Obesity and Coronary Artery Calcium in Diabetes: The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study

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Abstract

Background: The aim was to examine whether excess weight is associated with coronary artery calcium (CAC), independent of metabolic parameters in adults with type 1 diabetes (T1D).

Methods: Subjects between 19 and 56 years of age with T1D ($n=621$) from the Coronary Artery Calcification in Type 1 Diabetes study were classified as abnormal on four metabolic parameters: blood pressure $\geq 130/85$ mm Hg or on antihypertensive treatment; high-density lipoprotein-cholesterol of <40 mg/dL for men or <50 mg/dL for women; triglycerides of ≥ 150 mg/dL; or C-reactive protein of ≥ 3 $\mu\text{g/mL}$. Study participants with two or more abnormal parameters were classified as metabolically abnormal. Weight categories by body mass index were normal (<25 kg/m²), overweight (25 to <30 kg/m²), and obese (≥ 30 kg/m²). CAC was measured at two visits 6.0 $\pm$ 0.5 years apart. Progression of CAC was defined as an increase in square root transformed CAC volume of ≥ 2.5 mm³ or development of clinical coronary artery disease.

Results: Among subjects with T1D, 48% of normal, 61% of overweight, and 73% of obese participants were classified as metabolically abnormal ($P<0.0001$). Overweight and obesity were independently associated with presence of CAC, independent of presence of metabolically abnormal. Obesity but not overweight was associated with CAC progression, independent of the other cardiovascular risk factors.

Conclusions: Although obesity is known to increase cardiovascular disease risk through inducing metabolic abnormalities such as dyslipidemia, hypertension, and inflammation, it is also a strong predictor of subclinical atherosclerosis progression in adults with T1D independent of these factors.

Introduction

OBESITY IS AN IMPORTANT risk factor for cardiovascular disease (CVD), but it is unclear how much of this excess risk is mediated through the effects of obesity on hypertension, inflammation, dyslipidemia, and insulin resistance. Furthermore, it is unclear if overweight and obesity increase cardiovascular risk in the absence of metabolic abnormalities, especially in patients who are already at high risk for CVD, such as adults with type 1 diabetes (T1D). Adults with T1D are no more likely to be overweight or obese than individuals without diabetes, in contrast to patients with type 2 diabetes, among whom obesity is prevalent. However, excess weight is not an exclusive concern of patients with type 2 diabetes. Patients with T1D who gained weight after insulin intensive therapy had lower high-density lipoprotein (HDL) levels and

higher low-density lipoprotein (LDL) levels and blood pressure than patients who did not gain weight.¹ T1D subjects with higher body mass index (BMI) have more CVD risk factors than patients with lower BMI.^{2–4} High normal weight was associated with worse glycemic control, higher triglycerides, and higher systolic blood pressure compared with patients with lower BMI in a Japanese population of T1D.⁵ Several potential sources of excess weight in T1D patients have been suggested, including insulin therapy, low physical activity level, and increased food intake due to fear of hypoglycemia.^{6,7} Obesity has been associated with an elevated number of CVD risk factors, elevated risk of type 2 diabetes, increased risk of myocardial infarction, and increased mortality in the general population.^{8–10} However, the association between excess weight and CVD among individuals with T1D has been less well studied and may be an important modifiable

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risk factor in this high-risk group in an environment of increasing obesity worldwide.

This study examined whether excess weight is associated with the presence and progression of coronary artery calcium (CAC), a marker of subclinical atherosclerosis, independent of metabolic parameters in adults with T1D.

Research Design and Methods

Study participants

The Coronary Artery Calcification in Type 1 Diabetes Study is a prospective cohort study designed to determine the causes of accelerated development and progression of coronary atherosclerosis in subjects with and without diabetes. Participants ($n=1,416$) completed a baseline examination in 2000–2002 and were 19–56 years of age. The study assessed the extent of CAC in 652 participants with T1D and 764 control subjects without diabetes mellitus as reported previously.¹¹ Only the 652 subjects with T1D were included in this analysis, as there are likely different factors contributing to metabolic abnormalities in the setting of diabetes mellitus. All patients with diabetes had been diagnosed when younger than 30 years, had been treated with insulin within 1 year of diagnosis, and had disease duration of at least 4 years at enrollment. Of the 652 T1D individuals enrolled at baseline, 621 participants had data on CAC progression with a mean follow-up 6.0 ± 0.5 years later.

At the time of enrollment, all participants were asymptomatic for coronary artery disease and had no history of coronary artery bypass graft surgery, myocardial infarction, coronary angioplasty, or unstable angina. The study protocol was reviewed and approved by the Colorado Combined Institutional Review Board, and informed consent was obtained from all participants before enrollment.

Patient evaluation

Participants' height was measured to the nearest 0.1 cm using a stadiometer, and weight was measured to the nearest 0.1 kg. BMI (in kg/m^2) was calculated, and weight categories by BMI were normal ($<25 \text{ kg}/\text{m}^2$), overweight (between 25 and $<30 \text{ kg}/\text{m}^2$), and obese ($\geq 30 \text{ kg}/\text{m}^2$) for all subjects.¹⁰

Minimum waist and maximum hip measurements were obtained in duplicate, and the results were averaged. The average was used to calculate waist to hip ratio. Resting systolic blood pressure and diastolic blood pressure were measured three times after subjects had been seated for 5 min, and the second and the third measurements were averaged. Participants also completed standardized questionnaires, including medical history, medication inventory, rose angina questionnaire to assess history of chest pain, current and past smoking status, physical activity, food frequency, and family medical history of diabetes, CVD, and hypertension.

Participants were classified as abnormal on four metabolic parameters: blood pressure $\geq 130/85$ mm Hg or current antihypertensive treatment; HDL-cholesterol of $<40 \text{ mg}/\text{dL}$ for men or $<50 \text{ mg}/\text{dL}$ for women; triglycerides of $\geq 150 \text{ mg}/\text{dL}$; and C-reactive protein (CRP) of $\geq 3 \mu\text{g}/\text{mL}$ (patients with CRP $\geq 10 \mu\text{g}/\text{L}$ were excluded). Study participants with two or more abnormal parameters were classified as having metabolic abnormality (MA).

Laboratory analyses

After subjects fasted overnight for 12 h, blood was collected and centrifuged, and separated plasma was stored at 4°C until assayed. Total plasma cholesterol and triglyceride levels were measured using standard enzymatic methods, HDL-cholesterol was separated using dextran sulfate, and LDL-cholesterol was calculated using the Friedewald formula. High-performance liquid chromatography was used to measure glycosylated hemoglobin (Variant II, Bio-Rad, Hercules, CA). CRP was measured in the laboratory of Dr. Russell Tracy at the University of Vermont (Colchester, VT) with a BNII nephelometer from Dade Behring (Deerfield, IL), using a particle-enhanced immunonephelometric assay. Urinary albumin was measured by radioimmunoassay, and albumin excretion rate (AER) was determined by radioimmunoassay; the results of two timed overnight urine collections were averaged. Estimated glucose disposal rate (eGDR) 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.¹²

CAC

All participants underwent a coronary calcium scan using an ultrafast Imatron C-150XLP electron beam computer tomography scanner (GE/Imatron, San Francisco, CA) to obtain two sets of high-resolution, noncontrast, contiguous 3-mm tomographic images acquired at 100-ms exposure. Scanning started from near the lower margin of bifurcation of the main pulmonary artery with the subject holding his or her breath for 35–40 s and proceeded caudally. Calcified coronary artery lesions were identified as those with a minimum density of 130 Hounsfield units and a minimum area of three pixels (1.03 mm). A calcium score for each region was calculated by multiplying the area by the density score (1 for 130–199, 2 for 200–299, 3 for 300–399, and 4 for >399 Hounsfield units). A total CAC score in Agatston units was calculated by adding up scores for all slices separately for left main, left anterior descending, circumflex, and right coronary arteries.¹³ The calcium volume score was determined by the workstation using a standard algorithm. The scanner was recalibrated each day with a phantom. Effective radiation dose for an electron beam computer tomography sequence was 0.7–1.0 mSV for men and 1.0–1.3 mSV for women. A single technician obtained and scored all electron beam computed tomography scans, and the average of two scores obtained 5 min apart was used. CAC was measured twice at the baseline and twice at a follow-up 6.0 ± 0.5 years later and averaged at each visit.

Statistical analysis

Data are presented as arithmetic means and SDs for continuous variables, geometric means, and ranges for log-transformed variables and as percentages for categorical variables. The analysis of variance test was used for continuous variables, and the χ^2 test was used for categorical variables. The coronary calcium interpolated volume from each scan was square root transformed to reduce the variance across coronary calcium scores,¹⁴ and the square root transformed volumes were averaged for each visit. The difference between mean square root transformed coronary calcium

TABLE 1. CHARACTERISTICS OF PATIENTS ACCORDING TO WEIGHT AND THE PRESENCE OF METABOLIC ABNORMALITY

	Normal weight		Overweight		Obese	
	Metabolically abnormal (n = 129)	Metabolically normal (n = 141)	Metabolically abnormal (n = 154)	Metabolically normal (n = 100)	Metabolically abnormal (n = 71)	Metabolically normal (n = 26)
Age (years)	41 ± 9 ^a	37 ± 9	37 ± 9	37 ± 9	35 ± 9	34 ± 9
Men (%)	47	36	43	58	41	46
DDM (years)	24 ± 8	23 ± 9	24 ± 8	23 ± 9	22 ± 8	22 ± 7
SMK (%)	13	12	17	9	11	15
INS (U/kg)	0.57 ± 0.20	0.56 ± 0.23	0.69 ± 0.29 ^a	0.59 ± 0.22	0.82 ± 0.42 ^a	0.64 ± 0.26
SBP (mm Hg)	117 ± 17	114 ± 13	120 ± 12	117 ± 12	121 ± 14	119 ± 14
DBP (mm Hg)	74 ± 7	75 ± 8	81 ± 9 ^a	77 ± 8	82 ± 9	79 ± 10
HTN (%)	78 ^b	30	87 ^b	37	78 ^b	31
WHR	0.80 ± 0.09	0.79 ± 0.06	0.84 ± 0.07	0.82 ± 0.07	0.89 ± 0.08	0.85 ± 0.09
eGDR	6.2 (5.3–8.3) ^b	8.9 (7.6–10.8)	6.2 (5.3–7.3) ^b	8.2 (6.6–10.2)	5.6 (4.6–7.4) ^b	8.0 (6.9–9.9)
HbA1c (%)	8.8 ± 1.6 ^a	7.8 ± 1.6	8.3 ± 1.4 ^a	7.8 ± 1.0	8.5 ± 1.3 ^a	7.9 ± 1.3
TC (mg/dL)	169 ± 26	174 ± 33	179 ± 32	173 ± 31	184 ± 40	170 ± 34
HDL (mg/dL)	53 ± 17 ^a	61 ± 16	43 ± 11 ^b	56 ± 14	46 ± 14	52 ± 14
LDL (mg/dL)	94 ± 19	97 ± 31	107 ± 26	101 ± 26	106 ± 36	100 ± 25
TG (mg/dL)	270 (76–165) ^a	244 (56–91)	121 (94–178) ^b	71 (55–93)	311 (94–196) ^b	270 (62–102)
CRP (μg/mL)	2.3 (0.9–3.7) ^a	1.1 (0.8–1.5)	2.2 (1.0–4.4) ^a	1.3 (0.8–1.8)	2.5 (1.5–4) ^a	1.76 (0.9–2.6)
AER (μg/min)	29 (4–202) ^a	8 (3.7–12.6)	23 (5–52) ^a	9 (4.0–12.4)	16 (6–101)	11 (5.2–13.4)
GFR (mL/min/1.73 m ²)	58 ± 20	65 ± 13	62 ± 16	66 ± 13	66 ± 15	64 ± 14
CAC score	3.8 ± 8.0 ^b	1.8 ± 5.0	5.8 ± 10.7	3.7 ± 7.5	1.96 ± 3.2	2.0 ± 5.31

Data are mean ± SD values, percentages, or geometric means (interquartile interval).

^a $P < 0.05$, ^b $P < 0.0001$ for metabolically abnormal versus metabolically normal.

AER, albumin excretion rate; CAC, coronary artery calcium; CRP, C-reactive protein; DBP, diastolic blood pressure; DDM, duration of diabetes; eGDR, estimated glucose disposal rate (in mg/kg/min); GFR, glomerular filtration rate in the Modification of Diet in Renal Disease equation; HDL, high-density lipoprotein; HTN, hypertension; INS, insulin; LDL, low-density lipoprotein; SBP, systolic blood pressure; SMK, current smoking; TC, total cholesterol; TG, triglycerides; WHR, waist-hip ratio.

volumes was calculated from the baseline visit to the follow-up visit. Progression of coronary calcium was defined as an increase in square root transformed coronary calcium volume of $\geq 2.5 \text{ mm}^3$ over the course of the two visits¹⁴ or development of clinical coronary artery disease between the baseline and follow-up visit (myocardial infarction, coronary artery bypass graft surgery, or coronary angioplasty). Triglycerides, CRP, and AER were log transformed for these analyses.

Presence of CAC and CAC progression were used as dependent variables in logistic regression models, and age, sex, calcium volume score at baseline, AER, and presence of MA were tested as independent variables. Additionally, we replaced weight category by waist or waist-hip ratio; because they were highly correlated, each variable was included separately in the model, adjusted for age, sex, calcium volume score at baseline, and presence of MA. We tested for interactions between sex and waist and between sex and waist-hip ratio.

SAS version 9.2 (SAS Institute Inc., Cary, NC) was the statistical program used to perform these analyses, and all statistical tests were two sided, with $P < 0.05$ considered significant.

Results

The average age of the T1D subjects ($n = 621$) was 36 ± 9 years, and 47.7% (129 of 270) of normal, 60.6% (154 of 254) of overweight, and 73.2% (71 of 97) of obese participants were classified as MA ($P < 0.0001$). The baseline characteristics of study participants stratified by categories of weight and presence of MA are given in Table 1. T1D normal weight

patients with MA were older and had lower HDL-cholesterol levels, higher AER, and higher CAC score than T1D normal weight patients without MA. Individuals who were overweight/obese and had MA had higher insulin dose and higher AER levels than those without MA. Hypertension, higher glycosylated hemoglobin, higher triglyceride levels, and higher CRP levels were associated with MA in all groups of T1D compared with those without MA. Patients with MA had lower eGDR than patients without MA independently of the weight categories. Hypertension was the most common MA, as it was present in 269 subjects; CRP $\geq 3 \mu\text{g/dL}$ was present in 98 subjects, elevated triglycerides ($\geq 150 \text{ mg/dL}$) were found in 70 subjects, and low HDL ($< 40 \text{ mg/dL}$ for men and $< 50 \text{ mg/dL}$ for women) was present in 145 subjects. In the entire group, 55 subjects taking angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and 133 were taking statin medication, at baseline.

Presence of CAC (CAC > 0) was more prevalent among those with excess weight in MA T1D than in MA T1D with normal weight (Fig. 1). However, CAC progression was not more prevalent in patients with excess of weight, independent of MA status, in univariate analysis (Fig. 1).

Table 2 shows the odds for presence and progression of CAC by metabolic status and weight category. Table 2 compares patients with normal weight with those who are overweight and those with normal weight with those who are obese. Overweight was associated with the presence of CAC independent of metabolic status, whereas obesity was associated with both presence and progression of CAC independent of metabolic status.

FIG. 1. Presence of coronary artery calcium (CAC) >0 and progression of CAC by metabolic abnormality (MA) finding and weight group. *P* values are given for the difference among those with normal weight and obesity in MA and without MA type 1 diabetes (T1D) subjects.

When we used waist circumference or waist-hip ratio, replacing weight category, these markers were not associated with CAC progression in this sample of patients, and we did not find interaction between sex and waist or waist-hip ratio.

TABLE 2. ODDS RATIOS FOR PRESENCE AND PROGRESSION OF CORONARY ARTERY CALCIUM METABOLIC STATUS AND WEIGHT CATEGORY

	Odds ratio	95% confidence interval	P
Presence of CAC (0 vs. any CAC)			
Metabolically normal			
Normal weight	1.0 (reference)		
Overweight	1.99	1.21–3.29	0.004
Obese	5.79	3.11–10.78	<0.0001
Metabolically abnormal			
Normal weight	1.0 (reference)		
Overweight	2.22	1.04–4.74	0.04
Obese	5.72	1.71–19.11	0.004
Progression of CAC*			
Metabolically normal			
Normal weight	1.0 (reference)		
Overweight	1.35	0.71–2.56	0.36
Obese	2.86	1.31–6.24	0.008
Metabolically abnormal			
Normal weight	1.0 (reference)		
Overweight	1.01	0.37–2.72	0.98
Obese	6.78	1.62–28.38	0.008

The model was adjusted for age, sex, weight category, presence of metabolic abnormality, and albumin excretion rate.

*Adjusted also for calcium volume score at baseline.

CAC, coronary artery calcium.

Of note is that among the three groups, the change of the weight over the 6 years was 1.97 ± 5.5 , 1.51 ± 5.9 , and -0.06 ± 11.20 kg for normal weight, overweight, and obese, respectively, with no difference among them ($P=0.59$). Among the normal weight individuals only 54 subjects changed from normal to overweight/obese, and this was not associated with CAC progression. Thirty-four patients changed from overweight or obese to normal weight over 6 years, and this weight reduction was not associated with protection for CAC progression.

Additionally, we tested for the eGDR (a marker of insulin resistance in T1D patients). Obesity and eGDR were predictors of CAC progression (odds ratio 2.95 [95% confidence interval 1.05–8.26], $P=0.03$; and odds ratio 0.06 [95% confidence interval 0.006–0.60], $P=0.02$, respectively) in individuals with MA. In individuals without MA, the association of obesity with CAC progression had just borderline significance (odds ratio 2.14 [95% confidence interval 0.89–5.12], $P=0.08$) when eGDR was added to the model.

Discussion

Our data suggest that obesity predicts the presence as well the progression of CAC, and overweight was associated with the presence of atherosclerosis. Excess weight is not considered a typical feature of T1D, but we observed that it is frequent among patients with T1D (56.7% were above normal weight).

Several studies have shown that the aggregation of cardiovascular risk factors in T1D subjects predicts the development of micro- and macrovascular complications,^{2,3,15} and these studies showed that higher BMI is associated with more clustering of risk factors, but they did not evaluate if the presence of excess weight is an independent factor of the presence of MA in association with vascular complications. In

this study, we observed higher prevalence of MA among the subjects with overweight and obesity in adults with T1D. Recently, in a study that evaluated 5,440 participants of the National Health and Nutrition Examination Surveys 1999–2004, the authors reported that among U.S. adults there is a high prevalence of clustering of MA among normal weight individuals and a high prevalence of overweight and obese individuals who are metabolically healthy,¹⁰ reinforcing the role of obesity as heterogeneous and nonuniform in different individuals. However, we have shown obese individuals who appear to be metabolically healthy are nevertheless at increased risk for subclinical atherosclerosis.

Of note is that we observed the same prevalence of overweight and obesity in our sample as in the general U.S. adult population of the same age (20–39 years) (56.7% of excess weight in T1D vs. 57.5% in general population).¹⁶ When the general population is stratified by different ages, it is observed that the presence of MA among normal weight individuals is associated with older age and that the prevalence of the metabolically healthy phenotype among obese individuals decreased with increasing age.¹⁰ T1D subjects with normal weight and MA were older than normal weight T1D subjects without MA, in concordance with the results of the general population.¹⁰

As expected, the insulin dose was higher in excess weight T1D subjects with MA compared with individuals with an excess of weight and without MA. The association between insulin resistance and excess weight in T1D and its effects on the metabolic profile of these patients have been documented.¹ Although higher doses of insulin have been used in obese patients, they had no better glycemic control than the patients with lower doses. Worse insulin resistance (lower eGDR) was associated with the presence of obesity.

There is some evidence that obesity is not associated with an increased risk of future cardiovascular events among individuals without metabolic syndrome, but only in those participants with MA.^{9,17,18} In T1D, that appears to be different. Although we did not evaluate cardiovascular events, we observed that overweight and obesity were associated with the presence of atherosclerosis, assessed by CAC, and obesity was associated with progression of CAC. These findings were independent of the presence of MA or other factors, including AER, a known hard-risk factor associated with CVD in T1D. Overweight was associated with CAC progression, but it was not independent of the presence of the MA. These differences between the effect of overweight and obesity on the progression of atherosclerosis could be explained by data from the Diabetes Control and Complications Trial, which showed that weight gain had no homogeneous effect in all intensively treated group: patients with excessive weight gain (fourth quartile of weight gain) had an adverse lipid profile, higher blood pressure levels, greater insulin requirements, and increased waist–hip ratio, suggesting increased insulin resistance.¹ Our data show the effect of obesity on the atherosclerosis process in a prospective analysis. Although overweight was associated with the presence of CAC, it may have a limited burden on the evolution of atherosclerosis and may not be independent of MA. Furthermore, subjects with higher weight gain in the intensive treatment group during the Diabetes Control and Complications Trial study had increased CRP,¹⁹ a marker associated with early atherosclerosis lesions.²⁰ Higher BMI is

associated with elevated levels of CRP;²¹ in our sample CRP levels were higher in the entire group of obese, independently of the presence of MA.

Our data agree with the findings from the Pittsburgh Epidemiology of Diabetes Complications study cohort, which showed that at baseline BMI (as a continuous variable) was associated with the progression of CAC in T1D subjects.²² We evaluated excess weight as a categorical variable and believe that this way it allows a better visualization of the impact of obesity on the outcome and makes the interpretation of the data easier for clinical practice. However, even when BMI was evaluated as a continuous variable, it still had the same association with the outcomes (data not shown).

A possible limitation of our study is the very small group with obesity but without MA ($n=26$), which did not allow for observing the burden of obesity on CAC progression because we had just 15 obese individuals with CAC progression.

In summary, T1D patients with excess weight and obesity had higher odds for presence of subclinical atherosclerosis, but only obesity was strongly associated with the progression of CAC, independent of the presence of MA. Although obesity is known to increase CVD risk through inducing metabolic abnormalities such as dyslipidemia, hypertension, and inflammation, it is also a strong predictor of subclinical atherosclerosis progression in adults with T1D independent of these factors. One possible explanation is the insulin resistance associated with excess weight. Weight control should be pursued as one of the target treatments in T1D subjects, and further studies with reduction or prevention of gain of weight should be conducted to examine reduction/prevention of macrovascular complication in T1D individuals.

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Author Disclosure Statement

The authors have nothing to disclose.

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