Original Article

Relationship of Traditional and Nontraditional Cardiovascular Risk Factors to Coronary Artery Calcium in Type 2 Diabetes

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We evaluated correlates of coronary atherosclerosis, measured by coronary artery calcium, in a racially diverse group of male and female subjects with type 2 diabetes. Age, systolic blood pressure, sex, and race/ethnicity were significant determinants of coronary artery calcium. Among lipoproteins, cholesterol level contained in a particle excluded from direct measures of LDL and HDL cholesterol (designated triglyceride-rich lipoprotein cholesterol) was most strongly linked to coronary artery calcium. Neither inflammatory markers nor metabolic factors correlated with coronary artery calcium in models adjusted for age and sex, but measures of adipose distribution did. Waist-to-hip ratio and the ratio of visceral to total abdominal tissue were positively associated with coronary artery calcium. In fully adjusted multivariate models, the relationship of adiposity measures to coronary artery calcium was no longer significant after inclusion of apolipoprotein B or triglyceride-rich lipoprotein cholesterol. Traditional risk factors and race/ethnicity remain important correlates of coronary artery calcium in a cohort at elevated risk of cardiovascular disease because of type 2 diabetes. Adiposity measures are significantly associated with coronary artery calcium score, but their importance may be largely explained by apolipoprotein B or triglyceride-rich lipoprotein cholesterol. *Diabetes* 56:849–855, 2007

Patients with diabetes have a markedly increased risk of myocardial infarction and cardiovascular death due to accelerated coronary atherosclerosis (1). The pathophysiology leading to accelerated atherosclerosis in patients with diabetes is multifactorial and incompletely defined. For example, it has been suggested that traditional cardiovascular risk factors (age, systolic blood pressure [sBP], smoking, lipids) do not completely account for the increased cardiovascular mortality in patients with diabetes, and novel approaches are being sought to address additional factors that could contribute to accelerated atherosclerosis in diabetes (2–4).

The increased atherosclerosis seen in patients with diabetes is reflected in increased coronary artery calcium (CAC) measured by electron beam tomography (5,6). CAC is a measure of total coronary atherosclerotic burden that has been validated by autopsy and coronary angiography (7,8). In large studies, CAC has been found to be a significant predictor of cardiovascular events in symptomatic and asymptomatic subjects (9,10). In subjects with type 1 diabetes, CAC is an independent correlate of myocardial infarction and obstructive coronary artery disease (11). The amount of CAC has also been shown to correlate well with the amount of atheromatous plaque in patients with type 2 diabetes (12).

According to current formulations, cardiovascular events require a vessel wall diseased with atheromatous plaque along with superimposed plaque rupture and thrombosis. The detection and quantitation of coronary atherosclerosis by electron beam tomography in patients before cardiovascular events can be a powerful tool for identifying genetic and pathophysiological factors associated with atherosclerotic vascular disease separate from those factors producing plaque rupture and/or thrombosis (13,14). In this study, we evaluated lipoprotein, inflammatory, and metabolic correlates of CAC in a group of well-characterized subjects with type 2 diabetes and asymptomatic for coronary artery disease. We focused on a panel of factors found to be predictive of coronary atherosclerosis or coronary events in nondiabetic cohorts.

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apo, apolipoprotein; CAC, coronary artery calcium; CACS, coronary artery calcium score; sBP, systolic blood pressure; TAT, total abdominal adipose tissue; TRL, triglyceride-rich lipoprotein; VAT, visceral adipose tissue; WHR, waist-to-hip ratio.

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RESEARCH DESIGN AND METHODS

Study description. CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone) is a multicenter randomized 18-month clinical study comparing the effects of pioglitazone versus glimepiride on measures of atherosclerotic disease and biochemical indexes of cardiovascular risk. A secondary end point of this trial includes change in coronary artery calcium score (CACS). The information reported in this article represents a cross-sectional analysis of baseline information.

Eligible subjects were men and women 45–85 years of age, with a diagnosis of type 2 diabetes (based on American Diabetes Association diagnostic criteria). Subjects could be newly diagnosed with type 2 diabetes, diet controlled, or taking sulfonylurea or metformin monotherapy, or sulfonylurea-metformin combination therapy, or insulin. A1C levels ≥6.5 and <9% were permitted if taking hypoglycemic medication, or ≥6.5 and <10% if not on hypoglycemic medication. Subjects were excluded from the study if they had type 1 diabetes, symptomatic coronary artery, cerebrovascular, or peripheral vascular disease; if they were taking a thiazolidinedione medication within 12 weeks of randomization; or if they were discontinued from thiazolidinedione or sulfonylurea therapy because of a lack of efficacy or clinical or laboratory signs of intolerance. Subjects with New York Heart Association class 3 or 4 cardiac failure, left ventricular dysfunction (left ventricular ejection fraction <40%), serum alanine transaminase >2.5 the upper limit of normal, elevated serum creatinine, triglyceride level >500 mg/dl, unexplained microscopic hematuria, a body weight of >300 lb or a BMI >45 kg/m^2, uncontrolled hypertension, or significant cardiac valvular disease or who were anticipating an invasive cardiac intervention were also excluded. For those subjects started on statin medication at the screening visit for the trial, baseline data were collected 4 weeks after addition of this medication. The study protocol was approved by local review committees, and all subjects provided written informed consent.

Analytical methods. The following analyses on fasting samples were performed by clinical reference laboratory (CRL, Lenexa, KS): triglycerides, total cholesterol, and fasting plasma glucose in blood samples using standard enzymatic methods (Roche Diagnostics, Indianapolis, IN); HDL and LDL cholesterol by direct methods (HDL cholesterol plus and LDL cholesterol plus kits; Roche Diagnostics, Indianapolis, IN); free fatty acid by the Wako enzymatic method (Wako Chemicals, Richmond, VA); apolipoprotein (apo)-B and apoA1 by immunoturbidimetry (Hitachi/Roche Diagnostics, Basel, Switzerland); A1C by high-performance lipid chromatography (Bio-Rad, Hercules, CA); human insulin by enzyme-linked immunosorbent assay (Linco, St. Charles, MO); high sensitive C-reactive protein by immunoturbidimetry (Roche Diagnostics); lipoprotein-associated phospholipase A_2 by enzyme immunoassay (Dia-Dexus, South San Francisco, CA); and intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). HOMA2-IR was calculated using fasting plasma insulin and glucose values as described (15). Subjects using insulin were excluded from HOMA2-IR calculations. Because total, LDL, and HDL cholesterol were directly measured in fasting plasma, it was possible to calculate the amount of cholesterol not contained in LDL or HDL particles (total cholesterol minus LDL cholesterol minus HDL cholesterol), and this was designated triglyceride-rich lipoprotein (TRL) cholesterol.

All electron beam tomography measurements were done on the same machine by a single operator. Measurement of CAC was performed as previously described in detail (6). Briefly, two sets of 20 transverse 3-mm-thick slices were obtained in an axial fashion to image the entire heart using a C150 scanner (GE Imatron, South San Francisco, CA), using electrocardiographic triggering at 60–80% of the electrocardiogram R-R wave (ECG-RR) interval. The CAC was measured with a densitometric program available in the Imatron scanner. Areas of increased density overlying coronary arteries were evaluated. Lesions were scored with calcium, defined as present if found in at least two contiguous pixels where the attenuation was 130 Houndsfield units or more. The CACS was calculated using the Agatston method. Measurement of abdominal adipose tissue distribution was accomplished using a C-150 electron beam tomography scanner. The scan was performed at the L4-L5 vertebrate, and a single 3- to 6-mm slice was taken during suspended respiration after normal expiration. Total abdominal adipose tissue (TAT) area is calculated by delineating body surface with a region-of-interest tool and then computing the adipose tissue area with an attenuation range of −190 to −30 Houndsfields units. Visceral adipose tissue (VAT) area is quantified by delineating the abdominal cavity at the external-most aspect of the abdominal wall (transversalis fascia) and the posterior aspect at the vertebral body.

Statistical methods. Statistical analyses were performed using R version 2.3.0. Descriptive statistics were used to summarize subject characteristics by sex. Relationships of independent variables to coronary artery calcium were modeled using a Tobit analysis of log (CACS + 1) (16). We initially fit a model with base model factors including age, sex, and race/ethnicity. An expanded base model including these factors plus sBP, hypertension (defined as sBP >130 mmHg or on antihypertensive medication), smoking status, LDL cholesterol, and hyperlipidemia (defined as LDL cholesterol >3.4 mmol/l or on statin medication). To determine the significance of additional lipid and apolipoprotein factors (HDL cholesterol, triglycerides, TRL cholesterol, apoA1 and apoB, and total cholesterol/HDL ratio), we entered them one at a time into the expanded base model. Additional putative factors were organized by domain as follows: anthropometric measures: TAT, VAT, VAT-to-TAT ratio, waist circumference, waist-to-hip ratio (WHR), BMI; metabolic measures: A1C, log(HOMA-IR), free fatty acid level, duration of diabetes; and inflammatory markers: log(high sensitive C-reactive protein), log(intercellular adhesion molecule-1), log(vascular cell adhesion molecule-1), log(lipoprotein-associated phospholipase A_2). Each of these was added one at a time to a model adjusted for age and sex. Finally, beginning with age and sex in the model, we used forward- and backward-stepwise procedures to identify which factors remained significantly associated with CACS in a fully adjusted multivariate model. We compared models using likelihood ratio tests. Significance was set at 0.05. Nonparametric, bias-corrected, and accelerated bootstrap CIs (using 10,000 resamples) were constructed for estimates in Table 6 to confirm model-based estimates. The total number of subjects admitted to the study was 462. A total of 23 were missing baseline CAC score. Therefore, 439 subjects were available for analysis: 162 women and 277 men.

RESULTS

Table 1 presents characteristics of study subjects by sex. As shown, the average age was 59–60 years, and average blood pressure was at target level for subjects with diabetes, with the majority of subjects taking anti-hypertension medications. Median duration of known diabetes was 5 years. Subjects were obese with median BMIs ranging from 31 to 32 kg/m^2 and waist circumferences from 40 to 42 inches. Subjects were insulin resistant as demonstrated by an elevated HOMA2-IR of 2.5–2.6 (~40% of normal insulin sensitivity). Only a small minority of subjects were current smokers. A small number (<10%) of subjects had a statin medication added at the screening visit for the study; approximately half of the subjects were already taking statin drugs at initial screening. LDL cholesterol levels exceeded the target of 2.5 mmol/l by a modest degree in both sexes. Glycemic control approached American Diabetes Association A1C targets, with values of 7.1% in females and 7.2% in males. Only 12% of subjects used insulin.

Race/ethnicity was initially divided as Caucasian, African-American, Hispanic American, Oriental, or "Other." If subjects self-identified as Hispanic ethnicity, they were included only in this category. Those subjects who self-identified as "Other" were allowed to write in a description, and all of these were Asian. Therefore, the Oriental and "Other" categories were pooled into an Asian group. Of the 33 subjects in this category, 10 indicated Oriental, 4 only Asian, 1 Indian-Asian, 14 Indian, 1 Pakistani, and 3 Western Asian. A box plot of CACS for sex and ethnicity, showing median, 25th and 75th percentile, and 1.5× the interquartile range, is shown in Fig. 1. The results show that Caucasian and Asian categories have higher median CACS than African-Americans and Hispanics for both men and women. Race/ethnicity differences are larger in women. The prevalence data for CAC (% CAC >0) gave similar results; Caucasian and Asian groups had higher prevalence of CAC compared with African-Americans and Hispanics in subjects of both sexes (not shown).

Because of the larger number of Caucasians and African-Americans in the cohort, additional analyses were restricted to these groups. Table 2 shows the results of a multivariate analysis including age, sex, and race/ethnicity. All were important determinants of CACS. Table 3 adds sBP, hypertension, smoking status, LDL cholesterol,

TABLE 1
Characteristics of study participants by sex

	Female	Male
n	162	277
Numerical		
Age (years)	60 ± 8	59 ± 8
sBP (mmHg)	130 ± 14	130 ± 13
dBP (mmHg)	77 ± 8	78 ± 8
Ordered		
Duration of diabetes (years)	5.0 (2.3–10)	5.2 (2.3–9.5)
LDL (mmol/l)	2.9 (2.4–3.4)	2.7 (2.2–3.3)
Triglycerides (mmol/l)	1.5 (1.1–2.3)	1.8 (1.2–2.4)
HDL (mmol/l)	1.3 (1.1–1.5)	1.1 (0.9–1.2)
TRL cholesterol*	0.6 (0.4–0.9)	0.7 (0.5, 1.0)
Total cholesterol–to–HDL ratio	3.7 (3.1–4.5)	4.2 (3.5–4.9)
ApoB (g/l)	0.86 (0.73–0.97)	0.84 (0.70–1.00)
ApoA1 (g/l)	1.4 (1.3–1.6)	1.3 (1.1–1.4)
Fasting plasma glucose (mmol/l)	7.6 (6.1–9.2)	7.8 (6.6–9.8)
Fasting insulin (pmol/l)	120 (90–170)	130 (96–200)
A1C (%)	7.1 (6.7–8.1)	7.2 (6.7–8.0)
Waist (in)	40 (37–44)	42 (39–47)
BMI (kg/m^2)	32 (28–38)	31 (28–35)
HOMA2-IR	2.5 (1.8–3.2)	2.6 (1.9–3.8)
Categorical		
Insulin user	20 (12)	33 (12)
Smoking status		
Never-smoker	72 (45)	96 (35)
Ex-smoker	70 (44)	129 (47)
Current smoker	17 (11)	49 (18)
Statin prescribed at enrollment	19 (12)	29 (10)
Statin drugs before enrollment	77 (48)	141 (51)
Hyperlipidemic (LDL cholesterol ≥3.4 mmol/l or on statin medication)	122 (75)	200 (72)
Hypertension drugs at enrollment	115 (71)	175 (63)
Hypertensive (sBP ≥130 mmHg or on anti-hypertensive medication)	140 (86)	236 (85)
Race/ethnicity		
Caucasian	75 (46)	161 (58)
African-American	63 (39)	63 (23)
Hispanic	15 (9)	29 (10)
Asian	9 (6)	24 (9)

Data are means ± SD, medians (25th to 75th percentile), or *n* (%). *P* values were calculated using pooled *t* test for numerical, Mann-Whitney for ordered, or Pearson's χ^2 for categorical variables. *TRL cholesterol was calculated by subtracting the directly measured values for LDL and HDL cholesterol from total cholesterol. dBP, diastolic blood pressure.

and hyperlipidemia to the model. sBP was significantly related to CACS, and each 10-mmHg increase in sBP was associated with a 67% increment in CACS. Past or current smoking was associated with an increase in CACS, with the latter producing the larger increase; however, these differences did not reach statistical significance compared with never-smokers. Neither LDL cholesterol nor hyperlipidemia (based on LDL cholesterol or statin use) was significantly associated with CACS; this is most likely related to the history of statin use in the majority of subjects. In the expanded base model, age, sex, and race/ethnicity remained important correlates of CACS. Evaluation of baseline hyperglycemic medication use (divided as metformin only, sulfonylurea only, metformin plus sulfonylurea, or insulin plus oral agents) demonstrated no significant relationship to CACS (not shown).

In Table 4, we considered additional lipid and lipoprotein parameters added one at a time to the expanded base model for relationship to CAC. Increased HDL cholesterol was associated with less CAC with a trend toward significance. ApoA1 was not significantly associated with CAC. Increased triglycerides and increased apoB were each significantly associated with increased CACS. Because both LDL and HDL cholesterol were directly measured, a calculation of the fraction of total cholesterol not contained in LDL or HDL particles was possible (total cholesterol minus HDL cholesterol minus LDL cholesterol), designated as TRL cholesterol in Table 4. Increasing levels of TRL cholesterol were highly associated with increased CAC. The correlation between TRL cholesterol and apoB was 0.25. The partial correlation of TRL cholesterol and apoB after adjustment for LDL cholesterol was 0.52. The

TABLE 2
Multivariate analysis showing percentage increase in CACS for all subjects for base model measures: age, race, and sex

	P	% Difference	95% CI
Age (5 years)	<0.0001	130	81–180
Sex (M)*	<0.0001	730	290–1,700
Race/ethnicity*	<0.0001		
Caucasian		490	170–1,200

Results are expressed in terms of percentage differences between two subjects who are similar with the exception of the characteristic for the given row. *Reference group for race/ethnicity is African-American and for sex is female.

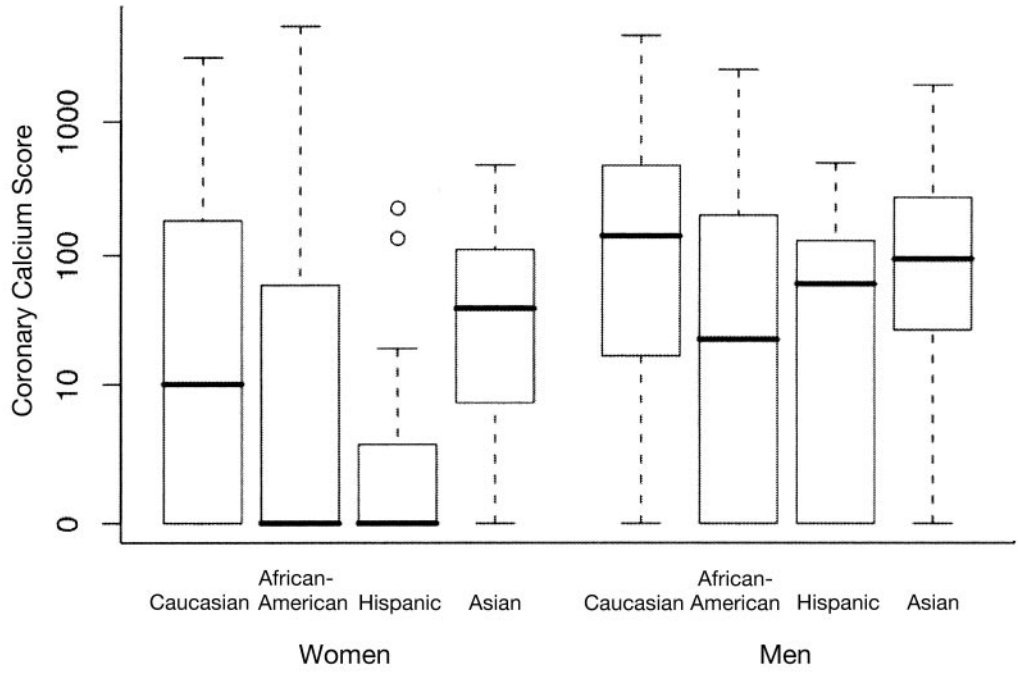

FIG. 1. Box plots of CACS by sex and race/ethnicity. Values shown are the median, 25th and 75th percentiles, and 1.5× the interquartile range for each group.

total cholesterol–to–HDL cholesterol ratio was also significantly associated with CACS. When all lipid/lipoprotein fractions were allowed to enter the model together, only TRL cholesterol retained a significant relationship to CACS. Statin use was not significantly associated with CAC either in the expanded base model or in the expanded base model plus lipid/lipoprotein factors.

Next, a panel of anthropometric, inflammatory, and metabolic factors were assessed for their relationship to CAC in models adjusted for age and sex (Table 5). None of the inflammatory or metabolic factors correlated with CAC in type 2 diabetes in adjusted models. Several anthropometric measures (TAT, VAT, VAT-to-TAT ratio, and WHR) were significantly associated with a higher CACS. Both VAT-to-TAT ratio and WHR were correlated with CAC over a restricted range, with limited association in those subjects with the highest ratios (not shown). For the results in Table 5, there were no significant interactions for race/ethnicity. Adding interaction terms for both race/ethnicity and sex gave significant interactions for VAT and WHR and suggested these may play a more important role in African-American women (not shown).

We next included the expanded base model (Table 3), additional lipoprotein factors (Table 4), inflammatory markers, metabolic factors, and anthropometric measures (Table 5) in an analysis to identify factors significantly related to CAC. The results are shown in Table 6. Age, sex, sBP, and race/ethnicity remain significantly associated with CAC in the fully adjusted model. The only other measure with a significant relationship to CAC in the fully adjusted model was TRL cholesterol. Refitting the model without TRL cholesterol allowed apoB to enter the model with a P value of 0.007. Refitting the model without TRL cholesterol or apoB allowed VAT-to-TAT ratio to enter the model with a P value of 0.028. There were no significant interactions with race/ethnicity or sex for the analysis in Table 6.

TABLE 3
Expanded base model correlates of CACS

	P	% Difference	95% CI
Age (per 5 years)	<0.0001	100	59–160
Sex (M)	<0.0001	780	310–1,800
Race/ethnicity*	<0.0001		
Caucasian		480	160–1,200
sBP (per 10 mmHg)	0.002	67	21–130
Hypertension†	0.25	99	−38–550
Smoking status	0.29		
Past		66	−24–260
Current		110	−28–530
LDL cholesterol (per 0.5 mmol/l)	0.43	9	−12–36
Hyperlipidemia‡	0.34	51	−35–250

Results are expressed in terms of percentage differences between two subjects who are similar with the exception of the characteristics for the given row. *Reference group is African-American. †Hypertension is defined as an sBP >130 mmHg or on antihypertensive medication. ‡Hyperlipidemia is defined as LDL cholesterol ≥3.4 mmol/l or on statin medication.

DISCUSSION

The accelerated atherosclerosis and increased risk of cardiovascular events in diabetes present important challenges. Pathophysiologically, there is an important need to understand the factors that accelerate atherosclerosis in diabetes. From a clinical perspective, more information is needed to determine if evaluating a large number of markers that have been proposed as "nontraditional" risk factors will improve detection of diabetic patients with more advanced vascular disease. Our results show that in subjects at high risk for cardiovascular disease because of type 2 diabetes, traditional cardiac risk factors (age, sex, and sBP) remain significantly associated with higher CAC. Smoking is also associated with increased CAC, but in our study did not reach statistical significance, perhaps be-

TABLE 4
Lipid/lipoprotein determinants of CACS

	P	% Difference	95% CI
HDL cholesterol (per 0.1 mmol/l)	0.09	−10	−20–2
ApoA1 (per 0.15 g/l)	>0.99	0	−19–24
Triglycerides (per 0.5 mmol/l)	0.01	20	4–38
ApoB (per 0.15 g/l)	0.00015	130	49–240
TRL cholesterol (per 0.3 mmol/l)	0.00011	55	24–94
Total cholesterol–to–HDL cholesterol ratio (per 0.7 change)	0.006	46	12–91

Results are expressed in terms of percentage differences between two subjects who are similar with the exception of the characteristic for the given row. Lipid/lipoprotein measures were added one at a time to the expanded base model shown in Table 3.

cause of the small number of smokers. Race is also an important correlate of CACS. Recently reported studies have also shown race/ethnicity to be important determinants of CAC in diabetic and nondiabetic subjects (17,18). In a study of diabetic subjects that included 126 Chinese Asians (18), Caucasian and Asian groups had a higher prevalence of CAC compared with African-Americans or Hispanic Americans. However, the prevalence of CAC and mean CACS were lower in Chinese Asians compared with Caucasians. The difference between these results and the results in this study regarding CAC in Asians could relate to the smaller number of Asian subjects available for analysis in our study or to the fact that our study included predominantly Western and Southern Asians.

With respect to lipids and lipoproteins, HDL cholesterol level was associated with less CAC with a trend toward statistical significance. Neither LDL cholesterol nor apoA1 was a significant correlate of CAC. LDL cholesterol as a target for reducing cardiovascular disease in diabetes has been validated in multiple studies, and the failure of LDL cholesterol to correlate with CACS in this cohort may relate to the high historical use of statins. However, it is of interest that in subjects with a high rate of statin use and LDL cholesterol levels close to 2.5 mmol/l, triglyceride, apoB, and TRL cholesterol level remained significant determinants of CAC. When all lipid and lipoprotein fractions were allowed to enter the models together, TRL cholesterol emerged as the only significant lipid/lipoprotein determinant of CAC. If lipid/lipoprotein models were refit without TRL cholesterol, only apoB entered as a significant correlate of CAC. The lipid fraction represented by TRL cholesterol in our study has not been evaluated in other large studies in which LDL cholesterol is usually calculated. A direct measurement of LDL cholesterol in our study (instead of its calculation using the Friedwald formula) allowed for an estimation of cholesterol contained in particles excluded by the HDL and LDL direct assays. Particles within this fraction are predominantly VLDL particles, but some portion of IDL will also be included. A number of recent large studies, however, do provide indirect support for the importance of a cholesterol-containing TRL particle for predicting cardiovascular disease by demonstrating the superiority of non-HDL cholesterol (which includes what we have designated as TRL cholesterol in our study plus LDL cholesterol) compared with LDL cholesterol for predicting cardiovascular events (19–21). Likewise, apoB has been found to be superior to LDL cholesterol for predicting cardiovascular events in subjects with diabetes (20).

An important finding of our study is that a panel of inflammatory and metabolic factors do not significantly associate with CAC in models adjusted for age and sex. Our data related to C-reactive protein is consistent with an emerging body of information indicating that C-reactive protein does not correlate with CAC in nondiabetic subjects, suggesting that each may make unique contributions to cardiovascular risk (22). In addition, neither metabolic factors nor duration of diabetes were significantly associated with CAC in our cohort. Patients may be asymptomatic for years with type 2 diabetes, and imprecision in determining the actual onset of diabetes may relate to the absence of a duration effect. The lack of influence of A1C on CAC differs from recent findings in type 1 diabetes (23). Insulin resistance, as measured by HOMA-IR, has been found to be an important correlate of CAC in nondiabetic

TABLE 5
Significance of nontraditional risk factors adjusted for age and sex

	P
Anthropometric	
TAT	0.01
VAT	0.02
VAT-to-TAT Ratio	0.001
Waist (inches)	0.12
WHR	0.04
BMI	0.90
Inflammatory markers	
log(high sensitive C-reactive protein)	0.74
log(intercellular adhesion molecule-1)	0.35
log(vascular cell adhesion molecule-1)	0.16
log(lipoprotein-associated phospholipase A_2)	0.57
Metabolic	
A1C	0.26
log(HOMA2-IR)	0.18
Free fatty acid	0.56
Duration of diabetes (years)	0.83

TABLE 6
Significant determinants of CACS. Variables considered in the model included the expanded base model in Table 3, lipoproteins from Table 4, and non-traditional factors in Table 5

	P	% Change (95% CI)
Age (per 5 years)	<0.001	120 (79–180)
SBP (per 10 mmHg)	0.005	47 (12–91)
Sex*	<0.0001	570 (220–1,300)
Race/ethnicity*	0.0001	
Caucasian		350 (110–870)
TRL-C (per 0.2 mmol/l)	<0.0006	30 (12–50)

*Reference group for race/ethnicity is African-American and for sex is female.

populations (24). However, in our cohort with type 2 diabetes, most of whom were insulin resistant, the measurement of HOMA-IR added no important information for level of CAC. Our study included measures of intra-abdominal obesity, and it is of interest that in a recent study of 1,160 predominantly nondiabetic subjects, inclusion of an intra-abdominal obesity measure eliminated HOMA2-IR as a significant correlate of CAC (25). In a recent report, various measures of obesity were associated with progression of CAC in a nondiabetic cohort at low risk for cardiovascular disease (26). In the current study of type 2 diabetic subjects, TAT, VAT, VAT-to-TAT ratio, and WHR correlated with CAC, but BMI and waist circumference did not.

In the multivariable analysis shown in Table 6, neither VAT-to-TAT ratio nor WHR entered the model as a significant determinant of CACS. However, a modified term for VAT-to-TAT ratio that took into account its contribution to CAC over a restricted range entered as a significant determinant when the model was refit without TRL cholesterol or apoB. This observation suggests that the association of VAT-to-TAT ratio with CAC is at least partially mediated by changes in apoB and/or TRL cholesterol levels. This observation also relates to information recently reported from the PREDICT trial (27). Significant factors correlating with CACS in type 2 diabetes in PREDICT study included WHR. Lipid parameters, including HDL cholesterol, LDL cholesterol, triglycerides, or non-HDL cholesterol did not associate with CACS; however, neither TRL cholesterol nor apoB was measured.

The major points of our study can be summarized as follows. In a large racially diverse group of male and female subjects at high risk for cardiovascular disease because of diabetes, traditional cardiac risk factors including age, male sex, and sBP remain important correlates of advanced CAC in models adjusted for a panel of lipid/lipoprotein, anthropometric, inflammatory, and metabolic factors. Among triglycerides, LDL cholesterol, HDL cholesterol, TRL cholesterol, apoB, and apoA1, only TRL cholesterol emerged as a significant independent correlate of CAC in a cohort with an LDL cholesterol level close to 2.5 mmol/l and a high rate of statin use. Race is an important determinant of CAC in subjects with type 2 diabetes, but race/ethnicity effects are much larger in women than in men. A panel of inflammatory and metabolic factors was not associated with CAC. In models adjusted for age and sex, measures of adipose tissue distribution were significantly associated with CACS. However, in fully adjusted multivariable models, the inclusion of lipid/lipoprotein measures reduced the significance of the relationship between adipose tissue distribution and CAC.

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NOTE ADDED IN PROOF

The complete description of the CHICAGO trial and its primary analysis have been published. See ref. 28.

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