Effect of Type 1 Diabetes on the Gender Difference in Coronary Artery Calcification: a Role for Insulin Resistance?

The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study

Dana Dabelea,[1] Gregory Kinney,[1] Janet K. Snell-Bergeon,[1] John E. Hokanson,[1] Robert H. Eckel,[2] James Ehrlich,[3] Satish Garg,[4] Richard F. Hamman,[1] and Marian Rewers[1,3]

The objective of this is study was to examine whether estimated insulin resistance and insulin resistance-related factors are associated with coronary artery calcification (CAC) in 1,420 asymptomatic participants in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study. A total of 656 patients with type 1 diabetes and 764 control subjects aged 20–55 years were examined. CAC was assessed by electron-beam computed tomography. Insulin resistance was computed with linear regression based on an equation previously validated in clamp studies on type 1 diabetic adults. Insulin resistance was associated with CAC (OR 1.6 in type 1 diabetes and 1.4 in control subjects, $P < 0.001$), independent of coronary artery disease risk factors. There was a male excess of CAC in control subjects (OR 2.7, adjusted for age, smoking, and LDL and HDL cholesterol levels) and in type 1 diabetic patients (OR 2.2, adjusted for the same factors and diabetes duration). After adjusting for insulin resistance, the CAC male excess in diabetic patients decreased from OR 2.2 ($P < 0.001$) to 1.8 ($P = 0.04$). After adjustment for waist-to-hip ratio, waist circumference, or visceral fat, the gender difference in CAC was not significant in diabetic subjects. In conclusion, gender differences in insulin resistance-associated fat distribution may explain why type 1 diabetes increases coronary calcification in women relatively more than in men. *Diabetes* 52: 2833–2839, 2003

From the [1]Department of Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, Denver, Colorado; the [2]Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado; the [3]Colorado Heart Imaging Center, Denver, Colorado; and the [4]Barbara Davis Center for Childhood Diabetes, Denver, Colorado.

Address correspondence to Dana Dabelea, MD, PhD, Department of Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, 4200 East 9th Ave., Campus Box C245, Denver, CO 80262. E-mail: dana.dabelea@uchsc.edu.

Received for publication 14 February 2003 and accepted in revised form 28 July 2003.

CAC, coronary artery calcification; CACTI, Coronary Artery Calcification in Type 1 Diabetes; CAD, coronary artery disease; DBP, diastolic blood pressure; EBCT, electron-beam computed tomography; EDC, Epidemiology of Diabetes Complications study; IAF, intra-abdominal fat; SBP, systolic blood pressure; WHR, waist-to-hip ratio.

Diabetic patients experience higher cardiovascular disease incidence and mortality (1,2). In patients with type 1 diabetes, coronary artery disease (CAD) occurs earlier in life (3) and affects women almost as often as men (4). The loss of relative protection from CAD in diabetic women is not well explained by differences in established risk factors (3,5,6).

Coronary artery calcification (CAC) measured by electron-beam computed tomography (EBCT) has been shown to correlate well with the amount of atheromatous plaque (7) and with the severity of coronary stenosis in nondiabetic subjects (8–10) and in symptomatic patients with type 2 diabetes (11). Prospectively, coronary calcification predicts cardiovascular events, even in asymptomatic individuals (12,13). In patients with type 1 diabetes, CAC is associated with CAD (14), and the prevalence of CAC has been reported to be similar in men and women (15). The loss of relative protection from coronary calcification in women with type 1 diabetes is not explained by standard CAD risk factors (15), differences in lipoprotein particle size (16), or activity of lipid transfer proteins (17).

Novel CAD risk factors, such as insulin resistance, hyperinsulinemia, visceral obesity, microalbuminuria, inflammation, and thrombosis appear to be associated with increased CAC in nondiabetic (18) and type 2 diabetic subjects (19). Insulin resistance, the hallmark of type 2 diabetes, has also been documented in type 1 diabetes (20–23) and may relate to increased CAD risk in these patients (24–26).

The aim of this study was to determine whether the association between type 1 diabetes and CAC is different in men than in women and, if so, to explore the role of estimated insulin resistance and central adiposity as possible explanations.

RESEARCH DESIGN AND METHODS

Study participants. The data presented in this report were collected as part of the baseline examination of 1,420 participants in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study. Participants were 20–55 years of age and included 656 men and women with type 1 diabetes and 764

TABLE 1
Baseline characteristics of patients with type 1 diabetes and nondiabetic control subjects stratified by gender

	Men		Women	
	Type 1 diabetic patients	Control subjects	Type 1 diabetic patients	Control subjects
n	301	382	355	382
Age (years)	37.2 ± 9.0	39.9 ± 8.8*	35.8 ± 9.3	37.1 ± 16.0†
Duration of diabetes (years)	23.6 ± 8.9		22.7 ± 8.7	
Insulin dose (units/kg^{-1} · day^{-1})	0.6 ± 0.3		0.6 ± 0.3	
HbA_{1c} (%)	7.8 ± 1.2	5.5 ± 0.5*	7.9 ± 1.3	5.3 ± 0.5*
Cholesterol (mg/dl)				
Total	175.9 ± 38.9	195.9 ± 34.4*	177.1 ± 32.9	183.9 ± 31.5‡
HDL	51.3 ± 12.2	42.9 ± 10.5*	60.5 ± 15.6	57.8 ± 14.5†
LDL	105.1 ± 31.7	122.2 ± 28.4*	98.3 ± 27.8	105.8 ± 26.7*
Triglyceride (mg/dl)	85.6 ± 17.8	131.6 ± 17.6*	83.0 ± 19.2	92.0 ± 19.2†
Hypertensive (%)	14.6	12.3	6.5	5.2
SBP (mmHg)	122 ± 11.9	118 ± 10.6*	115 ± 12.6	110 ± 12.2*
DBP (mmHg)	80 ± 8.2	81 ± 7.1‡	76 ± 8.1	76 ± 7.8
BMI (kg/m^2)	26.7 ± 4.1	27.1 ± 3.6	26.0 ± 5.2	25.0 ± 4.9†
BMI ≥27 kg/m^2 (%)	42.2	46.9	31.8	25.6
WHR	0.88 ± 0.06	0.89 ± 0.05†	0.79 ± 0.07	0.78 ± 0.07‡
Waist (cm)	87.2 ± 8.1	87.2 ± 7.5	78.6 ± 9.6	76.4 ± 9.2*
IAF L23 (cm^3)	52.5 ± 17.9	72.5 ± 20.2*	28.3 ± 19.5	27.1 ± 20.2
Serum creatinine (mg/dl)	1.4 ± 0.4	1.3 ± 0.3†	1.2 ± 0.3	1.1 ± 0.2*
Albumin excretion rate (μg/min)	134.2 ± 18.8	19.4 ± 3.0*	65.2 ± 8.2	6.1 ± 2.6‡
Homocysteine (μmol/l)	9.4 ± 3.5	9.2 ± 3.1	7.5 ± 2.5	7.5 ± 2.4
Ever smoked (%)	27.9	29.6	31.3	30.4
Insulin resistance	0.126 ± 0.02	0.106 ± 0.01*	0.104 ± 0.02	0.088 ± 0.09*

Data are group means ± SD for most data, geometric means for triglycerides and IAF 23, and interquartile range for albumin excretion rate and insulin resistance, all after adjustment for age. $N = 1{,}420$. *$P < 0.001$, †$P < 0.05$, ‡$P < 0.01$ for difference between type 1 diabetic patients and control subjects of same gender. Hypertensive = SBP ≥135 mmHg or DBP ≥85 mmHg or on treatment; insulin resistance = 1/estimated glucose disposal rate (EGDR), where EDGR = 24.31 − 12.22 (WHR) − 3.29 (hypertension) − 0.57 (HbA_{1c}).

nondiabetic control subjects. All subjects were asymptomatic for CAD and had no history of coronary artery bypass graft, coronary angioplasty, or unstable angina. All patients with diabetes had been diagnosed when younger than 30 years, had been treated with insulin within 1 year of diagnosis, and had to have a disease duration of at least 10 years on enrollment. All nondiabetic control subjects had fasting blood glucose <110 mg/dl and were generally spouses, friends, and neighbors of the cases. All subjects provided informed consent and the study was approved by the Colorado Combined Institutional Review Board.

Examination and laboratory measurements. Participants completed the baseline examination between March 2000 and April 2002. Current height, weight, waist (measured at the smallest point between the 10th rib and the iliac crest over the bare skin) and hip (measured at the maximum circumference of the buttocks) were recorded, and BMI (weight/height^2) and waist-to-hip ratio (WHR) were calculated. Resting systolic blood pressure (SBP) and fifth-phase diastolic blood pressure (DBP) were measured three times while the subjects were seated, and the second and the third measurements were averaged. Hypertension was defined as current SBP ≥135 mmHg or DBP ≥85 mmHg or current antihypertensive therapy. Participants completed a standardized questionnaire including medical history and medication inventory, Rose angina, current and past smoking status, physical activity, food frequency, daily insulin dose, and family history of diabetes, CAD, and hypertension.

After an overnight fast, blood was collected and centrifuged, and separated plasma was stored at 4°C until assayed. Total cholesterol and triglyceride levels were measured using standard enzymatic methods. HDL cholesterol was separated using dextran sulfate, and LDL cholesterol was calculated using the Friedewald formula. High-performance liquid chromatography was used to measure HbA_{1c} (HPLC; BioRad variant).

Insulin resistance was assessed as the inverse of the estimated glucose disposal rate (27), calculated according to the formula: estimated glucose disposal rate = 24.31 − 12.22*(WHR) − 3.29*(hypertension) − 0.568*(HbA_{1c}). The equation was derived from hyperinsulinemic-euglycemic clamps performed in 24 type 1 diabetic participants in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study (27).

CAC measurement by EBCT scan. An ultrafast Imatron C-150XLP EBCT scanner (Imatron, San Francisco, CA) was used to obtain two sets of high resolution, noncontrast, contiguous 3-mm tomographic images acquired at 100-ms exposure. Scanning started from near the lower margin of bifurcation of the main pulmonary artery with the subject breathholding for ~35–45 s and proceeded caudally. Calcified coronary artery areas were identified as those with a minimum density of 130 Hounsfeld units (HU) and a minimum area of three pixels (1.03 mm^2). A calcium score for each region was calculated by multiplying the area by the density score (1 for 130–199, 2 for 200–299, 3 for 300–399, and 4 for >399 HU). A total CAC score in Agatston units (AU) was calculated by adding up scores for all slices separately for left main, left anterior descending, circumflex, and right coronary arteries. The scanner was recalibrated every day with a phantom. No adjustments were made to noise due to excess BMI. Effective radiation dose for an EBCT sequence was 1.0 mSV for men and 1.3 mSV for women. A single technician obtained and scored all EBCT scans, and the average of two scores obtained 5-min apart was used.

Abdominal computed tomography scan. An abdominal computed tomography scan at the L2-L3 levels was obtained on each participant. The L2-L3 disc space was located by counting the lumbar vertebra with L1 being the first non–rib-bearing vertebra. A single 6-mm thick image was obtained though the L2-L3 disc space during suspended respiration.

Statistical analysis. Differences in risk factors between subjects with type 1 diabetes (cases) and without diabetes (control subjects) in men and women were examined using ANOVA, adjusted for age. CAC scores were positively skewed with a high frequency of zero values. Therefore, logistic regression was used to examine the age-adjusted ORs of having any coronary calcification (CAC score >0) in diabetic patients versus control subjects, as well as the age-adjusted ORs of having any coronary calcification in men versus women. We tested the effect of gender on having any calcification (CAC score >0) and on having a CAC score ≥20, adjusted for covariates, in patients with type 1 diabetes and in nondiabetic control subjects. The covariates entered in the models were standard risk factors for CAD (age, total, HDL, and LDL cholesterol, triglycerides, smoking, SBP, DBP, and diabetes duration for type 1 diabetic patients only), estimated insulin resistance, individual components of the equation used to assess insulin resistance (HbA_{1c}, hypertension, and WHR), and insulin resistance syndrome–related factors (waist circumference, visceral fat measured at L23 level [IAF {intra-abdominal fat}L23], BMI) with different distributions by gender in type 1 diabetic patients and nondiabetic control subjects. To examine whether the ORs for diabetes-associated CAC were the same in men and in women, we included a diabetes-by-gender interaction and examined the effect of adjusting for CAD risk factors, estimated insulin resistance, and insulin resistance syndrome–related features

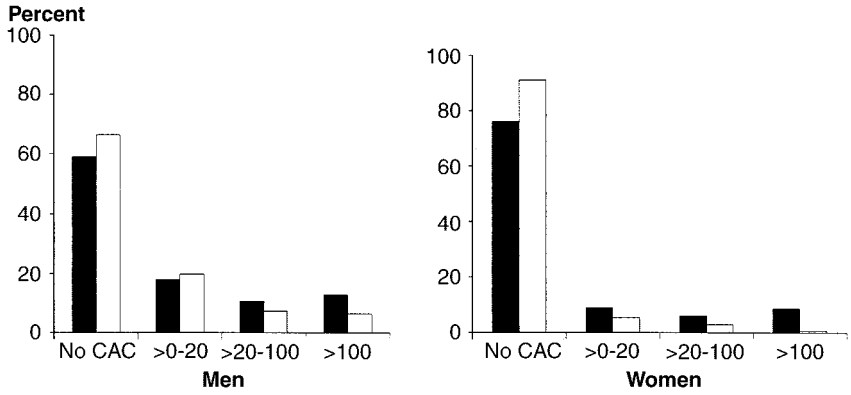

FIG. 1. Distribution of CAC scores by diabetes status (■, type 1 diabetes; □, control subjects) in CACTI men and women.

on the interaction. Because triglyceride and visceral fat levels had skewed distributions they were logarithmically transformed before analysis.

RESULTS

Table 1 shows the baseline characteristics of type 1 diabetic patients and nondiabetic control subjects, stratified by gender and adjusted for age. Both men and women with type 1 diabetes had a significantly better fasting lipid profile (lower total and LDL cholesterol and triglyceride levels and higher HDL cholesterol levels) than nondiabetic control subjects, but the lipid profile was less beneficial with type 1 diabetes in women than in men. In men, type 1 diabetes was associated with slightly lower WHR and dramatically lower visceral fat (IAF L23), while women with type 1 diabetes had slightly higher BMI, WHR, and waist circumference but similar visceral fat compared with nondiabetic women. Estimated insulin resistance was higher in both men and women with type 1 diabetes compared with the nondiabetic control subjects of the same gender.

The distribution of CAC scores by diabetes status for each gender is shown in Fig. 1. The distribution was skewed, with a high frequency of 0 values. There were more diabetic than nondiabetic people with scores >0, especially among women ($P = 0.01$ for the age-adjusted diabetes by gender interaction). In each age-group examined, diabetes was associated with a higher prevalence of any calcification (Fig. 2, $P < 0.001$ for each gender, adjusted for age). In men, diabetes was associated with a 2.1-fold higher age-adjusted prevalence of CAC, while in women the age-adjusted effect of diabetes on CAC was 3.6 times higher (Table 2). In the nondiabetic group there was a larger gender difference in the prevalence of calcification than in type 1 diabetic subjects, so that the 4.6-fold higher age-adjusted OR for CAC in men versus women observed in control subjects was reduced to 2.5 in type 1 diabetes.

Table 3 shows the age-adjusted ORs for the association between CAC (>0) and risk factors in which the effect on diabetes-by-gender interaction was later examined, by diabetes status. The associations were significant for most factors, except for total and LDL cholesterol in patients with type 1 diabetes, and for smoking in both type 1 diabetic and nondiabetic participants.

In multivariate regression, estimated insulin resistance was associated with CAC in patients with type 1 diabetes and in nondiabetic control subjects, independent of age, gender, LDL and HDL cholesterol, smoking, and diabetes duration [ORs (95% CI) 1.6 (1.2–2.0) and 1.4 (1.2–1.7), respectively, $P < 0.001$ for 1-SD change in insulin resistance]. Among the components used to derive the insulin resistance equation, HbA_{1c} and WHR were associated with CAC in both type 1 diabetic patients and nondiabetic control subjects, as were waist and IAF L23, independent of age, gender, LDL and HDL cholesterol, smoking, and diabetes duration (data not shown).

Table 4 shows which covariates explain the effect of gender (male versus female) on CAC prevalence (CAC >0) in type 1 diabetic patients and nondiabetic control subjects. In model 1, adjustment for LDL and HDL cholesterol and diabetes duration (in type 1 diabetic patients only) in addition to age, explained some of the male excess in CAC in patients with type 1 diabetes and ~40% of the male excess in CAC in control subjects. In model 2, addition of estimated insulin resistance further reduced, but did not completely eliminate, the male CAC excess in both type 1 diabetic patients and control subjects. In models 3–5 individual components of the insulin resistance equation

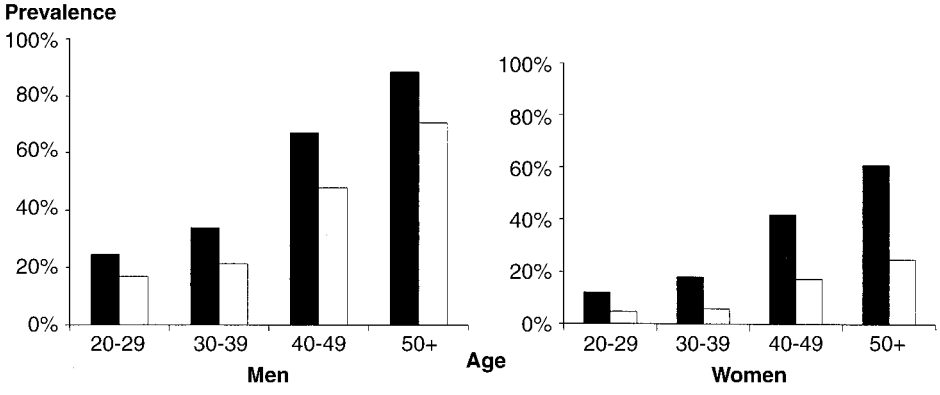

FIG. 2. Prevalence of coronary calcification (CAC scores >0) by age-group and diabetes status (■, type 1 diabetes; □, control subjects) in CACTI men and women.

TABLE 2
Prevalence of CAC >0 by diabetes status and gender among CACTI participants

	Prevalence of CAC		OR for CAC in type 1 diabetic patients vs. control subjects*
	Type 1 diabetic patients	Control subjects	
Men	145 (48.0)	149 (39.1)	2.1 (1.5–2.9)
Women	98 (27.5)	48 (12.5)	3.6 (2.4–5.5)
OR for CAC in men vs. women*	2.5 (1.7–3.6)	4.6 (3.2–6.9)	

Data are *n* (%) and OR (95% CI) *Age-adjusted with logistic regression.

are added to model 1: neither HbA_{1c}, nor hypertension appeared to contribute substantially to the male excess. However, WHR (the third component of the insulin resistance formula) explained a large part of the male CAC excess in both type 1 diabetic patients and nondiabetic control subjects (model 5). Adjustment for WHR (model 5), waist circumference (model 6), or IAF L23 (model 7) reduced the male CAC excess by a similar magnitude in type 1 diabetic patients and control subjects. As a result, the male CAC excess in diabetic subjects became statistically nonsignificant, although after accounting for these factors men were still 30–40% more likely to have CAC. Simultaneous adjustment for age, diabetes duration, HDL and LDL cholesterol, smoking, hypertension, HbA_{1c}, waist circumference, and visceral fat (model 8) did not further reduce the gender difference. Other standard CAD risk factors (total cholesterol, triglycerides, and BMI) explained little of the gender difference in CAC in both groups. Similar results were obtained with a different cut point for calcification (CAC >20 vs. <20) (data not shown).

Figure 3 shows the ORs for the CAC association with diabetes in women relative to men (the diabetes-by-gender interaction on CAC) for eight different models. The first model shows a 1.9-fold (95% CI 1.2–3.4, $P = 0.01$) higher OR for CAC associated with diabetes in women than in men, after controlling only for age. The next models show the effect of adjustment for insulin resistance–related factors on the significantly higher OR for calcification associated with diabetes in women than in men. On adjustment for HbA_{1c} (model 2) or hypertension (model 3), the diabetes-associated OR for CAC still remains significantly higher in women than in men. On adjustment for WHR (model 4), waist (model 5), visceral fat (model 6), or HDL and LDL cholesterol (model 7), the diabetes-by-gender interaction loses significance. Finally, in model 8, HDL and LDL cholesterol together with visceral fat and HbA_{1c} explain almost all of the increased diabetes-associated CAC in women versus men (model 8).

TABLE 3
Age-adjusted ORs* and 95% CIs for the association between CAC >0 vs. CAC = 0 and risk factors by diabetes status

	Type 1 diabetic patients	Control subjects
n	656	764
Insulin resistance†	2.2 (1.7–2.8)	2.0 (1.7–2.4)
Hypertensive (yes/no)	1.9 (1.3–2.7)	2.7 (1.7–4.3)
HbA_{1c} (%)	1.3 (1.1–1.5)	1.5 (1.2–1.8)
WHR	1.8 (1.5–2.2)	2.1 (1.7–2.5)
Waist (cm^2)	1.8 (1.5–2.4)	1.6 (1.3–2.1)
IAF L23 (cm^3)	2.2 (1.8–2.7)	2.5 (1.9–3.1)
BMI (kg/m^2)	1.8 (1.5–2.1)	2.2 (1.8–2.7)
HDL Cholesterol (mg/dl)	0.7 (0.6–0.9)	0.5 (0.4–0.6)
LDL	1.2 (0.9–1.4)	1.3 (1.1–1.6)
TC	1.1 (0.9–1.3)	1.3 (1.1–1.5)
Triglycerides (mg/dl)	1.5 (1.3–1.8)	1.8 (1.5–2.1)
Smoking ever (yes/no)	0.7 (0.5–1.1)	0.8 (0.5–1.2)

*For continuous variables, ORs are per change in 1 SD; †insulin resistance = 1/estimated glucose disposal rate (EGDR), where EDGR = 24.31 − 12.22 (WHR) − 3.29 (hypertension) − 0.57 (HbA_{1c}) (27).

DISCUSSION

This study confirms earlier reports from the U.K. (15) showing that type 1 diabetes reduces the gender difference in CAC, or that type 1 diabetes has a greater effect on calcification in women than in men. In the British study, the gender difference in CAC was absent in patients with type 1 diabetes, whereas in CACTI the age-adjusted OR for CAC in men versus women with type 1 diabetes was 2.5. The factors explored in the British study had little effect in explaining the gender-diabetes interaction. In CACTI, men had higher estimated insulin resistance, more abdominal fat, higher WHR and waist circumference, and higher LDL and lower HDL cholesterol than women among both patients with type 1 diabetes and nondiabetic control subjects. The factors that contribute to the gender difference in calcification in the control population may be different from those in patients with diabetes. However, in CACTI, estimated insulin resistance assessed according to the equation developed by the EDC Study, LDL and HDL cholesterol, as well as body fat distribution, and each substantially explained the gender difference in CAC in control subjects and abolished the already reduced gender difference in calcification in subjects with diabetes (Table 4). In addition, type 1 diabetes had an unfavorable effect on fat distribution in women but not in men, while the beneficial lipid profile with type 1 diabetes was less pronounced in women than in men (Table 1). Therefore, on adjustment for either waist, WHR, visceral fat, or LDL and HDL cholesterol, the significant diabetes-by-gender interaction on coronary calcification disappeared (Fig. 3). The effect of WHR on the diabetes-by-gender interaction was not accounted for by BMI.

Recent studies have suggested that insulin resistance, relatively newly documented in type 1 diabetes (20–23), may contribute to the increased CAD risk in these patients (24–26,28). Excess coronary calcification has been reported in subjects with impaired glucose tolerance and insulin resistance (19). Our cross-sectional data show that estimated insulin resistance is independently associated with coronary calcification in patients with type 1 diabetes and substantially explains the gender difference in CAC in patients with type 1 diabetes and nondiabetic control

TABLE 4
Effects of gender (men vs. women) on CAC prevalence (CAC >0 vs. CAC = 0), adjusted for covariates by logistic regression in patients with type 1 diabetic and nondiabetic control subjects

Model	Participants		Covariates	OR (95% CI)	
	Type 1 diabetic	Control		Type 1 diabetic	Control
1	610	763	Age, LDL and HDL cholesterol, smoking, diabetes duration*	2.2 (1.5–3.3)	2.7 (1.7–4.2)
2	606	753	Model 1 + insulin resistance	1.8 (1.2–2.7)	2.1 (1.3–3.4)
3	607	755	Model 1 + HbA_{1c}	2.3 (1.5–3.4)	2.6 (1.6–4.1)
4	610	763	Model 1 + hypertension	2.2 (1.4–3.3)	2.5 (1.6–4.0)
5	606	753	Model 1 + WHR	1.3 (0.8–2.1)	2.1 (1.2–3.7)
6	606	753	Model 1 + waist	1.7 (0.9–2.7)	2.7 (1.5–4.8)
7	604	762	Model 1 + IAF L23	1.4 (0.9–2.3)	1.9 (1.2–3.2)
8	603	760	Model 1 + Hb_{1c}, hypertension, waist, IAF L23	1.5 (0.9–2.5)	2.7 (1.5–4.9)

*Diabetes duration only included in models involving patients with type 1 diabetes.

subjects. Most of this effect is accounted for by the WHR, a component of the equation used to estimate insulin resistance (27) and a measure of abdominal fat (29). Visceral fat accumulation has been associated with reduced HDL cholesterol and raised LDL cholesterol, hypertension, and insulin resistance (30). Although the difference in WHR could statistically explain the gender difference in CAC, it may simply represent another way of determining sex. However, this explanation does not account for the association between WHR and CAC within each sex group or the fact that the association is independent of sex, in both patients with type 1 diabetes and control subjects.

In CACTI, type 1 diabetes was associated with adverse features related to central adiposity (higher WHR, larger waist circumference, and more intra abdominal fat) in women but not in men, i.e., women with type 1 diabetes had a more android deposition of adipose tissue (Table 1). By contrast, men with type 1 diabetes had lower WHR and IAF than nondiabetic men. The CACTI data therefore suggest that the diabetes-associated increase in coronary calcification, and possibly in CAD, may be accounted for by different factors, or may follow somewhat different pathways, in women than in men.

An inverse relationship between glycemic control and insulin sensitivity has been demonstrated in type 1 diabetes (31). CACTI patients had a fair glycemic control, as determined by an HbA_{1c} mean of 7.8 ± 1.2. Whether there is a threshold in HbA_{1c} levels associated with impaired hepatic insulin sensitivity, whether less than optimal glycemic control over a period of time longer than that determined by a single measurement contributes more to impaired insulin action, and whether these relationships are similar in men and women, is still unknown.

This study is larger than previous reports concerning coronary calcification in type 1 diabetes and includes a sizable nondiabetic control population. We obtained consistent results with different measures of central adiposity, with HDL and LDL cholesterol, with different calcification cut points, and with different statistical approaches. Nevertheless, our report has several important limitations. This is a cross-sectional association phase of the study and any inferences concerning causality have to await confirmation during prospective follow-up of the cohorts. Also, no direct assessment of insulin resistance is available for the study participants that would be reliable and valid in both type 1 diabetic patients and nondiabetic control subjects. Existing validated measures of insulin sensitivi-

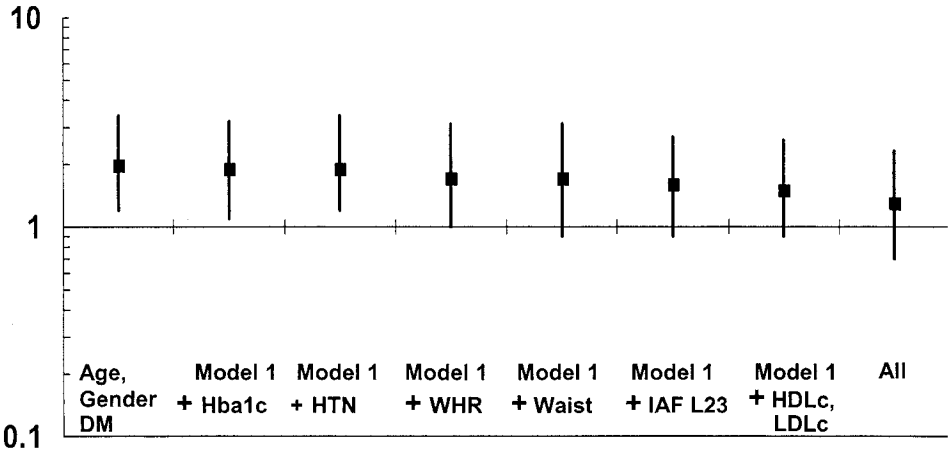

FIG. 3. OR for diabetes-associated CAC in women relative to men. The effect of adjustment for covariates on the increased odds for calcification associated with diabetes in women versus men (diabetes-by-gender interaction). ORs and 95% confidence intervals are plotted for eight different models on a logarithmic scale. *OR for CAC >0. Covariates: model 1 = age, gender (men/women), diabetes (yes/no), and diabetes-by-gender interaction; model 2 = model 1 + HbA_{1c}; model 3 = model 1 + hypertension; model 4 = model 1 + WHR; model 5 = model 1 + waist; model 6 = model 1 + IAF L23; model 7 = model 1 + HDL and LDL cholesterol; model 8 = age, gender, diabetes, diabetes-by-gender interaction, HDL and LDL cholesterol, IAF l23, and HbA_{1c}.

ty/resistance such as euglycemic clamps or the insulin-boosted minimal model are not practical for large epidemiological studies. The estimated glucose disposal rate used in this study is an equation derived from euglycemic-hyperinsulinemic clamp studies performed on subjects with type 1 diabetes, which was significantly related to measured glucose disposal rate ($r = 0.64$) (27). However, it is hard to evaluate to what extent the formula measures insulin resistance in other cohorts of patients with type 1 diabetes. The equation has not been validated in nondiabetic control subjects, and any comparison of insulin resistance between the two groups in this study should be made carefully. WHR, although a component of the equation and reportedly a marker of insulin resistance in the general population (32), is primarily a measure of abdominal fat. While both men and women with type 1 diabetes had higher estimated insulin resistance than nondiabetic control subjects, diabetes was associated with lower central adiposity in men. Whether type 1 diabetic men and women are more insulin resistant than nondiabetic control subjects and whether this is the reason for their increased coronary calcification remains to be answered.

Similar to previous studies (15), the CACTI study excluded individuals with diagnosed CAD at entry. If CAD is undetected more often in women than in men, the exclusion of individuals with known CAD may have resulted in an underestimate of the gender difference in CAC prevalence in both type 1 diabetic and nondiabetic CACTI participants.

The validity of CAC as a measure of plaque burden in the general population is well established (9). There is concern that some of the signal detected by EBCT in type 1 diabetes represents medial rather than intimal calcification. Although pathology studies suggest that calcification in coronary arteries primarily involves the intimal layer (33), more research is needed to assess the potential of EBCT to discriminate between medial and intimal calcification in diabetes. Importantly for this study, however, coronary calcification has been shown to be related to coronary atherosclerosis on autopsy similarly in men and women (8,34).

In conclusion, the CACTI study has shown that type 1 diabetes increases the prevalence and the severity of coronary calcification and reduces the gender difference in CAC. Gender differences in insulin resistance–associated fat deposition, and HDL and LDL cholesterol distribution may explain why diabetes increases coronary calcification and likely coronary artery disease, in women relatively more than in men.

ACKNOWLEDGMENTS

Support for this study was provided by the National Heart, Lung and Blood Institute (National Institutes of Health/NHLBI R01 HL61753), the Adult General Research Center (National Institutes of Health M01 RR00051), and Diabetes and Endocrinology Research Center Clinical Investigation Core (P30 DK57516).

This study was performed at the Adult General Research Center at the University of Colorado Health Sciences Center, at the Barbara Davis Center for Childhood Diabetes in Denver, Colorado, at the Colorado Heart Imaging Center in Denver, Colorado.

REFERENCES

1. Kanel WB, McGee DL: Diabetes and cardiovascular disease: the Framingham Study. *JAMA* 241:2035–2038, 1979
2. Pyorala K, Laakso M, Uusitupa M: Diabetes and atherosclerosis: an epidemiologic view. *Diabete Metab Rev* 3:463–524, 1987
3. Krolewski AS, Kosinski EJ, Warram JH, Leland OS, Busick EJ, Asmal AC, Rand LI, Christlieb AR, Bradley RF, Kahn CR: Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. *Am J Cardiol* 59:750–755, 1987
4. Lloyd CE, Kuller LH, Ellis D, Becker DJ, Wing RR, Orchard TJ: Coronary artery disease in IDDM: gender differences in risk factors but not risk. *Arterioscler Thromb Vasc Biol* 16:720–726, 1996
5. Jensen T, Borch-Johnsen K, Kofoed-Enevoldsen A, Deckert T: Coronary heart disease in young type 1 (insulin-dependent) diabetic patients with and without diabetic nephropathy: incidence and risk factors. *Diabetologia* 30:144–148, 1987
6. American Diabetes Association: Consensus Development Conference on the Diagnosis of Coronary Heart Disease in People with Diabetes. *Diabetes Care* 21:1151–1159, 1998
7. Detrano RC, Doherty TM, Davies MJ, Stary HC: Predicting coronary events with coronary calcium: pathophysiologic and clinical problems. *Curr Probl Cardiol* 25:374–402, 2000
8. Rumberger JA, Sheedy PF, Breen JF, Schwartz RS: Electron-beam computed tomographic coronary calcium score cut-points and severity of associated angiographic lumen stenosis. *J Am Coll Cariol* 29:1542–1548, 1997
9. Rumberger JA, Brundage BH, Rader DJ, Kondos G: Electron-beam computed tomographic coronary calcium scanning: a review and guidelines for use in asymptomatic persons. *Mayo Clin Proc* 74:243–252, 1999
10. Arad Y, Sapardo LA, Goodman K, Lleo-Perez A, Scherman S, Lerner G, Guerci AD: Predictive value of electron-beam computed tomography of the coronary arteries: 19-month follow-up of 1173 asymptomatic subjects. *Circulation* 93:1951–1953, 1996
11. Hosoi M, Sato T, Yamagami K, Hasegawa T, Yamakita T, Miyamoto M, Yoshioka K, Tamamoto T, Ishi T, Tanaka S, Itoh A, Haze K, Fujii S: Impact of diabetes on coronary stenosis and coronary artery calcification detected by electron-beam computed tomography in symptomatic patients. *Diabetes Care* 25:696–701, 2002
12. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD: Prediction of coronary events with electron-beam computed tomography. *J Am Coll Cardiol* 36:1253–1260, 2000
13. Raggi P, Callister TQ, Cooil B, He ZX, Lippolis NJ, Russo DJ, Zelinger A, Mahmarian JJ: Identification of patients at increased risk of unheralded acute myocardial infarction by Electron-Beam Computed Tomography. *Circulation* 101:850–855, 2000
14. Olson JC, Edmundowicz D, Becker DJ, Kuller LH, Orchard TJ: Coronary calcium in adults with type 1 diabetes: a stronger correlate of clinical coronary artery disease in men than in women. *Diabetes* 49:1571–1578, 2000
15. Colhoun HM, Rubens MB, Underwood R, Fuller JH: The effect of type 1 diabetes mellitus on the gender difference in coronary artery calcification. *J Am Coll Cardiol* 36:2160–2167, 2000
16. Colhoun HM, Otvos JD, Rubens MB, Taskinen MR, Underwood SR, Fuller JH: Lipoprotein subclasses and particle size and their relationship with coronary artery calcification in men and women with and without type 1 diabetes. *Diabetes* 51:1949–1965, 2002
17. Colhoun HM, Scheek LM, Rubens MB, Van Gent T, Underwood SR, Fuller JH, Van Tol A: Lipid transfer protein activities in type 1 diabetic patients without renal failure and nondiabetic control subjects and their association with coronary artery calcification. *Diabetes* 50:652–659, 2001
18. Arad Y, Newsteun D, Cadet F, Roth M, Guerci AD: Association of multiple risk factors and insulin resistance with increased prevalence of asymptomatic coronary artery disease by an Electron-Beam Computed Tomography Study. *Arterioscler Thromb Vasc Biol* 21:2051–2058, 2001
19. Meigs JB, Larson MG, D'Agostino RB, Levy D, Clouse ME, Nathan DM, Wilson PWF, O'Donnell CJ: Coronary artery calcification in type 2 diabetes and insulin resistance: the Framingham Offspring Study. *Diabetes Care* 25:1313–1319, 2002
20. DeFronzo RA, Simson D, Ferrannini E: Hepatic and peripheral insulin resistance: a common feature of type 2 (non-insulin-dependent and type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 23:313–319, 1982

21. De Fronzo RA, Hendler R, Simonson D: Insulin resistance is a prominent feature of insulin-dependent diabetes. *Diabetes* 31:795–801, 1982
22. Greenbaum CJ: Insulin resistance in type 1 diabetes. *Diabete Metab Res Rev* 18:192–200, 2002
23. Orchard TJ, Chang YF, Ferrell RE, Petro N, Ellis DE: Nephropathy in type 1 diabetes: a manifestation of insulin resistance and multiple genetic susceptibilities? Further evidence from the Pittsburgh Epidemiology of Diabetes Complication Study. *Kidney Int* 62:963–970, 2002
24. Erbey JR, Kuller LH, Becker DJ, Orchard TJ: The association between a family history of type 2 diabetes (NIDDM) and coronary artery disease in a type 1 diabetes (IDDM) population. *Diabetes Care* 21:610–614, 1998
25. Forrest KTZ, Becker DJ, Kuller LH, Wolfson SK, Orchard TJ: Are predictors of coronary heart disease and lower extremity arterial disease in type 1 diabetes the same? A prospective study. *Atheroclerosis* 148:159–169, 2000
26. Olson JC, Erbey JR, Williams KV, Becker DJ, Edmundowicz D, Kelsey SF, Tyrrell KS, Orchatrd TJ: Subclinical atheroclserosis and estimated glucose disposal rate as predictors of mortality in type 1 diabetes. *Ann Epidemiol* 12:331–337, 2002
27. Williams KV, Erbey JR, Becker D, Arslanian S, Orcahrd TJ: Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes* 40:626–623, 2000
28. Martin FIR, Hopper JL: The relationship of acute insulin sensitivity to the progression of vascular disease in long-term type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 30:149–153, 1987
29. Peiris AN, Hennes MI, Evans DJ, Wislon CR, Lee MB, Kissebach AH: Relationship of the anthropometric measurements of body fat distribution to metabolic profile in premenopausal women. *Acta Med Scand Suppl* 723:179–188, 1988
30. Després J-P, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C: Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. *Arteriosclerosis* 10:497–511, 1990
31. Yki-Järvinen H, Koivisto VA: Natural course of insulin resistance in type 1 diabetes. *N Engl J Med* 315:224–230, 1986
32. Pedersen SB, Borglum JD, Schmitz O, Bak JF, Sorensen NS, Richelsen B: Abdominal obesity is associated with insulin resistance and reduced glycogen synthetase activity in skeletal muscle. *Metabolism* 42:998–1005, 1993
33. Burke AP, Weber DK, Kolodgie FD, Farb A, Taylor AJ, Virmani R: Pathophysiology of calcium deposition in coronary arteries. *Herz* 26:239–244, 2001
34. Kajinami K, Seiki H, Takekoshi N, Mabuchi H: Coronary calcification and coronary atherosclerosis: site by site comparative morphologic study of electron-beam computed tomography and coronary angiography. *Am J Cardiol* 25:76–82, 1995