Progression of Coronary Artery Calcification in Type 1 Diabetes

The importance of glycemic control

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OBJECTIVE — Coronary artery disease (CAD) occurs earlier in life and is more often fatal in people with type 1 diabetes. This excess risk seems to be higher than in those with type 2 diabetes and is poorly explained by conventional risk factors. The role of glycemic control is controversial and has not been previously addressed in a prospective manner using a reliable marker for subclinical CAD, such as coronary artery calcification (CAC), measured by electron beam computed tomography (EBCT).

RESEARCH DESIGN AND METHODS — We measured CAC twice during an interval of 2.7 years in 109 men and women with type 1 diabetes (aged 22–50 years). Progression of CAC was found in 21 patients, based on change in the square root–transformed volume score.

RESULTS — In multiple logistic regression, CAC progression was associated with baseline hyperglycemia (odds ratio [OR] 7.11, 95% CI 1.38–36.6, $P = 0.02$), adjusted for the presence of CAC at baseline ($P = 0.01$), duration of diabetes ($P = 0.02$), sex ($P = 0.09$), and age ($P = 0.27$). There was also a significant interactive effect of higher insulin dose and higher BMI ($P = 0.03$).

CONCLUSIONS — In conclusion, in this young cohort with type 1 diabetes, suboptimal glycemic control (HbA_{1c} >7.5%) was a strong risk factor for progression of CAC. Insulin resistance may also play a role.

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Coronary artery disease (CAD) is the leading cause of mortality in people with type 1 diabetes and accounts for a large proportion of premature morbidity and mortality in the general population. CAD in patients with type 1 diabetes occurs earlier in life and affects women as often as men (1,2). By 55 years of age, 35% of patients with type 1 diabetes die of CAD, in contrast to only 8% of nondiabetic men and 4% of nondiabetic women (1).

In patients with type 1 diabetes, atherosclerosis is more diffuse (3,4), leading to higher case fatality (5,6), higher incidence of cardiac failure (7) and restenosis (8), and shorter survival (8–12), compared with the general population. These poor outcomes emphasize the need for primary prevention of CAD in patients with type 1 diabetes. Silent ischemia is common: 24% of asymptomatic patients aged >35 years have stress test/perfusion abnormalities (exercise treadmill and nuclear thallium), and 10% have coronary stenosis, >50% by angiography (13). Small clinical studies using B-mode imaging of carotid arteries have suggested that patients with type 1 diabetes have significant atherosclerosis as early as 10–19 years of age, and it is strongly associated with duration of diabetes (14). However, very little is known about the prevalence of subclinical CAD and the risk factors for its progression.

Although conventional CAD risk factors (male sex, hypertension, smoking, low HDL cholesterol, high LDL cholesterol, and high triglycerides), as well as proteinuria, increase the risk, they account for less than half the excess mortality associated with diabetes (15). Therefore, it is difficult to determine which patients need more aggressive preventive measures. Electron beam–computed tomography (EBCT) is a promising method for noninvasively measuring subclinical atherosclerosis. The quantification of coronary artery calcium is a surrogate for total atherosclerotic plaque burden (16,17), and this method has been shown to predict future coronary events (9,18,19). EBCT is particularly suited to detection of subclinical atherosclerosis among patients who are presumed to be at moderate to high risk for CAD (20), and so it may be an appropriate screening test for patients with type 1 diabetes.

The ability to track progression of CAC to assess the effectiveness of therapies has been elegantly demonstrated (21,22). Use of CAC progression for de-

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Abbreviations: CAC, coronary artery calcification; CAD, coronary artery disease; EBCT, electron beam–computed tomography; EDC, Epidemiology of Diabetes Complications Study; SRV, square root–transformed volume.

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

termining which patients are in need of further cardiac testing or revascularization is very promising as well. In this study, we hypothesized that progression of CAC in patients with type 1 diabetes is due to identifiable risk factors and may be related to glucose control.

RESEARCH DESIGN AND METHODS

Study subjects

A total of 135 patients with type 1 diabetes were enrolled over 3 months (November 1997 to January 1998) and were asked to return for a follow-up visit in 3 years (mean follow-up 2.7 ± 0.3 years). Patients were referred for participation by physicians at local diabetes/endocrinology clinics and by a cohort study of childhood diabetes. All patients were asymptomatic for CAD and had no history of coronary artery bypass grafting (CABG), coronary angioplasty, or unstable angina. Of the patients enrolled, 48% were women and 52% were men; the mean duration of diabetes was 22 years (range 2–48). Patients were aged 22–50 years at the time of entry into the study. Two patients died of complications of diabetes before follow-up, and three women were unable to complete the follow-up examination due to pregnancy. Of the remaining 129 patients, 109 (85%) completed the follow-up examination.

The study protocol was reviewed and approved by the Colorado Combined Institutional Review Board, and informed consent was obtained from all patients before enrollment. We measured height and weight and calculated BMI. Current and former smoking status was obtained by questionnaire, and for smokers, the total number of pack-years was calculated. Daily insulin dose per kilogram of body weight was calculated. Resting systolic blood pressure and fifth-phase diastolic blood pressure were measured three times while the patient was seated, and the second and third measurements were averaged (23). Hypertension was defined as current antihypertensive therapy or untreated hypertension (blood pressure ≥140/90 mmHg) at the time of the study visit. All patients had total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride levels, and HbA_{1c} measured.

Imaging

All patients underwent a single EBCT scan without contrast at baseline and two EBCT scans without contrast at follow-up. Images were obtained of the entire epicardial system using an Imatron C-150 Ultrafast CT scanner with a 100-ms exposure (Imatron, South San Francisco, CA). The standard acquisition protocol, as previously described, was used (24). Scanning started from the lower margin of bifurcation of the main pulmonary artery. Images were electrocardiographically triggered at 80% of the R-R interval, and 30–40 contiguous 3-mm slices were acquired.

The threshold for CAC was set at a CT density of 130 Hounsfield units (HU) in at least three contiguous pixels. A region of interest was encircled within each coronary artery, and computer-driven measurement of the lesion area and maximum density were recorded. A CAC score for each region was calculated by multiplying the area by the density score (1 for 130–199 HU, 2 for 200–299 HU, 3 for 300–399 HU, and 4 for >399 HU) according to the standard Agatston method (24). A total CAC score was calculated by adding scores for all slices, and calculated separately for left main, left anterior descending, circumflex, and right coronary arteries (24). A single skilled technician obtained and scored all of the EBCT scans. The total volume score and separate volume scores for the left main, left anterior descending, circumflex, and right coronary arteries were also reported for the baseline and the two follow-up EBCT scans. The volume scores were calculated using the volumetric method, which is based on isotropic interpolation, as previously described (25).

Statistical analysis

Progression status was determined using a novel method described by Hokanson (J.E.H., T.M., G.K., J.S.-B., J.E., R.H.E., M.R., unpublished observations). Based on the analysis of a separate cohort of 1,074 patients who had two EBCT scans performed 5 min apart, it was concluded that CAC testing error has an unstabilized variance. For example, the magnitude of testing error is much larger in patients with actual CAC of ≥100 than in patients with actual CAC of 0–10. Further analysis identified that the square root– transformed volume (SRV) has a stable variance. Therefore, we defined progression as a change in SRV of ≥2.5 because a change of this magnitude is very unlikely to be due to testing error. The difference between the average follow-up SRV and the baseline SRV was calculated, and then patients were categorized as progressors if the change in SRV was ≥2.5. Regression of CAC would similarly be defined as a reduction in the SRV of ≥2.5; however, none of the patients in our study experienced regression according to this definition.

Variables were examined for a linear relationship with progression of coronary calcium and were categorized if necessary. Variables that were nonnormally distributed were transformed using an appropriate transformation (square root or natural log). Demographic and other variables of interest were evaluated in a univariate logistic regression model to determine their relationship to progression of coronary calcium. A limited number of interactions were considered, and they were considered significant if the *P* value was <0.05.

Logistic regression analysis with forward selection was then used to identify risk factors that were significantly related to the progression of coronary calcium while adjusting for sex, age, and duration of diabetes.

RESULTS — The current investigation examined coronary calcification measured by EBCT in a young cohort of patients with type 1 diabetes (aged 22–50 years) who were asymptomatic for CAD. EBCT was performed twice at an interval of 2.7 ± 0.3 years. Most (62%) of the 109 patients studied had no calcification at baseline. However, progression of coronary calcium in people with type 1 diabetes has not been previously reported, and it is unknown how quickly this population progresses from no detectable coronary calcium to a substantial score. The progression algorithm used in this study allows for the evaluation of progression from 0 using the criteria of a ≥2.5 change in SRV. Therefore, participants who had a baseline score of 0 and a follow-up score of ≥6.25 could be considered to have progressed. Among those with no calcification at baseline ($n = 68$), progression occurred in 6% ($n = 4$), and this important group accounted for 19% of progressors in our study.

An examination of the baseline CAC and volume score demonstrated that the

Table 1—*Baseline characteristics of patients who progressed versus those who did not*

	Progressors (n = 21)	Nonprogressors (n = 88)	Standardized OR (95% CI)‡	P value
Sex (% men)	71	46	3.00 (1.07–8.45)	0.04
Age in years	42 ± 7	36 ± 8	2.56 (1.43–4.56)	0.002
Duration of diabetes (years)	30 ± 9	20 ± 9	3.51 (1.86–6.63)	<0.001
Systolic blood pressure (mmHg)	127 ± 13	120 ± 15	1.50 (0.94–2.40)	0.09
Diastolic blood pressure (mmHg)	79 ± 8	78 ± 8	1.09 (0.67–1.78)	0.72
On antihypertensive medication (%)	52	30	2.62 (0.99–6.93)	0.05
Ever a smoker (%)	33	25	1.50 (0.54–4.19)	0.44
Current smoker (%)	14	11	1.30 (0.32–5.21)	0.71
BMI (kg/m^2)	24.4 ± 3.2	25.2 ± 3.7	0.79 (0.46–1.34)	0.38
Total cholesterol (mg/dl)	185 ± 35	180 ± 37	1.14 (0.71–1.84)	0.58
LDL cholesterol (mg/dl)	112 ± 36	106 ± 30	1.20 (0.76–1.92)	0.44
HDL cholesterol (mg/dl)	58 ± 18	58 ± 16	0.96 (0.59–1.58)	0.88
Triglyceride (mg/dl)*	74 (43–99)	65 (44–89)	1.01 (0.62–1.65)	0.96
Treated with statins (%)	14	15	1.04 (0.27–4.04)	0.96
HbA_{1c} (%)	7.2 ± 1.7	6.5 ± 1.0	1.47 (0.94–2.29)	0.10
Glycemic control (HbA_{1c} >7.5%)	28.6	15.9	2.11 (0.70–6.39)	0.19
Insulin dose per kg body wt/day	0.65 ± 0.20	0.64 ± 0.22	1.04 (0.64–1.68)	0.89
Baseline CAC >0	81	27	11.33 (3.46–37.1)	<0.001
Baseline CAC†	8.8 (6.2–16.0)	0 (0–0.7)	15.10 (4.24–53.9)	<0.001
Baseline volume score†	2.3 (1.5–10.2)	0 (0–0.7)	3.80 (1.66–8.70)	0.002

Data are means ± SD, percent, or median (interquartile range). *Log transformed; †square root transformed; ‡ORs are presented per SD; age 7.94, duration of diabetes 10.02, systolic blood pressure 14.98, diastolic blood pressure 8.19, BMI 3.59, total cholesterol 36.32, LDL cholesterol 31.1, HDL cholesterol 16.47, triglyceride (log transformed) 0.62, HbA_{1c} 1.18, insulin dose 0.22, baseline CAC (square root transformed) 7.73, and baseline volume score (square root transformed) 6.07.

distribution of both measures of calcification was positively skewed and quite variable, but the volume score showed less variability. The average volume change per year of follow-up among progressors was 32.1 units (SD 32.6). The range for total volume change per year in progressors was from 2.6–124.4 units. The average CAC score change per year of follow-up among progressors was 26.1 units (SD 38.8, range 3.5–151.6 units). Although some participants experienced a reduction in CAC score over the follow-up period, none experienced a significant enough change to qualify as regression of CAC according to our criteria.

The glycemic control in this cohort was generally very good; the average HbA_{1c} was 6.8%. However, 30% of the participants had an HbA_{1c} above the American Diabetes Association's recommended clinical goal of 7%, and 21 of the 109 participants (19%) had HbA_{1c} >7.5% (26). The average insulin dose per kilogram body weight per day was 0.64 units, and most patients (76%) were on intensive insulin therapy, consisting of either continuous insulin infusion by pump (n = 33) or more than two daily injections (n = 50). The average BMI of the cohort was 25.03 kg/m^2, and 8% of the participants were obese (BMI ≥30 kg/m^2). Most participants had normal triglyceride levels (median 66 mg/dl, 10% >150 mg/dl) and HDL cholesterol levels (men, mean 54 mg/dl, 33% <45 mg/dl; women, mean 63 mg/dl, 33% <55 mg/dl) (26). However, 56% of men and 43% of women who participated in this study had an elevated baseline LDL cholesterol level (≥100 mg/dl) (26). Only a small proportion of patients in our cohort were treated with statins, although use doubled (to 14%) between the baseline and follow-up examinations.

Table 1 summarizes the characteristics of the patients who demonstrated progression of CAC volume compared with those patients who did not. In univariate regression models, male sex, age, duration of diabetes, presence of CAC at baseline, baseline calcium score, and baseline volume score were significantly related to progression of CAC. HbA_{1c} (P = 0.10), treatment with antihypertensive medications (P = 0.05), and systolic blood pressure (P = 0.09) seemed related to progression of CAC. The relationship between HbA_{1c} and progression of CAC was explored for linearity (Fig. 1), and we found a nonlinear relationship. As a result, we dichotomized HbA_{1c} into categories of good (HbA_{1c} ≤7.5%) or poor (HbA_{1c} ≥7.5%) glycemic control.

A multiple logistic regression analysis was conducted for the variables of interest, including interaction terms, while adjusting for age, duration of diabetes, and sex. When adjusted for the other covariates (Table 2), duration of diabetes (P = 0.02) was significant, but sex (P = 0.09) and age (P = 0.27) were no longer significantly related to progression of CAC. Adjusting for these variables as well as the presence of CAC at baseline, suboptimal glycemic control (HbA_{1c} >7.5%) was a strong risk factor for progression of CAC. In addition, there was a significant interaction between BMI and daily insulin dose, such that higher insulin dose increased the risk of progression of CAC, but only in overweight individuals. BMI was categorized by determining the quartiles of BMI in this cohort and then rounding up. Four groups of BMI were therefore created, which roughly corresponded to the quartiles in our cohort. The groups were *1*) BMI <23, *2*) BMI 23 to <25, *3*) BMI 25 to <27, and *4*) BMI ≥27 kg/m^2.

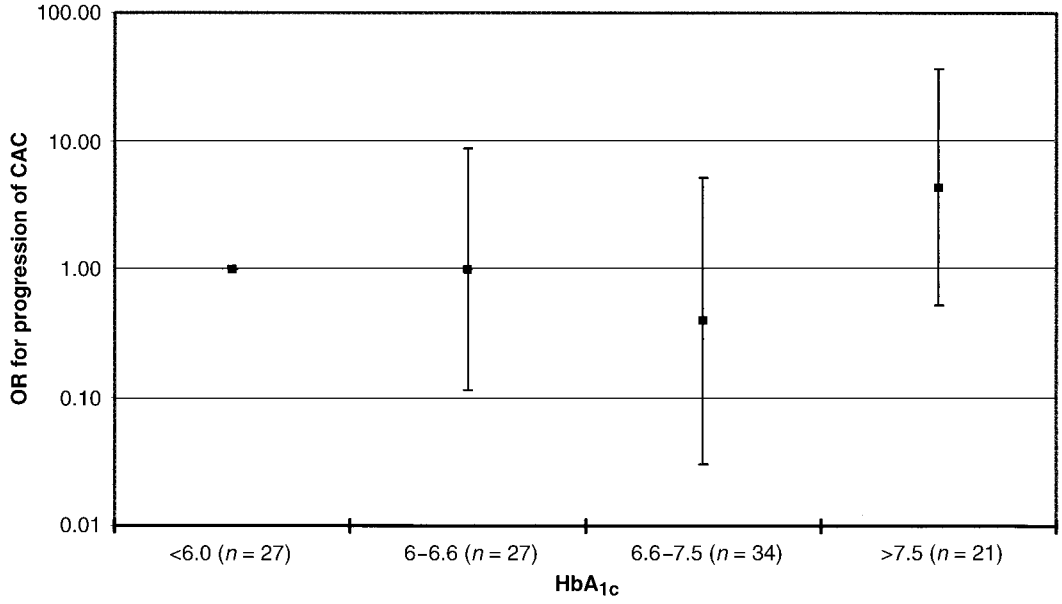

Figure 1—*Nonlinear relationship of HbA_{1c} and progression of CAC.*

An increase in daily insulin dose of 0.2 units significantly increased the risk of progression of CAC among overweight individuals (BMI ≥25 kg/m^2) more than sevenfold.

Other known risk factors for CAD were then added to the "best" model (Table 2) to explore whether these risk factors significantly added to the prediction of progression of CAC. Variables that were tested included baseline systolic and diastolic blood pressure, smoking status, baseline lipids (HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides), current antihypertensive medication, and statin treatment. None of these CAD risk factors were significantly related to progression of CAC, and the addition of these covariates did not substantially change the significance or risk estimates of the variables in the best model described in Table 2 (data not shown).

CONCLUSIONS — In this relatively young group of people with type 1 diabetes, the most important predictor of progression of CAC was suboptimal glycemic control. A relationship between glycemic control and CAD has not been clearly demonstrated previously, but our findings suggest that HbA_{1c} >7.5% is a strong risk factor for increasing atherosclerotic plaque burden among young people with type 1 diabetes who are asymptomatic for CAD. In addition, the risk of progression of CAC seems to be increased by higher insulin dose among overweight individuals. A possible explanation for this finding is that a high insulin requirement among overweight individuals may be a marker of insulin resistance. Obesity increases the risk of coronary atherosclerosis (27), although it is unknown whether this risk is independent of associated conditions, such as hypertension and dyslipidemia (28). Both obesity and insulin resistance are part of a cluster of symptoms known as the metabolic syndrome, which may also contribute to increased CAD (16,29). A recent report from the Pittsburgh Epidemiology of Diabetes Complications Study (EDC) (30) found an association between characteristics of the metabolic syndrome and CAD events in a very young cohort of people with type 1 diabetes, which further supports that insulin resistance may be an important risk factor for CAD in type 1 diabetes.

In contrast to our findings, the EDC found that hypertension was associated with progression of CAC, and there was no relationship between HbA_{1c} and progression of CAC (T. Orchard, personal communication). However, the EDC (n = 113) included patients with known CAD (n = 23), and the average duration of diabetes in their cohort was longer than in our cohort (27.9 ± 6.6 years). In addition, the EDC defined progression of CAC as the development of first CAC or at least a 50% increase in total CAC, using the Agatston score (T. Orchard, personal communication). Using this definition of CAC progression, 55% of their study participants demonstrated significant progression over a period of 3.8 ± 0.4 years. A definition of CAC progression that uses

Table 2—*Multivariate logistic regression for progression of coronary calcium: best model*

Variable	Standardized OR (95% CI)	*P* value
Age	1.72 (0.65–4.56)	0.27
Sex (men versus women)	3.90 (0.82–18.61)	0.09
Duration of diabetes	3.24 (1.27–8.26)	0.02
Glycemic control (HbA_{1c} >7.5%)	7.11 (1.38–36.6)	0.02
Baseline CAC >0	9.66 (1.83–50.9)	0.01
BMI and insulin interaction (per 0.2-unit increase in insulin)		0.02
<23	0.31 (0.07–1.39)	0.13
23–25	2.36 (0.43–12.91)	0.32
25–27	6.55 (0.59–73.0)	0.13
>27	7.69 (1.02–57.8)	0.048

*ORs are presented per SD (age 7.77 and duration of diabetes 10.12).

a percent change in Agatston score or a change from 0 to any positive score is problematic and may result in misclassification because a change from 0 to a small score may represent testing error, and a small change from a low initial score produces a large percent change (31). In addition, using the volume score to assess progression may be more accurate than using the Agatston score (25). Applying the same definition of progression to our cohort (development of first CAC or at least 50% increase in total CAC) would increase the number of progressors from 21 to 31, with 14 nonprogressors misclassified as progressors and 4 progressors misclassified as nonprogressors. Nine of the 14 people who would be misclassified as progressors by the EDC definition of progression had a baseline volume score of 0 and a follow-up volume score <1. This clearly demonstrates that it is problematic to define progression as any new CAC in people with an initial score of 0, because such small changes fall well within the error rate of this test. Some studies of progression have used a cutoff, such as a baseline CAC score of 30 to avoid this problem (32); however, in a young cohort with type 1 diabetes, it is important to be able to assess when meaningful CAC appears and to evaluate progression in those people with a relatively low initial CAC score.

There are some important limitations in the current study, which we are addressing in the ongoing large (n = 1,420) prospective Coronary Calcification in Type 1 Diabetes (CACTI) study. This pilot investigation did not include a control group of patients without diabetes that would also allow for the comparison of the progression rate among patients with diabetes compared with those without diabetes. Whereas traditional risk factors for CAD, such as LDL cholesterol, smoking, and hypertension, did not contribute to the risk of progression of CAC, additional factors such as family history of CAD, diet, physical activity, alcohol consumption, homocysteine, apolipoprotein B, C-reactive protein, fibrinogen, plasminogen activator inhibitor 1, and microalbuminuria should be examined as potential risk factors for subclinical CAD and progression of atherosclerosis among patients with type 1 diabetes. Finally, we were not able to evaluate the effect of change in risk factors, such as LDL cholesterol and HbA_{1c}, due to changes in laboratory measurement methods over the study period.

In conclusion, in this young cohort of people with type 1 diabetes, significant progression of CAC was strongly related to suboptimal glycemic control. In addition, it seems that insulin resistance may play a role in the progression of subclinical CAD in type 1 diabetes.

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