Delineation of Prevalence and Risk Factors for Early Coronary Artery Disease by Electron Beam Computed Tomography in Young Adults With Type 1 Diabetes

HAROLD S. STARKMAN, MD[1]
GREGORY CABLE, PHD[2]
VIRGINIA HALA, RN[3]
HARVEY HECHT, MD[4]
CHRISTINE M. DONNELLY, MD[5]

OBJECTIVE — Type 1 diabetes increases the risk for coronary artery disease (CAD), but limited information is available regarding the early natural history of this process. Electron beam tomography (EBT) can measure coronary artery calcification (CAC), an early marker for CAD. This study was designed to assess the prevalence and risk factors for CAC in young adults with established type 1 diabetes.

RESEARCH DESIGN AND METHODS — A total of 101 subjects aged 17–28 years with type 1 diabetes of over 5 years' duration and no history of heart disease underwent cardiac EBT with calcium scoring. Medical histories were obtained and physical examinations were conducted to document the presence of cardiac risk factors as well as evidence of microvasculopathy and diabetic arthropathy. Laboratory evaluation included measurement of fasting lipoproteins, homocysteine concentration, lipoprotein(a) [Lp(a)], urinary microalbumin, and HbA_{1c}. Contingency table analysis was used to assess bivariate relationships. Logistic regression was employed to construct a parsimonious model of independent risk factors.

RESULTS — Eleven subjects (10.9%) had CAC. Smokers were nearly five times more likely than nonsmokers to have CAC ($P = 0.03$). In addition, each 0.36-mm/l increment of Lp(a) was associated with a 10% increased risk for CAC ($P = 0.05$) after controlling for potentially confounding factors. There was no association of other CAD or diabetes risk factors studied with CAC.

CONCLUSIONS — The prevalence of early CAD as evidenced by CAC in young adults with type 1 diabetes is significant. Smoking and Lp(a) levels independently predict the presence of CAC. Additional study is necessary to delineate the natural history of CAC and the role of risk factor modification to prevent progression of CAD in this high-risk population.

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Patients with type 1 diabetes have an increased risk for developing early and severe coronary artery disease (CAD). Krolewski et al. (1) reported that by 55 years of age, the cumulative mortality rate from CAD in this population was 30–40%. This finding compares with an overall mortality rate of 4–8% in nondiabetic subjects as reported in the Framingham Study (2).

Findings consistent with early coronary atherosclerosis have been documented in late adolescence and early adulthood. Both pathological and intravascular ultrasound studies have demonstrated atheromatous lesions and coronary wall abnormalities consistent with early CAD (3–6). These findings, however, have not been associated with clinically apparent disease. Indeed, the clinical diagnosis of CAD is usually made when symptoms of coronary insufficiency or myocardial infarction have occurred. Diagnosis at this late stage places individuals at an increased risk for chronic cardiac morbidity and mortality.

Earlier identification of CAD may afford the opportunity for timely and aggressive risk factor modification that has the potential to alter the natural history of atherosclerosis and slow CAD progression.

Intramural coronary calcification has been shown to be a marker for coronary atherosclerosis and can be accurately and reproducibly measured using electron beam computed tomography (EBT) (7–10). This noninvasive diagnostic tool has been demonstrated to be highly sensitive for the detection of small intimal calcium deposits which correlate with early coronary atherosclerosis even in the absence of luminal narrowing (11). EBT has also served as an effective tool for screening of adolescents and young adults at increased risk for coronary atherosclerosis, including those with hyperlipidemia (12,13), end-stage renal disease (14), and other CAD risk factors (15).

We used EBT to study a cohort of young adult subjects with established type 1 diabetes to determine the prevalence of coronary artery calcification (CAC). In addition, we assessed cardiovascular and other potential CAD risk factors and their association with the presence of CAC.

RESEARCH DESIGN AND METHODS

Subjects

We studied 101 subjects 17–29 years of age with type 1 diabetes of at least 5 years'

From the [1]BD Diabetes Center for Children and Adolescents, Atlantic Health System, Morristown, New Jersey; the [2]Atlantic Health System, Florham Park, New Jersey; the [3]Department of Pediatrics, Morristown Memorial Hospital, Atlantic Health System, Morristown, New Jersey; the [4]Princeton Longevity Center, Princeton, New Jersey; and the [5]Children's Heart Center, Atlantic Health System, Morristown, New Jersey.

Address correspondence and reprint requests to Harold Starkman, MD, BD Diabetes Center for Children and Adolescents, Morristown Memorial Hospital, Atlantic Health System, 100 Madison Ave., Morristown, NJ 07962-1953. E-mail: harold.starkman@ahsys.org.

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Abbreviations: CAC, coronary artery calcification; CAD, coronary artery disease; EBT, electron beam computed tomography; ECAC, Epidemiology of Coronary Artery Calcification; Lp(a), lipoprotein(a).

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

See Point-Counterpoint, p. 541–544.

Table 1—*Demographic characteristics of EBT-positive and EBT-negative subjects*

	EBT positive	EBT negative
n	11	90
Female	3 (26.3)	45 (50.0)
Male	8 (73.7)	45 (50.0)
Smoker	5 (45.5)	19 (21.0)
Use of angiotensin converting enzyme (ACE) inhibitor	3 (27.3)	21 (23.3)
Presence of limited joint mobility	3 (27.3)	35 (38.9)

Data are *n* (%).

duration. Subjects were recruited from our diabetes clinic, and those with a history of preexisting heart disease were excluded. Female subjects were required to have a negative pregnancy test to participate in this study.

All subjects and parents of those <18 years of age were required to sign an informed consent/assent reviewed and approved by the Morristown Memorial Hospital Institutional Review Board.

Clinical evaluation

A medical history was obtained from each subject with attention to cardiovascular risk factors (smoking, ethanol use, and family history of CAD or CAD risk factors). A diabetic history was obtained, which included diabetes duration, hospitalizations for hyperglycemia or hypoglycemia, insulin dosage, and diabetes-related complications. Details related to medication intake were noted as well as other significant medical history.

All subjects underwent physical examination with measurement of weight and height and calculation of BMI. Blood pressures were measured manually using a sphygmomanometer in the sitting position. Cardiac auscultation and qualitative screening for the presence of limited joint mobility of the hand and peripheral neuropathy were performed.

Laboratory evaluation

Fasting blood was drawn for the measurement of basic metabolic profile, creatinine, calcium, magnesium, phosphorous (Ortho Clinical Diagnostics, Rochester, NY), HbA_{1c} (Bio-Rad Laboratories, Hercules, CA), cardiac lipid risk profile (Polymedco, Cortlandt Manor, NY), and determination of lipoprotein(a) [Lp(a)] and homocysteine levels (Quest Diagnostics, Teterboro, NJ). In addition, a spot urine sample was obtained for calculation of microalbumin-to-creatinine ratio (Ortho Clinical Diagnostics).

EBT

All subjects underwent electron beam computed tomography of the heart utilizing an Imatron C-150 XP Ultrafast CT Scanner (Imatron, South San Francisco, CA). Forty contiguous 3-mm axial sections were obtained from the carina to diaphragm with electrocardiogram gating at end-inspiratory breath hold.

Scans were reviewed on a slice-by-slice basis, and three contiguous pixels, each in excess of 130 Houndsfield units, were automatically highlighted and reviewed by the radiologist for confirmation of coronary artery calcification. This process included measurement of the highest Houndsfield units of noncoronary tissue in each slice. To be considered calcified coronary plaque, an area in question had to exceed this value.

All calcium scoring was performed on an independent computer workstation using commercially available software (AccuScore; Acculmage Diagnostics, South San Francisco, CA).

The radiologist reading EBT scans was blinded to all clinical data, and those subjects with calcium scores >0 were classified as EBT positive.

Statistical analysis

Contingency table analysis was used to examine bivariate relationships. Statistical relationships between binary variables were tested using Fisher's exact test, and those between two variables with greater than two categories were tested using an appropriate χ^2 approximation to Fisher's exact test. Logistic regression was employed using the method suggested by Hosmer and Lemeshow (16) to construct a parsimonious model of independent risk factors that predict the presence of a positive cardiac EBT. All statistical hypotheses were tested at $\alpha = 0.05$.

In addition, the jackknife technique (17) was used to assess the impact of potentially influential individual outliers that might meaningfully alter the interpretation of model results.

RESULTS

In our study population, the overall prevalence of positive cardiac EBT was 11 of 101 (10.9%); 8 of 53 (15.1%) in male and 3 of 48 (6.3%) in female subjects. Mean calcium score in EBT-positive subjects was 12.5 ± 27.5 (mean ± SD; range, 1.0–95.8).

CAC was more common in males, smokers, and those with elevations of Lp(a), although this relationship did not quite reach statistical significance because of our cohort size. Demographic characteristics, risk factors, and laboratory data for subjects with positive and negative EBT scans are shown in Tables 1, 2, and 3.

Logistic regression model results are presented in Table 4. This model indicates that smokers were nearly five times more likely than nonsmokers to have a positive EBT ($P = 0.03$). In addition, each 0.36 mmol/l increase in Lp(a) level was associated with a 10% increased risk for positive EBT ($P = 0.05$). These effects were present after controlling for duration of diabetes postpuberty, triglyceride levels, BMI, and treatment with ACE in-

Table 2—*Characteristics of EBT-positive and EBT-negative subjects*

	EBT positive	EBT negative
Age (years)	20.4 ± 3.2 (17–28)	20.9 ± 2.8 (17–29)
Duration of diabetes (years)	12.6 ± 4.2 (6.7–18.9)	12.7 ± 3.7 (5.7–21.3)
Duration of diabetes postpuberty (years)	8.5 ± 3.6 (4.4–16.1)	9.6 ± 3.4 (4.5–19.2)
Insulin dosage (units · kg^{-1} · day^{-1})	0.76 ± 0.22 (0.20–1.0)	0.81 ± 0.27 (0.23–1.78)
Systolic BP (mmHg)	114.9 ± 6.9 (104–130)	116.4 ± 11.2 (92–142)
Diastolic BP (mmHg)	74.4 ± 7.2 (62–86)	73.9 ± 7.3 (56–92)
BMI	26.0 ± 3.4 (20.1–30.8)	24.5 ± 3.1 (18.1–38.7)
HbA_{1c} (%)	9.1 ± 1.9 (6.8–12.8)	8.4 ± 1.6 (5.5–14.3)
Calcium score	12.5 ± 27.8 (1.0–95.8)	0

Data are means ± SD (range). BP, blood pressure.

Table 3—*Lipid data for EBT-positive and EBT-negative subjects*

	EBT positive	EBT negative
Cholesterol (mmol/l)	4.59 ± 0.88 (3.59–5.77)	4.57 ± 0.80 (2.82–6.80)
HDL (mmol/l)	1.32 ± 0.41 (0.75–1.86)	1.35 ± 0.35 (0.78–2.69)
LDL (mmol/l)	2.66 ± 0.86 (1.47–3.96)	2.67 ± 0.71 (0.49–4.76)
Cholesterol/HDL	3.9 ± 1.60 (2.0–7.6)	3.5 ± 0.89 (2.0–5.3)
VLDL (mmol/l)	0.61 ± 0.55 (0.26–2.17)	0.52 ± 0.24 (0.16–1.40)
Triglycerides (mmol/l)	1.32 ± 1.12 (0.64–1.71)	1.14 ± 0.53 (0.35–3.01)
Lp(a) (mmol/l)*	1.69 ± 1.32 (0.22–3.50)	0.97 ± 1.25 (<0.14–7.05)

Data are means ± SD (range). *$P = 0.07$.

hibitors. Results obtained using the jackknife technique indicate that our original model estimates were stable and were not affected by influential outlier cases within the study sample.

There was no association demonstrated for CAC with age, BMI, duration of diabetes, duration of diabetes postpuberty, insulin dosage (per kg/day), family history of CAD, or quantity of ethanol intake. CAC prevalence was not increased in subjects with systolic or diastolic hypertension or limited joint mobility of the hand. In addition, CAC was not associated with elevations in serum calcium or creatinine, HbA_{1c}, homocysteine, or fasting lipid concentrations. The presence of early diabetic nephropathy as evidenced by elevated urine microalbumin-to-creatinine ratio or use of ACE inhibitors was unrelated to the presence of CAC.

CONCLUSIONS

Our data suggest that coronary artery calcification on EBT is not an uncommon finding in young adults with established type 1 diabetes. Moreover, the presence of type 1 diabetes is associated with an increased risk for CAC. In the community-based Epidemiology of Coronary Artery Calcification (ECAC) Study (18), the prevalence of CAC was 8.8% in men and 1.2% in women aged 20–30 years with no history of diabetes. This finding is in contrast to a prevalence of 15.1% for men and 6.3% for women in our study population.

Several recent studies have reported a prevalence of CAC in those with type 1 diabetes (19,20). These study populations, however, were older than our cohort. This limitation, as well as variance in minimum calcium threshold reported, makes direct comparison of our data with other studies problematic. The most comparable data are those of Olson et al. (21), who documented an 11% overall risk for CAC in a small number of type 1 diabetic subjects <30 years of age. This finding is nearly identical to the 10.9% prevalence noted in our study population.

Of the known cardiovascular risk factors studied, only three—male sex, smoking, and elevated Lp(a) level—were found to be associated with increased risk for CAC in our young diabetic population. Others have reported increased risk for CAC in the type 1 diabetic population to be associated with diabetes duration and age (19,21), hypertension (19–21), and BMI (20). This finding was not corroborated in our younger subjects. This divergence may suggest that risk factors related to early CAD may differ from those associated with later disease.

Although CAC in our study population was more common in male subjects, a significantly increased risk for CAC in diabetic compared with ECAC nondiabetic female subjects was noted (18). This finding supports the hypothesis that the presence of type 1 diabetes can attenuate the protection of female sex on the risk for coronary atherosclerosis, an effect that has been noted by other investigators (19–21).

Smoking increased risk for CAC fivefold in our young diabetic cohort. This increased risk for smokers was noteworthy given the relatively limited tobacco exposure (mean 0.82 ± 1.2 pack years) in our EBT-positive population.

Subjects with elevated Lp(a) levels, an independent CAD risk factor (22), also had an increased prevalence of CAC. CAC risk was incrementally related to absolute Lp(a) levels but independent of other fasting lipid values. This finding is of clinical significance, since Lp(a) levels are often elevated in those with type 1 diabetes (23) but appear to be unrelated to glycemic control (24).

Mean calcium score for our EBT-positive subjects was 12.5, a value unlikely to be associated with significant coronary artery narrowing. The presence of any calcification on cardiac EBT, however, is indicative of intimal changes consistent with atherosclerosis and established CAD (11). Huskey et al. (25) have reported progression of CAD as assessed by CAC over short periods of time in adult subjects with type 1 diabetes. This finding reinforces the importance of early identification of this high-risk subgroup. Aggressive modification of CAD risk factors may alter the natural history of coronary atherosclerosis in this population, slow the progression of coronary artery narrowing, and lower risk for myocardial infarction.

The power of our univariate data analysis was limited by our cohort size. In addition, the cross-sectional nature of our study design has allowed us only a small glimpse into the early natural history of CAD. We are continuing to expand our study population as well as follow our initial cohort over a longer time course to more clearly delineate the natural history of CAC and its association with CAD risk factors in this high-risk population.

In conclusion, early coronary atherosclerosis as manifested by CAC on EBT is not uncommon in young adults with type 1 diabetes. Those at highest risk for CAC

Table 4—*Odds ratios for CAC for selected risk factors*

Risk factor	Odds ratio parameter estimate	Wald 95% confidence limits
Triglycerides	1.01	0.99–1.01
Lp(a)*	1.02	1.01–1.03
BMI	1.13	0.93–1.38
Duration of diabetes postpuberty	0.85	0.67–1.07
Smoker†	4.97	1.14–21.62

Hosmer and Lemeshow's C statistic = 5.4, 8 df, $P = 0.71$. *$P = 0.05$; †$P = 0.03$.

include males, smokers, and those with elevated Lp(a) levels. The presence of CAC may identify a subgroup of diabetic subjects at higher risk for progressive CAD. Longitudinal studies will be necessary to determine whether early and aggressive intervention to modify cardiovascular risk factors can be effective in altering the course of CAD in this population.

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