI, hypertension, and smoking	0.397	0.403	0.234	0.038

with diabetes are available. These studies have generally examined correlates of the presence of CAC (not the extent) and include individuals with type 1 (32,33) and type 2 diabetes (29). Consistent cross-sectional correlates of CAC are duration of diabetes (29,32,33), albuminuria or overt proteinuria (29,33), smoking (29,33), hypertension (29,32,33), and central adiposity (29,33). The present study has also found relationships of extent of CAC with duration of disease, ACR, and smoking. None of the previous studies in individuals with diabetes identified lipids or lipoproteins, HbA_{1c}, or BMI as correlates of CAC. We report a similar lack of association except for HDL, which was found to be a correlate of the extent of CAC. None of the studies have found that sex correlates with presence of CAC (29,32,33), but male sex was associated with extent of CAC in the study of type 2 diabetes (29) and in the present study. None of the studies was able to examine ethnicity as a correlate of CAC; in the present study, a trend (nonsignificant) toward a lower prevalence of CAC is observed in African-Americans. Hsia et al. (31) were unable to document a difference in CAC scores between African-American and white women. The strong consistent association between use of lipid-lowering medications and presence and extent of CAC in the present study is likely a result of medical treatment occurring among individuals with significant known CAD.

In this study, measures of glycemia, measured concurrently with CAC, did not correlate with either the presence or extent of CAC. This finding suggests that other metabolic and/or genetic factors may be more powerful in predicting CAC or that fasting glucose and HbA_{1c} are poor surrogates of long-term exposure to excess circulating glucose. Duration of diabetes did correlate with extent ($P = 0.032$) but not presence of CAC ($P = 0.91$). Although this may indicate that increased exposure to the metabolic derangements of diabetes is a risk factor for the quantity of CAC, the confounding of duration of disease with age cannot be ruled out.

The analysis approach used here intentionally does not assume that similar mechanisms both establish calcification and predict progression, i.e., presence of CAC was modeled separately from extent of CAC. Although the two analytical approaches test different hypotheses, it is interesting to contrast the two sets of observed associations. For both outcomes, strong positive relationships were observed for age, use of lipid-lowering medication, pack-years of exposure to tobacco, and history of vascular procedures. Notable differences in relationships include *1*) a strong positive relationship between ACR and extent of CAC ($P = 0.0075$) but no significant relationship to presence of CAC; *2*) a positive association between duration of diabetes and extent of CAC ($P = 0.032$) but no significant relationship to presence of CAC; and *3*) a stronger (but nonsignificant) relationship between triglycerides and extent of CAC (and fasting glucose and CAC) but again no relationship to presence of CAC. These results are consistent with a hypothesis that posits both shared and independent mechanisms for the presence and progression of CAC.

A limitation of this analysis is the inclusion of 15 individuals with history of CABG surgery, all of whom had diabetes. In 12 of these 15 individuals, the CAC score exceeded 400. It is known that bypassed coronary vessels can develop extensive calcification; however, these vessels are not necessary for circulation. Therefore, the presence and extent of calcification in this cohort may be inflated above those of a cohort of individuals with diabetes without history of CABG surgery. We hypothesized that including individuals with inflated calcium scores due to history of CABG surgery would tend to bias the heritability estimate toward lower values because none of the sibling pairs were concordant on history of CABG surgery. Indeed, restricting our sample to individuals without history of CABG surgery resulted in a statistically significant heritability estimate of 0.50.

In conclusion, CAC is present in a large proportion of individuals with type 2 diabetes, many of whom have extensive clinically significant atherosclerotic plaque burden. CAC is less prevalent in siblings without diabetes. A modest proportion of the extent of CAC can be explained by traditional CVD risk factors, with much of the remaining variance explained by genetic factors. Indeed, both atherosclerosis and diabetes may share common genetic and environmental antecedents, described by Stern (34) as a "common soil." Thus, gene-mapping studies designed to identify the unique and pleiotropic type 2 diabetes and atherosclerosis-predisposing genes, as well as the interaction of these genes with environmental characteristics, are warranted. Such studies will be important in delineating the factors that mediate the development of these interrelated diseases.

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