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Progression of Coronary Artery Calcium in Type 1 Diabetes Mellitus

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Abstract

Coronary artery calcium (CAC) has been previously associated with atherosclerotic plaque disease and coronary events. Thus, identifying predictors of CAC progression may provide new insights on early risk factor intervention and subsequent reduction of more severe atherosclerotic disease. We aimed to identify risk factors of CAC progression and evaluate whether risk factor change relates to CAC progression in a cohort of type 1 diabetes mellitus (DM). Participants of the Pittsburgh Epidemiology of Diabetes Complications study, a prospective investigation of childhood-onset type 1 DM, who received 2 electron beam computed tomography screenings 4 years apart were selected for study (n=222). CAC was calculated by the Agatston method of scoring and progression was defined as an increase >2.5 in the square root-transformed CAC score. Adjusting for diabetes duration and initial CAC score, body mass index (BMI, OR=1.13 95% CI=1.01-1.26), non-high density lipoprotein cholesterol (OR=1.01, 95% CI=1.003-1.03), and albumin excretion rate (OR=1.30, 95% CI=1.03-1.63) were associated with CAC progression. When considering change in risk factors, an increase in BMI (OR=1.38, 95% CI=1.10-1.72) was also associated with CAC progression after adjustment. In conclusion, in this cohort of type 1 DM, in addition to baseline BMI, non-high density lipoprotein cholesterol and albumin excretion rate, all known coronary artery disease risk factors, weight gain further added to the prediction of CAC progression. Thus, weight control, in addition to lipid and renal management may help retard atherosclerosis progression in type 1 DM.

Keywords

coronary artery calcification; progression; type 1 diabetes mellitus; BMI

Introduction

Electron beam computed tomography (EBT) is a non-invasive method for quantifying the extent of calcium formation present in the coronary arteries. Coronary artery calcium (CAC) measured by EBT can be used as an indicator of atherosclerotic burden (1). Furthermore, among persons with type 1 diabetes mellitus (DM), CAC has been previously shown to correlate with coronary artery disease (2). Thus, identifying modifiable risk factors associated with CAC progression may provide new targets for early intervention and potentially reduction of the

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rates of more severe atherosclerotic disease. However, with the exception of the CAC in Type 1 DM (CACTI) study (3-6), we are not aware of other investigations on predictors of CAC progression in type 1 DM. We, therefore, aimed to identify risk factors of CAC progression and to evaluate whether risk factor change relates to CAC progression in a type 1 DM cohort. Ultimately, upon sufficient follow-up and cardiovascular events, we will assess whether progression is a better predictor of events than the baseline score and thus, whether CAC progression can be used for monitoring.

Methods

Participants for this evaluation were selected from the Pittsburgh Epidemiology of Diabetes Complications (EDC) study cohort, a prospective investigation of childhood-onset type 1 DM now entering its 20th year of follow-up. The EDC study has been previously described in detail (7). Briefly, participants were diagnosed prior to their 17th birthday, or seen within 1 year of such diagnosis, at Children's Hospital of Pittsburgh between 1950 and 1980. Although clinic based, this population has been shown to be representative of the type 1 DM population in Allegheny County, Pennsylvania (8). Baseline examinations for the EDC study were conducted between 1986 and 1988, when the cohort's mean age was 28 and diabetes duration was 19 years. Participants were subsequently invited to biennial examinations. At the 10-year follow-up examination (1996-1998), EBT screening was made available first to all participants aged ≥ 30 years and subsequently to all those over 18 years of age. A total of 304 participants underwent EBT screening (2); 228 thereof also had a repeat scan approximately 4 years later. The University of Pittsburgh Institutional Review Board approved the study protocol.

All complications and risk factors were assessed at the time of the 2 EBT screenings, the first of which occurred during the 10-year follow-up examination (1996-1998) and the second approximately 4 years later. Prior to each biennial clinic visit, participants were sent questionnaires concerning demographic, health care, medical history, and physical activity information. An "ever smoker" was defined as a person who smoked ≥ 100 cigarettes over their lifetime. Intensive insulin therapy was defined as ≥ 3 insulin shots daily or insulin pump use. Depressive symptomatology was assessed by the Beck Depression Inventory (9). Hypertension was defined as blood pressure $\geq 140/90$ mmHg or current antihypertensive medication treatment.

CAC was assessed via EBT using a GE-Imatron ultrafast computed tomography scanner (GE-Imatron, San Francisco, CA). Scans were triggered by electrocardiogram signals at 80% of the R-R interval and obtained in 3 mm contiguous sections of the heart. CAC was calculated by the Agatston method (10) and progression was defined as an increase >2.5 in the square root-transformed CAC score (11), as this transformation provided the best fit. Previous use of a suggested modification (12) to address the potential systematic bias of elevated calcium scores in those with higher body mass index (BMI) did not appear to significantly alter scoring. While the use of a phantom may be helpful in cross-sectional observations of a population, we have not found that it adds to longitudinal analyses within our study. EBT results were made available to participants and their physicians and cardiovascular risk factor reduction was stressed for those with significant CAC. Further evaluation was decided upon by the participants' physicians, although a cardiologist was available for consultation. Coronary artery disease was defined as EDC physician-diagnosed angina, myocardial infarction confirmed by Q-waves on an electrocardiogram (Minnesota codes 1.1 or 1.2) or hospital records, angiographic stenosis $\geq 50\%$, revascularization, or ischemic ECG changes (Minnesota codes 1.3, 4.1-4.3, 5.1-5.3, and 7.1).

Original hemoglobin A₁ (1986-1998) and hemoglobin A_{1c} (1998-2004) were converted to DCCT standard hemoglobin A_{1c} values using regression formulae derived from duplicate

analyses (DDCT hemoglobin A_{1c} = (0.83 * EDC hemoglobin A₁) + 0.14; and DCCT hemoglobin A_{1c} = (EDC hemoglobin A_{1c} - 1.13) / 0.81). Cholesterol and triglycerides were measure enzymatically (13,14). High density lipoprotein cholesterol was determined using a modified (15) heparin and manganese chloride precipitation technique of the Lipid Research Clinics method (16). Low density lipoprotein cholesterol was calculated by using the Friedewald equation (17). Non high density lipoprotein cholesterol was calculated as total minus high density lipoprotein cholesterol. Estimated glucose disposal rate (insulin sensitivity) was estimated by a regression equation derived from hyperinsulinemic euglycemic clamp studies on 24 subjects chosen to represent the full spectrum of insulin resistance as represented by insulin resistance risk factors (18). White blood cell count was obtained using a counter S-plus IV.

Serum and urinary albumin were measured by immunonephelometry (19,20), and creatinine was assayed by an Ectachem 400 Analyzer (Eastman Kodak Co., Rochester, NY), which unlike picric acid-based methods, does not overestimate creatinine concentrations in diabetes individuals (21). Overt nephropathy was defined as albumin excretion rate >200 µg/min in 2 of 3 timed urine collections or, in the absence of urine, a serum creatinine >153 µmol/l (>2 mg/dl) or, renal failure or renal transplantation.

Variables not following a normal distribution were log transformed (i.e. triglyceride concentration, Beck depression inventory, serum creatinine, and albumin excretion rate). When normality was not achieved by transformation (i.e. for change in the following variables: BMI, low density lipoprotein, non high density lipoprotein, total cholesterol, Beck depression inventory, and serum creatinine), non-parametric procedures were used. The student's t-test and chi square (or Fisher's exact, as appropriate) tests were used to examine univariate associations, whereas multiple logistic regression models were constructed to assess significant predictors of CAC progression, as well as the predictive value of risk factor change. To evaluate the effect of risk factors over the 10 years up to the initial CAC measurement on progression, analyses were also conducted using updated means of risk factors. Data were analyzed using SAS version 9.1 (Cary, NC). Results were considered significant at $p < 0.05$.

Results

Of the 304 individuals with a first EBT, 22 (7.2%) died, whereas another 54 (17.8%) did not return for a second EBT. Compared to persons with a repeat EBT, those who did not return for a second EBT had a higher hemoglobin A_{1c} ($p=0.03$) and white blood cell counts ($p=0.01$) and were more insulin resistant ($p=0.003$), but had similar CAC scores at first assessment ($p=0.85$). Of the 228 persons with 2 EBT scans performed, 222 had full information on the covariates examined and their characteristics by progression of CAC are shown in Table 1. Surprisingly, glycemic control was not related to CAC progression in this cohort and there was no evidence of a threshold effect. Generally, similar univariate risk factors were observed for male and female participants, although measures of body fatness and the Beck depression inventory were associated with CAC progression only among men. Interestingly, although baseline hemoglobin A_{1c} was not in itself related to CAC progression, a greater proportion of non-progressors used more than 3 insulin injections daily among females ($p=0.07$); however, the proportion on intensive insulin therapy who also regularly monitored their blood glucose (≥ 3 times daily) did not differ significantly ($p=0.14$). In multivariable logistic regression analyses, the final model included diabetes duration, baseline calcification level, BMI, non high density lipoprotein cholesterol, and albumin excretion rate (Table 2, Model 1) as significant predictors of CAC progression. These results were not altered when analyses were restricted to persons free of cardiovascular disease ($n=183$; 83 progressors). When logistic regression was conducted separately for male and female participants, with the exception of baseline CAC score (OR=1.51, 95% CI=1.22-1.86), BMI was the only significant predictor of CAC

progression among males (OR=1.31, 95% CI=1.09-1.59), whereas in females significant risk indicators included the baseline CAC score (OR=1.46, 95% CI=1.20-1.77), duration of diabetes (OR=1.13, 95% CI=1.04-1.23), non high density lipoprotein cholesterol (OR=1.02, 95% CI=1.001-1.04), and albumin excretion rate (OR=1.63, 95% CI=1.11-2.40). The final model using updated means of risk factors from study initiation to first EBT scan is presented in Table 2 (Model 2). Although results were quite similar to those using risk factors from the time of the first EBT scan, years with hypertension and years of angiotensin converting enzyme inhibitor use now also became significant whereas albumin excretion rate was no longer selected.

In assessing change in risk factors (follow-up – baseline) by CAC progression, generally, greater increases in BMI and weight and greater decreases in lipid levels (due to increased use of lipid lowering medication) were noted among progressors. Despite greater use of hypertension medication among progressors, no differences were observed in blood pressure levels. Once again, change in hemoglobin A_{1c} was not related to CAC progression in this cohort (not shown). Logistic models were constructed for 182 individuals with risk factor data available both at baseline and at follow-up. Univariately significant change variables were included in logistic regression models, adjusting for diabetes duration, baseline CAC level, as well as the baseline level of the change variable (not shown). Only change (increase) in BMI was significantly associated with CAC progression. This association was somewhat stronger among male than female (OR for a unit increase in BMI was 1.76 (95% CI=1.17-2.65) and 1.28 (95% CI=0.997-1.65), respectively) participants (p-value for interaction=0.08). Including, one at a time or in backward elimination, univariately significant change variables to Model 1 from Table 2, change in BMI was the only significant change covariate (final model presented in Table 3).

Discussion

In this cohort of individuals with a long duration of type 1 DM, consistent baseline predictors of CAC progression were BMI, non-high density lipoprotein cholesterol, and albumin excretion rate, all recognized CAD risk factors. Diabetes duration was also a predictor of CAC progression. In examining the value of risk factor change on CAC progression, we found that only an increase in BMI was associated with progression of CAC.

Contrary to a previous report on CAC progression by the CACTI study (3) and another on lower calcium prevalence in the primary prevention cohort from the DCCT/EDIC (22), glycemic control was not related to CAC progression in this cohort and we were not able to identify a threshold. In the late 90's, glycemic control was far from optimal among EDC participants, with only 14.0% of the study cohort keeping their hemoglobin A_{1c} levels below 7.0%. Nevertheless, the proportion who progressed was similar, if not slightly higher, among those with optimal glycemic control compared to persons with higher levels of hemoglobin A_{1c} (58.1% versus 48.2%, p=0.31). Snell-Bergeon et al. (3) also reported an increased risk of CAC progression with higher insulin dose among overweight individuals. This relationship differed for the female and male participants of the EDC study. In contrast to the CACTI results, both insulin dose (47.0 versus 39.4, p=0.17) as well as the dose of insulin per body weight (0.64 versus 0.51, p=0.05) were slightly increased among overweight women who did not progress despite similar insulin sensitivity, as measured by eGDR. However, none of these relationships were significant after adjustment for duration of diabetes and baseline CAC score. As in CACTI (3) though, there was an indication of lower units of insulin (55.6 versus 64.0, p=0.06) and insulin dose per body weight (0.67 versus 0.76, p=0.09) in overweight men who did not progress compared to progressors, even after adjustment for diabetes duration and baseline CAC score.

Despite the small sample size, analyses of risk factor change in relation to CAC progression identified BMI as the only covariate for which elevations appear to increase risk of CAC progression. No considerable decline in hemoglobin A_{1c} was observed during the follow-up period in either group (an increase of 0.07 units for the stable versus a decrease of 0.19 units for the progressing group) and thus, hemoglobin A_{1c} change was associated with progression. Nevertheless, we have previously shown that although baseline hemoglobin A_{1c} was not related to coronary artery disease incidence, hemoglobin A_{1c} elevations during the follow-up period increased risk of disease (23). Together, these findings might suggest that hemoglobin A_{1c} is not related to the underlying atherosclerotic process but rather to the precipitation of events.

CACTI investigators have previously reported that adiponectin levels are inversely associated with CAC progression in both persons with type 1 DM and non-diabetic adults (4). Unfortunately, data on adiponectin are not currently available in this subset of the EDC population, although we have also previously observed a relationship between adiponectin and the incidence of coronary artery disease (24). Two further reports from CACTI also identified a marker of T-cell activation, soluble interleukin-2 receptor (sIL2r) and the APOA4 Gln360His polymorphism as risk factors for CAC progression in type 1 DM (5,6). However, information on these polymorphisms are not available in EDC and thus, their effect could not be assessed.

Study limitations include risk factor differences between those with and without a repeat EBT scan; despite similar baseline CAC scores, if those without a repeat scan had a greater rate of CAC progression, it is likely that the true relationship between risk factors and CAC progression is stronger than observed here. It is further possible that, depending on their initial CAC score, participants' physicians intervened to manage risk factors. Indeed, as previously reported (25), further cardiac testing increased with increasing initial CAC score. Such management may have led to weaker associations between baseline risk factors and CAC progression, although evaluation of risk factor change addresses this problem.

Our ultimate goal is to identify what rate of progression best predicts subsequent cardiovascular events. Although sufficient follow-up time and events have not yet occurred to fully address this issue, a very preliminary look suggests that in our population CAC score is the best single predictor of CAD events (OR=8.57, 95% CI=1.16-50.27 for a CAC score ≥100) (26). Approximately 9% of our population developed this risk level over the 4-year period.

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Table 1
Baseline characteristics (means (standard deviation) or sample size (percent)) and coronary artery calcium progression

Participant characteristics	Overall (n=222; 110 progressed)		Males (n=104; 54 progressed)		Females (n=118; 56 progressed)	
	Stable	Progressed	Stable	Progressed	Stable	Progressed
Age (years)	34.1 (6.5)	41.6 (7.0)*	34.2 (5.8)	40.1 (7.1)*	33.9 (7.1)	43.1 (6.5)*
Diabetes duration (years)	25.8 (6.4)	32.1 (6.8)*	26.1 (5.9)	31.1 (6.8)*	25.5 (6.8)	33.0 (6.8)*
Females	62 (55.4%)	56 (50.9%)				
Waist to hip ratio	1.00 (1.2)	1.03 (1.2)	1.1 (1.3)	1.1 (1.2)	0.79 (0.07)	0.80 (0.05)
Body mass index (kg/m ²)	24.6 (3.4)	25.5 (3.8)	24.7 (2.8)	26.4 (3.1)*	24.6 (3.8)	24.4 (4.2)
Height (m)	167.8 (8.3)	167.9 (9.5)	174.1 (5.8)	174.4 (7.4)	162.7 (6.3)	161.5 (6.7)
Weight (kg)	69.4 (10.8)	71.2 (14.1)	74.9 (9.7)	80.3 (11.2)*	65.0 (9.6)	63.8 (11.7)
Ever smoked (n)	34 (30.4%)	38 (34.6%)	17 (34.0%)	19 (35.2%)	17 (27.4%)	19 (33.9%)
Estimated glucose disposal rate (mg/kg/min)	8.0 (2.0)	7.1 (2.3)*	7.3 (1.7)	6.3 (2.1)*	8.6 (2.0)	7.8 (2.2)
Hemoglobin A _{1c} (%)	8.3 (1.3)	8.2 (1.3)	8.4 (1.2)	8.3 (1.3)	8.1 (1.4)	8.2 (1.3)
Quartiles of hemoglobin A _{1c} (%)						
<7.3	24 (21.4%)	29 (26.4%)	8 (16.0%)	15 (27.8%)	16 (25.8%)	14 (25.0%)
7.3 - <8.2	32 (28.6%)	24 (21.8%)	15 (30.0%)	12 (22.2%)	17 (27.4%)	12 (21.4%)
8.2 - <9.0	27 (24.1%)	26 (23.6%)	12 (24.0%)	9 (16.7%)	15 (24.2%)	17 (30.4%)
≥9.0	29 (25.9%)	31 (28.2%)	15 (30.0%)	18 (33.3%)	14 (22.6%)	13 (23.2%)
Hemoglobin A _{1c} above median (8.2%)	56 (50.0%)	57 (51.8%)	27 (54.0%)	27 (50.0%)	29 (46.8%)	30 (53.6%)
Intensive insulin therapy	44 (40.4%)	38 (36.2%)	13 (26.5%)	20 (38.5%)	31 (51.7%)	18 (34.0%)* p=0.06
Intensive insulin therapy and checking blood glucose ≥3 times daily [†]	29 (27.4%)	21 (20.4%)	9 (18.8%)	10 (20.0%)	20 (34.5%)	11 (20.8%)
Insulin / kg body weight / day	0.67 (0.19)	0.64 (0.22)	0.70 (0.20)	0.72 (0.22)	0.65 (0.18)	0.55 (0.19)*
Systolic blood pressure (mmHg)	111.3 (13.2)	120.5 (17.3)*	113.6 (12.2)	122.2 (18.4)*	109.4 (13.9)	119.0 (16.4)*
Diastolic blood pressure (mmHg)	69.8 (8.7)	70.1 (12.9)*	72.9 (8.4)	76.0 (13.4)*	67.4 (8.2)	64.2 (9.4)*
Hypertension	16 (14.3%)	37 (33.6%)*	6 (12.0%)	19 (35.2%)*	10 (16.1%)	18 (32.1%)*
Angiotensin converting enzyme inhibitor use	22 (19.6%)	29 (26.4%)*	12 (24.0%)	15 (27.8%)	10 (16.1%)	14 (25.0%)*
Blood pressure medication use	0 (0.0%)	5 (4.6%)*	0 (0.0%)	2 (3.7%)*	0 (0.0%)	3 (5.4%)*
High density lipoprotein (mg/dl)	55.9 (14.2)	54.0 (14.4)	48.8 (10.1)	47.5 (11.2)	61.6 (14.7)	60.5 (14.4)*
Low density lipoprotein (mg/dl)	110.6 (28.3)	190.4 (34.0)*	114.9 (26.9)	118.8 (30.1)*	106.4 (28.8)	120.7 (38.0)*
Triglycerides (mg/dl) ^{†,‡}	91.0 (44.3)	107.4 (56.6)*	97.3 (51.0)	120.5 (66.6)*	86.1 (38.1)	93.0 (40.6)*
Non-high density lipoprotein (mg/dl)	126.9 (31.4)	142.5 (36.4)*	131.7 (30.7)	147.3 (32.7)*	122.3 (31.4)	138.0 (39.8)*
Total cholesterol (mg/dl)	182.9 (31.6)	196.5 (37.7)*	180.5 (30.1)	194.8 (33.7)*	184.0 (32.5)	198.6 (41.7)*
Beck depression inventory ^{†,‡}	5.3 (6.8)	6.9 (6.8)*	3.7 (6.8)	5.9 (6.6)*	6.8 (6.6)	7.7 (7.0)
Pulse rate	71.5 (10.8)	70.0 (9.1)	72.7 (11.3)	69.6 (8.9)	70.5 (10.5)	70.4 (9.5)
White blood cell count ×10 ³ /mm ²	6.6 (1.8)	7.0 (2.0)	6.8 (2.1)	6.8 (1.8)	6.4 (1.5)	7.2 (2.2)*
Coronary artery disease	12 (10.7%)	27 (24.6%)*	4 (8.0%)	13 (24.1%)*	8 (12.9%)	14 (25.0%)*
Serum creatinine (mg/dl) [†]	0.98 (0.75)	1.1 (0.69)*	0.97 (0.30)	p=0.03	0.93 (0.83)	p=0.09
Albumin excretion rate (μg/min) [†]	89.9 (334.9)	140.2 (344.8)*	152.3 (478.8)	163.2 (332.5)*	40.2 (120.1)	120.0 (360.8)*
Overt nephropathy	18 (16.1%)	33 (30.0%)*	9 (18.0%)	16 (29.6%)	9 (14.5%)	17 (30.4%)*

* p-value < 0.05

[†] Logarithmically transformed before statistical testing

‡The sample size for intensive insulin therapy (≥ 3 insulin injections/day) was 214 (109 non-progressors, 105 progressors), for intensive insulin therapy and regular (≥ 3 times daily) blood glucose testing was 209 (106 non-progressors, 103 progressors), for low density lipoprotein cholesterol and triglycerides was 201 (106 non-progressors, 95 progressors) and for Beck depression inventory it was 213 (108 non-progressors; 105 progressors)

Note: Among overweight women, insulin dose per body weight was 0.64 for the stable vs. 0.51 for the progressor group ($p=0.05$); among overweight men, insulin dose per body weight was 0.67 for the stable vs. progressor 0.76 group ($p=0.09$)

Table 2
Logistic regression derived odds ratios (95% CI) linking calcium progression to specified predictors (n=222)

Risk factors	Model 1: Risk factors at first EBT scan (1996-1998)	Model 2: Updated means of risk factors (1986-1998)
Square root of baseline CAC score	1.44 (1.25-1.66)	1.44 (1.24-1.67)
Diabetes duration (years)	1.10 (1.04-1.17)	1.10 (1.04-1.17)
Body mass index (kg/m ²)	1.13 (1.01-1.26)	1.24 (1.07-1.44)
Hemoglobin A _{1c} (%)	Not selected	Not selected
Insulin dose per body weight	Not made available	Not selected
Hypertension [†]	Not selected	1.44 (1.12-1.82)
Systolic blood pressure (mmHg)	Not selected	Not selected
High density lipoprotein cholesterol (mg/dl)	Not made available	Not selected
Non high density lipoprotein cholesterol (mg/dl)	1.01 (1.003-1.03)	5.82 (0.96-35.22)
White blood cell count ×10 ³ /mm ²	Not selected	Not selected
Albumin excretion rate (µg/min) [*]	1.30 (1.03-1.63)	Not selected
Angiotensin converting enzyme inhibitor use [†]	Not made available	0.68 (0.49-0.93)
Akaike's Information Criterion	181.685	179.075

* Logarithmically transformed

[†] A dichotomous variable (yes/no) is included in Model 1 whereas years of hypertension or angiotensin converting enzyme inhibitor use is used Model 2

Table 3

Logistic regression derived odds ratios (95% CI) linking calcium progression to change in specified predictors (n=182; 91 progressors)

Covariates	Final model
Square root of baseline CAC score	1.34 (1.17-1.53)
Diabetes duration (years)	1.18 (1.09-1.29)
Body mass index (kg/m ²)	1.16 (1.02-1.32)
Non-high density lipoprotein cholesterol (mg/dl)	1.02 (1.003-1.03)
Log albumin excretion rate (µg/min)	1.25 (0.98-1.61)
Change in body mass index (kg/m ²)	1.38 (1.10-1.72)
Change in non-high density lipoprotein (mg/dl)	Not selected
Change in log albumin excretion rate (µg/min)	Not selected
Akaike's Information Criterion	145.523