

Coronary Artery Calcification in Type 2 Diabetes and Insulin Resistance

The Framingham Offspring Study

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OBJECTIVE — To assess risk for subclinical coronary atherosclerosis using electron beam-computed tomography in subjects with or without insulin resistance and with normal glucose tolerance (NGT) or impaired glucose tolerance (IGT/impaired fasting glucose [IFG]) or type 2 diabetes.

RESEARCH DESIGN AND METHODS — We categorized glucose tolerance by type 2 diabetes therapy (diagnosed diabetes) or with an oral glucose tolerance test (OGTT) (IFG, IGT, and OGTT-detected diabetes) and insulin resistance as an elevated fasting insulin level, in subjects attending the fifth examination (1991–1995) of the Framingham Offspring Study. A representative subset of subjects without clinical atherosclerosis was selected for electron beam computed tomography in 1998–1999 from age- and sex-stratified quintiles of the Framingham risk score. The presence of subclinical atherosclerosis was defined as the upper quartile of the Agatston score distribution (score >170). We assessed risk for subclinical atherosclerosis using multivariable logistic regression.

RESULTS — Of 325 subjects aged 31–73 years, 51% were men, 11.2% had IFG/IGT, and 9.9% had diabetes (2.8% with diagnosed diabetes); 14.5% had insulin resistance. Compared with NGT, subjects with IFG/IGT tended to be more likely (adjusted odds ratio 1.5, 95% CI 0.7–3.4) and those with diabetes were significantly more likely (2.7, 1.2–6.1) to have subclinical coronary atherosclerosis. In age- and sex-adjusted models, subjects with insulin resistance were more likely to have subclinical atherosclerosis than those without insulin resistance (2.1, 1.01–4.2), but further risk factor adjustment weakened this association. In adjusted models including insulin resistance, diabetes remained associated with risk for subclinical atherosclerosis (2.8, 1.2–6.7); diagnosed diabetes (6.0, 1.4–25.2) had a larger effect than OGTT-detected diabetes (2.1, 0.8–5.5).

CONCLUSIONS — Individuals with diabetes have an elevated burden of subclinical coronary atherosclerosis. Aggressive clinical atherosclerosis prevention is warranted, especially in diagnosed diabetes.

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Abbreviations: CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; EBCT, electron beam-computed tomography; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; OR, odds ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Type 2 diabetes is a potent risk factor for cardiovascular disease (CVD), including myocardial infarction, stroke, and intermittent claudication. However, the basis for excess risk for CVD in patients with diabetes remains incompletely defined. A greater prevalence of elevated established CVD risk factors (e.g., hypertension and low HDL cholesterol levels) as well as a greater prevalence of 'novel' CVD risk factors, including insulin resistance and insulin resistance syndrome-related features (e.g., central obesity, microalbuminuria, impaired fibrinolysis, and subclinical inflammation), are all likely to contribute to excess risk (1). However, elevated CVD risk factors may be present many years before diagnosis of diabetes, and clinical CVD is often present at the time of diagnosis of diabetes (2–4). These observations suggest that subclinical atherosclerosis develops as a consequence of the prediabetic metabolic milieu or that diabetes, insulin resistance, and CVD are all a mutual expression of a common pathogenic precursor state (5,6).

If type 2 diabetes and CVD arise from a common antecedent, there should be subclinical atherosclerosis in subjects with clinically undetected diabetes and subdiabetic glucose intolerance or with insulin resistance. It is reasonably well established that patients with diagnosed diabetes have a higher prevalence of subclinical atherosclerosis as assessed by carotid artery ultrasonography (4,7–9). However, data are inconsistent regarding the relationship between subclinical carotid atherosclerosis and subdiabetic or clinically undetected glucose intolerance (7,10–13) or measures of insulin resistance, including fasting hyperinsulinemia (7,14–16). Furthermore, data are scant on associations between glucose intolerance and subclinical atherosclerosis in other vascular beds, particularly the coronary arteries; few studies have focused only on subjects with diagnosed diabetes (17–20). In this study, we assessed subclinical atherosclerosis of the coronary ar-

teries using electron beam-computed tomography (EBCT) in a representative sample from a community-based cohort. Subjects had no CVD, were with or without insulin resistance, and were with or without impaired glucose tolerance (IGT) or type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study subjects

Study subjects were participants in the Framingham Offspring Study, a community-based observational study of risk factors for CVD (21). From January 1991 through June 1995 (examination cycle 5), a total of 3,799 participants fasted overnight, provided written informed consent, underwent standardized clinical examination, and provided fasting blood samples; subjects without diagnosed diabetes underwent an oral glucose tolerance test (OGTT). From subjects without prevalent CVD (including coronary heart disease [CHD], peripheral vascular disease, and stroke, as defined previously) (22), we selected a subsample for EBCT. The objective of the sampling scheme was to obtain a subgroup from the overall Framingham Offspring cohort representing the entire spectrum of atherosclerosis risk. We randomly recruited 13–15 men and women from strata defined by quartiles of the age distribution and quintiles of the Framingham CHD risk score. This score incorporates age, sex, blood pressure, smoking, total and HDL cholesterol, and diagnosed diabetes in estimating the 10-year risk for CHD events (23). We sampled twice as many subjects in the highest quintile of coronary risk score as in each of the lower quintiles. This scheme yielded 327 subjects (167 men and 160 women); of these, fasting glucose levels were missing for two subjects, leaving 325 subjects for analysis of glucose tolerance; fasting insulin levels were missing for 13 subjects, leaving 314 subjects for analyses of insulin resistance. The sampling scheme contributed to a greater proportion of undiagnosed diabetes among diabetic study subjects than would be expected if the sample were strictly population based; however, sampling weights used in the analysis (see below) should account for imbalances in the sampling design.

Clinical definitions and laboratory methods

We defined diagnosed diabetes as use of hypoglycemic drug therapy at any study examination; one subject with fasting plasma glucose levels ≥ 7.0 mmol/l at each of three prior quadrennial study examinations but who was not on drug therapy was also classified as having diagnosed diabetes. OGTT results were interpreted using 1998 World Health Organization criteria, which incorporate information from both fasting and 2-h postchallenge glucose levels to establish glucose tolerance categories (24). OGTT-detected diabetes was defined as a fasting plasma glucose level ≥ 7.0 mmol/l or 2-h postchallenge glucose level ≥ 11.1 mmol/l, and impaired fasting glucose (IFG)/IGT was defined as either a fasting plasma glucose level ≥ 6.1 mmol/l and < 7.0 mmol/l or a 2-h postchallenge glucose level ≥ 7.8 mmol/l and < 11.1 mmol/l. Normal glucose tolerance (NGT) was defined as a fasting plasma glucose level < 6.1 mmol/l and a 2-h postchallenge glucose level < 7.8 mmol/l. Three subjects were classified as having NGT despite lacking 2-h postchallenge glucose measurement, on the basis of normal fasting glucose levels at all study examinations attended. We defined insulin resistance as a fasting insulin level > 94 pmol/l (corresponding to the 90th percentile of the distribution among Framingham Offspring Study subjects with NGT). Hyperinsulinemia reflects insulin resistance: a single fasting insulin level serves as a reasonably reliable measure of insulin resistance across the spectrum of glucose tolerance as compared with assessment using clamp or minimal model methods (25). Alternatively, we used the homeostasis model to assess insulin resistance (HOMA-IR) (26); analyses using this index instead of fasting insulin gave essentially identical results, so only findings using fasting insulin as a surrogate measure of insulin resistance are presented. Subjects were categorized by insulin resistance status or separately by glucose tolerance status. Among subjects with NGT, 10.5% had insulin resistance; among subjects with IFG/IGT, 27.0% had insulin resistance; among subjects with OGTT-detected diabetes, 51.9% had insulin resistance; and among subjects with diagnosed diabetes, 41.7% had insulin resistance.

Blood pressure was assessed on the

basis of two measurements taken after subjects had been seated for at least 5 min; we used the averaged value. We classified subjects reporting smoking at least one cigarette per day during the year before the examination as current smokers. Fasting plasma glucose was measured in fresh specimens with a hexokinase reagent kit (A-gent glucose test; Abbott, South Pasadena, CA). Glucose assays were run in duplicate; the intra-assay coefficient of variation was $< 3\%$. Fasting insulin was measured in EDTA plasma as total immunoreactive insulin (Coat-A-Count Insulin; Diagnostic Products, Los Angeles, CA) and calibrated to serum levels for reporting purposes. Cross-reactivity of this assay with proinsulin at midcurve is $\sim 40\%$, the intra- and interassay CV ranged from 5.0 to 10.0% for concentrations reported here, and the lower limit of sensitivity was 8 pmol/l. Total cholesterol levels were measured enzymatically, and the HDL cholesterol fraction was measured after precipitation of low-density and very-low-density lipoproteins with dextran sulfate-magnesium. The Framingham laboratory participates in the lipoprotein cholesterol laboratory standardization program administered by the Centers for Disease Control and Prevention in Atlanta, GA.

EBCT

EBCT studies were conducted in 1998–1999 using a modified standard imaging protocol (27). We obtained 40–45 3-mm axial slices during two breath-holds from the apex of the aortic arch to the diaphragm. Image analysis for coronary artery calcium (CAC) used a threshold of > 130 Hounsfield units. We counted the number of calcifications in each major coronary artery and calculated a CAC score according to Agatston et al. (28). We divided the CAC score distribution into quartiles and, in this analysis, used the upper quartile to define the presence of coronary artery subclinical atherosclerosis (29). The CAC scores were 0–0.7 in quartile 1, 0.8–28.5 in quartile 2, 28.6–170.3 in quartile 3, and 170.4–3,266 in quartile 4.

Statistical analysis

Differences in proportions of subjects with various characteristics were assessed with χ^2 tests or Mantel-Haenszel tests of trend. We conducted weighted analyses to account for different sampling fractions

Table 1—Study subject characteristics by quartile of the CAC score

	CAC score quartile				P value, trend
	1	2	3	4	
n	80	83	80	82	
Age (years)	51.7	56.0	59.7	63.6	0.0001
Women (%)	73.8	44.6	42.5	34.2	0.001
Insulin resistance (%)	7.8	23.5	12.8	24.4	0.04
High HOMA-IR (%)	13.0	40.7	33.3	38.5	0.004
Glucose tolerance (%)					
Normal	91.3	75.9	77.5	57.3	
IFG/IGT	5.0	13.3	11.3	18.3	
OGTT-detected diabetes	1.3	9.6	7.5	15.9	
Diagnosed diabetes	2.5	1.2	3.8	8.5	0.001
Cigarette smoking (%)	13.8	10.8	22.5	17.1	0.3
Total/HDL cholesterol ratio	3.6	4.9	5.1	5.2	0.0001
LDL cholesterol (mg/dl)	119.5	129.6	135.5	138.4	0.001
Triglycerides (mg/dl)	90.3	143.2	146.5	160.9	0.0001
Systolic blood pressure (mmHg)	115.4	126.8	127.6	134.6	0.0001
Framingham risk score	3.7	8.3	10.7	13.9	0.0001

HOMA, homeostasis model to assess insulin resistance.

in different risk strata (with the highest risk stratum weighted 1/2 relative to the others), except for estimation of medians. We compared median CAC scores across categories with Wilcoxon's rank-sum tests. We used logistic regression to calculate odds ratios (ORs) and 95% CI for IFG/IGT and type 2 diabetes (diagnosed, OGTT, or both, with NGT as the referent group) or insulin resistance (with subjects without insulin resistance as the referent group) predicting subclinical coronary atherosclerosis (top quartile CAC score versus bottom three quartiles). Models were adjusted for age and sex, as well as for age, sex, cigarette smoking, total/HDL cholesterol ratio, and systolic blood pressure. In additional multivariable models predicting risk associated with IFG/IGT and diabetes, further adjustment was made for insulin resistance. Analyses were performed using SAS statistical software (SAS Institute, Cary, NC) (30). We defined statistical significance as a two-tailed P value <0.05 .

RESULTS— Of 325 study subjects, the mean age was 58 years (range 31–73); 49% were women, 14.5% had insulin resistance, 11.2% had IFG/IGT, 2.8% had diagnosed diabetes, and 7.2% had OGTT-detected diabetes. The mean predicted 10-year CHD risk was 9.2%. The median CAC score was 29 (interquartile range 0.7–170.3; range 0–3,266; 90th percentile 444.3). The distribution of risk factors

for subclinical atherosclerosis is shown in Table 1. All risk factors except smoking were significantly elevated in the fourth quartile of the CAC score distribution compared with the first quartile.

Median CAC scores were higher in subjects with insulin resistance versus

those without (50.9 vs. 25.9, $P = 0.0001$; Fig. 1). There was a graded increase in median CAC score with increasing glucose intolerance, from 14.4 in subjects with NGT to 179.9 in those with diagnosed diabetes ($P = 0.0001$ for trend; Fig. 1). Of subjects in the highest quartile of

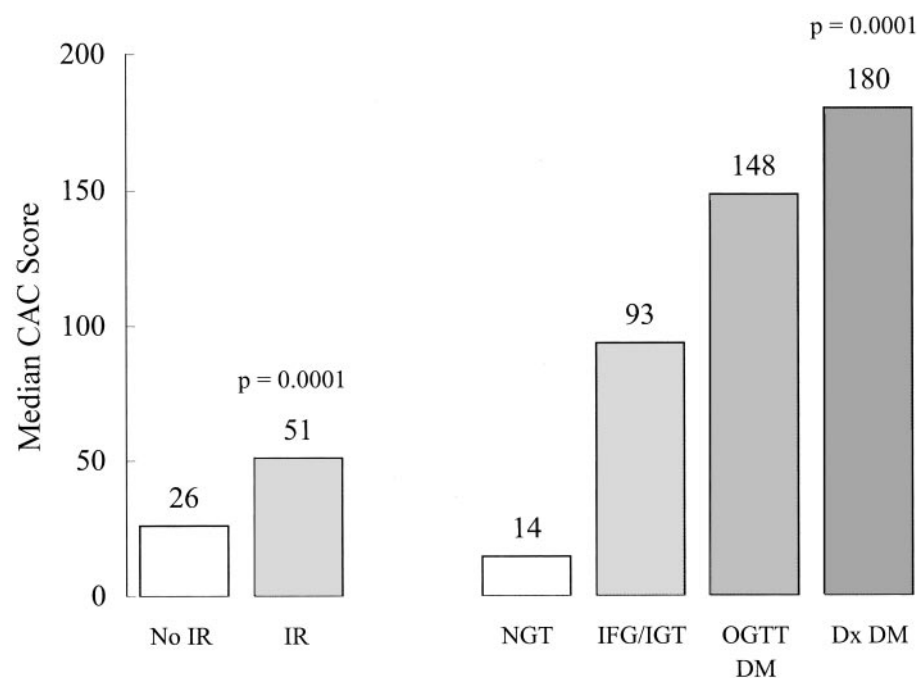


Figure 1—Median CAC scores by insulin resistance (IR) or glucose tolerance status. OGTT diabetes, unsuspected, OGTT-detected diabetes mellitus; Dx DM, previously diagnosed type 2 diabetes mellitus). P value for glucose tolerance reflects significance of the trend in median values across categories.

the CAC score distribution, 24% had insulin resistance; 18% had IFG/IGT, 16% had OGTT-detected diabetes, and 9% had previously diagnosed diabetes. Therefore, 43% (18 + 16 + 9%) of subjects with subclinical coronary atherosclerosis had impaired glucose homeostasis.

Risk of subclinical coronary atherosclerosis was significantly increased in subjects with insulin resistance (age- and sex-adjusted OR 2.05, 95% CI 1.01–4.18). This association was attenuated after further adjustment for cigarette smoking, total/HDL cholesterol ratio, and systolic blood pressure (multivariate-adjusted OR 1.60, 0.73–3.52). Risk for subclinical atherosclerosis tended to be higher in subjects with IFG/IGT (age- and sex-adjusted OR 1.79, 0.81–3.98) and was significantly higher in those with type 2 diabetes (3.04, 1.41–6.57). These associations remained similar after further adjustment for standard CVD risk factors (IFG/IGT: multivariate-adjusted OR 1.49, 0.65–3.38; diabetes 2.69, 1.16–6.13), as well as after further adjustment for CVD risk factors and insulin resistance (IFG/IGT 1.48, 0.63–3.50; diabetes 2.82, 1.18–6.72). When stratified by OGTT-detected or -diagnosed diabetes (Fig. 2), there was a graded increase in risk of subclinical atherosclerosis across categories of increasingly severe glucose intolerance, with risk tending to be increased in OGTT-detected diabetes (multivariate OR 2.07, 0.77–5.51) and significantly increased in diagnosed diabetes (6.01, 1.43–25.2).

CONCLUSIONS— In this subsample of the population-based Framingham Offspring Study, subjects with insulin resistance or IFG/IGT and type 2 diabetes had an increased burden of coronary artery subclinical atherosclerosis. Risk of subclinical atherosclerosis associated with insulin resistance was largely explained by concomitant elevations in standard CVD risk factors. Increased risk associated with IFG/IGT in this small sample was not statistically significant. Subjects with type 2 diabetes had increased risk of subclinical coronary atherosclerosis independent of standard CVD risk factors; those with diagnosed diabetes were at greater risk than those with clinically unsuspected OGTT-detected diabetes. The increasing risk for subclinical atherosclerosis across categories

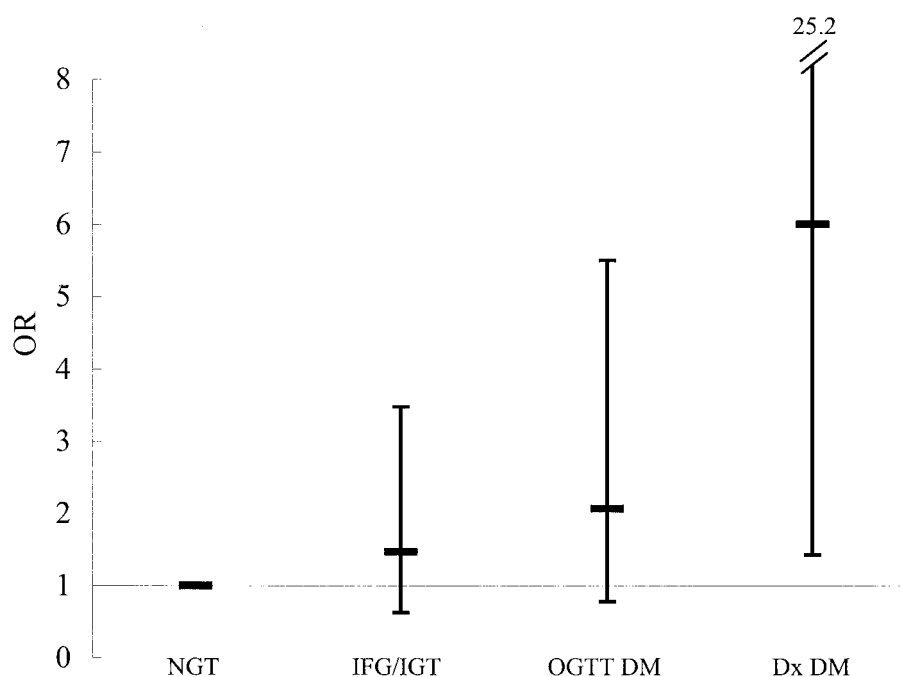


Figure 2—Age-, sex-, smoking-, total/HDL cholesterol-, systolic blood pressure-, and insulin resistance-adjusted ORs and 95% CIs for IFG/IGT, for unsuspected OGTT-detected diabetes mellitus (OGTT diabetes), and for previously diagnosed type 2 diabetes mellitus (Dx DM) predicting coronary artery subclinical atherosclerosis. The referent group is NGT.

from IFG/IGT to OGTT-detected diabetes to diagnosed diabetes is consistent with prior observations in Framingham and other populations suggesting that risk of CVD is graded and continuous across the spectrum of glucose tolerance (31,32). Our small sample size constrained analytic power, but despite this, we found significant associations with diagnosed diabetes and a clear pattern of an increasing burden of subclinical coronary atherosclerosis with increasing severity of glucose intolerance. Considered from another perspective, we found that almost half of subjects with subclinical coronary atherosclerosis had impaired glucose homeostasis.

A handful of previous studies have reported excess subclinical coronary atherosclerosis in glucose intolerance, but these studies only examined subjects with diagnosed diabetes. Among a group of patients referred to Wong et al. (17) for EBCT, 6.4% had self-reported diabetes; these subjects had a 2.32 (1.06–5.08) increased risk for having any detectable coronary artery calcification compared with nondiabetic subjects in the referral sample. Among 103 patients with type 2 diabetes examined by Yoshida et al. (18), the mean CAC score was 245 vs. 149 ($P <$

0.05) in a group of matched control subjects. In this study, CAC scores were also correlated with duration of diabetes. Schurgin et al. (19) also demonstrated an increased prevalence (26%) of CAC scores >400 (indicating extensive disease) comparing patients with diabetes to matched control subjects (14%, $P = 0.004$). In this study, the left anterior descending artery was most commonly affected. Autopsy data on young adults also suggest a significant association between advanced left anterior descending calcium deposition and glucose intolerance (defined as a glycohemoglobin level ≥ 8.0) (33). Using clinic-based family data, Wagenknecht et al. (20) recently reported a high prevalence (27%) of extensive CAC in probands with diagnosed type 2 diabetes compared with nondiabetic siblings (8%, $P = 0.003$). The extent of coronary artery calcification was associated with duration of diabetes; furthermore, the extent of coronary artery calcification was moderately heritable ($h^2 \geq 40\%$) in these families. Our findings from a subsample of a community-based cohort extend these observations, providing further evidence of substantial subclinical coronary atherosclerosis in people with diagnosed type 2 diabetes.

Furthermore, we found that this excess risk for subclinical coronary atherosclerosis in diagnosed type 2 diabetes was independent of elevations in standard risk factors for atherosclerosis.

Our data also extend current knowledge by suggesting that there may be excess coronary artery calcification in subjects with subdiabetic or clinically undetected glucose intolerance or with insulin resistance. No previous study of IFG/IGT or OGTT-detected diabetes has used EBCT, but several studies have examined subclinical atherosclerosis in other vascular beds. The Cardiovascular Health Study defined subclinical atherosclerosis among elderly subjects without clinical CVD as a composite of elevated ankle-brachial index, elevated carotid wall thickness, or silent myocardial ischemia by electrocardiography (4). In this study, there was a graded increase in the prevalence of subclinical atherosclerosis from 40% in NGT to 42% in IFG/IGT to 44% in diabetic participants ($P < 0.001$ for trend). In the Insulin Resistance Atherosclerosis Study, carotid wall thickness showed a weak graded relationship with increasing insulin resistance (14) or glucose intolerance (11), but these associations were substantially attenuated by statistical control for standard CVD risk factors. In addition, duration of diabetes was not associated with carotid intima-media thickness (34). The Atherosclerosis Risk in Communities Study also found graded relationships between glucose tolerance status or fasting insulin levels and carotid wall thickness; again, these associations were weakened by control for other CVD risk factors (7). Bonora et al. (13) did not find an association between glycemia in the normal range and carotid atherosclerosis and found a "U-shaped" relationship between insulinemia and carotid atherosclerosis (16). Other studies have also found weak or inconsistent relationships between glycemia or insulinemia and carotid wall thickness after standard CVD risk factor adjustment (15,35). Again, our small sample size limits the certainty with which we can draw conclusions, but our data seem to suggest a relationship between glucose intolerance and subclinical atherosclerosis of the coronary arteries that extends into the subclinical range of glucose intolerance. Much of this association is explained by concomitant elevations in standard CVD risk factors. Differences between findings

in the carotid and coronary circulation may plausibly be explained by vascular-bed-specific differences in the expression of endothelial dysfunction giving rise to atherosclerosis (36).

The observed graded increase in coronary artery subclinical atherosclerosis with increasing glucose intolerance or insulin resistance is consistent with the hypothesis that these conditions arise together over time from a common antecedent (6). However, the data are also consistent with an association between subclinical atherosclerosis and duration of established diabetes (18,20). This suggests that the mechanism of development of subclinical atherosclerosis may be linked, in part, to chronic exposure to hyperglycemia or associated atherogenic abnormalities closely associated with hyperglycemia, including chronic subclinical inflammatory signaling or elevated levels of small, dense LDL cholesterol or plasminogen activator inhibitor-1 (37). Chronic hyperglycemia is also associated with medial arterial calcification, another vascular pathology more common in type 2 diabetes than in nondiabetic subjects and associated with excess risk for CVD events (38,39). Although it is possible that some of the CAC signal detected by EBCT in type 2 diabetes represents medial rather than intimal calcification, medial calcification is a condition found predominantly in the legs, and pathology data suggest that calcification in coronary arteries primarily involves the intimal layer (40). Further work is needed to assess the role of EBCT in assessing medial arterial calcification and to discriminate mechanisms of development of medial versus intimal calcification.

Other study limitations include assessment of glucose tolerance on the basis of a single OGTT, potentially resulting in some misclassification of subjects, especially those with IFG/IGT. The effect of this would be to weaken effect sizes and underestimate associations of glucose intolerance with subclinical atherosclerosis. In addition, we did not have a direct assessment of insulin resistance. Whereas use of fasting insulin levels as a surrogate marker of insulin resistance also likely results in some misclassification by insulin resistance status, fasting insulin correlates well (correlation coefficients between ~ 0.4 and 0.7 , depending on glucose tolerance status) with insulin resistance as-

essed using clamp or minimal model methods (25), and accounts for a substantial amount of the ability of direct measures of insulin resistance to predict CVD risk (41). Finally, it is uncertain whether our findings are generalizable to non-Caucasians.

Our study findings have important implications for prevention. Overtly diabetic patients without clinical CVD are at substantial risk for incident CVD events (42). Coronary artery subclinical atherosclerosis assessed by EBCT seems to predict incident fatal and nonfatal CHD events (43). Our data suggest that some of the elevated CVD risk in glucose intolerance may be explained by a substantial burden of subclinical atherosclerosis. The large, independent association of diagnosed diabetes and coronary artery subclinical atherosclerosis in our data underline that aggressive CVD risk factor interventions in type 2 diabetes (particularly control of cigarette smoking, hyperlipidemia, and hypertension) are imperative to prevent progression of atherosclerosis from subclinical to clinical disease (1). The apparent increased burden of coronary artery subclinical atherosclerosis in subjects with clinically undetected glucose intolerance also suggests that it is appropriate to initiate aggressive CVD prevention in all patients at the time of diagnosis of type 2 diabetes.

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