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## Coronary artery calcification is associated with insulin resistance index in patients with type 1 diabetes

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# Coronary artery calcification is associated with insulin resistance index in patients with type 1 diabetes

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## Abstract

The objective of the present study was to evaluate the risk factors associated with the presence of coronary artery calcification (CAC) in patients with type 1 diabetes (T1D). A cross-sectional study was conducted on 100 consecutive T1D patients without coronary artery disease, with at least 5 years of diabetes and absence of end-stage renal disease. Mean age was  $38 \pm 10$  years and 57% were males. CAC score was measured by multidetector computed tomography (Siemens Sensation 64 Cardiac). The insulin resistance index was measured using the estimated glucose disposal rate (eGDR). The eGDR was lower among CAC-positive patients than among CAC-negative patients, suggesting an increased insulin resistance. In a logistic regression model adjusted for age (at 10-year intervals), eGDR, diabetic nephropathy and gender, CAC was associated with age [OR = 2.73 (95%CI = 1.53-4.86),  $P = 0.001$ ] and with eGDR [OR = 0.08 (95%CI = 0.02-0.21),  $P = 0.004$ ]. In T1D subjects, insulin resistance is one of the most important risk factors for subclinical atherosclerosis.

Key words: Type 1 diabetes; Coronary artery calcification; Insulin resistance

## Introduction

Patients with type 1 diabetes (T1D) are at increased risk for coronary artery disease (CAD) (1). The detection of coronary artery calcification (CAC) has been used as a new tool to assess CAD and to predict coronary events beyond standard risk factors in the general population, independent of the presence of diabetes (2). There is a good correlation between CAC and coronary atherosclerotic plaque burden (3) and CAC is a powerful predictor of clinical CAD in non-diabetic subjects (4). Patients with diabetes have higher CAC scores than non-diabetic individuals (5), including a greater extent and progression of CAC than non-diabetic subjects (6). The presence of CAC is correlated with CAD in both men and women with T1D (7). The factors associated with the presence of CAC in patients with T1D are still not fully defined. Insulin resistance in T1D subjects increases progressively with disease duration and its prevalence in these patients is 12 to 42% (8-11). Moreover, insulin resistance has been associated with micro- and macrovascular complications in individuals with T1D (11-13). Although prospective data for the power of CAC to predict coronary heart disease events in

T1D subjects are still lacking, measurement of CAC could help in deciding about preventive therapy in this group of patients. Therefore, the aim of the present study was to evaluate the risk factors associated with the presence of subclinical atherosclerosis, assessed by CAC, in a sample of T1D patients and especially to evaluate the association between CAC and insulin resistance.

## Material and Methods

We performed a cross-sectional study on 100 consecutive T1D patients attending the Endocrine Division's outpatient clinic at Hospital de Clínicas de Porto Alegre. These patients are part of a cohort that has been followed since 2000. T1D was defined as onset of diabetes before the age of 40 years, a previous episode of ketoacidosis or documented ketonuria, and mandatory use of insulin for survival. Inclusion criteria were age  $>18$  years, at least 5 years duration of diabetes, absence of end-stage renal disease (dialysis or renal transplant) and absence of known cardiovascular disease defined on the basis of a normal

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resting ECG and a negative medical history of myocardial infarction, angina, intermittent claudication, coronary artery revascularization procedure, or stroke. Mean age of the patients in this study was  $38 \pm 10$  years, the proportion of males was 57%, and the mean duration of diabetes was  $18 \pm 9$  years.

The Ethics Committee of the Hospital approved the study, and informed written consent was obtained from all patients.

### Patient evaluation

All T1D patients answered a standardized questionnaire as previously described (14), and underwent a complete physical examination including measurement of waist circumference (mid-axillary line midway between the highest point of the iliac crest and lowest point of the costal margin), height, and weight while wearing light clothing and no shoes. Body index mass was calculated as  $\text{weight (kg)}/\text{height}^2$  (m). Blood pressure (BP) was measured twice in the sitting position after a 10-min rest with a standard 12.5-cm cuff mercury sphygmomanometer (Korotkoff phases I and IV). The mean of 2 measures was used for analysis. Hypertension was considered to be present if systolic BP levels were  $\geq 130$  mmHg and/or diastolic BP was  $\geq 85$  mmHg, or if the patient was using antihypertensive medication. After fasting for 12 h, a blood sample was obtained by venipuncture from each subject. Patients with microalbuminuria [urinary albumin excretion rate (UAER)  $\geq 20$  and  $\leq 200$   $\mu\text{g}/\text{min}$ ] and macroalbuminuria (UAER  $>200$   $\mu\text{g}/\text{min}$ ) were analyzed as a diabetic nephropathy group.

### Laboratory measurements

UAER was measured by immunoturbidimetry (Microal; Ames-Bayer, USA; intra- and interassay coefficients of variation of 4.5 and 11%, respectively). Hemoglobin (A1c) was measured by a high-performance liquid chromatography (normal range 4-6%; Merck-Hitachi 9100, Germany). Fasting plasma glucose was measured by the glucose-peroxidase colorimetric enzymatic method (Biodiagnostica, Brazil), serum creatinine by the Jaffé method, and the glomerular filtration rate was estimated (eGFR) using the formula of the Modification of Diet in Renal Disease Study (15). The lipid profile was measured by an enzymatic-colorimetric method (Merck Diagnostica; Boeringher Mannheim, Germany). Estimated glucose disposal rate (eGDR), a measure of insulin sensitivity, was calculated using an equation involving A1c, waist-to-hip ratio and hypertension derived from hyperinsulinemic-euglycemic clamp studies (16).

### Coronary artery calcification

CAC was measured with a multidetector computed tomography (CT) system that acquired 64 simultaneous 2.5-mm slices for each cardiac cycle with prospective ECG-triggered scan acquisition at 60% of the RR interval in a sequential scan mode (Somatom Sensation 64 Cardiac,

Siemens Medical Solutions, Germany). All scans were analyzed for the presence of CAC on an offline workstation (Circulation, Siemens). A calcified lesion was defined as an area with CT attenuation  $>130$  Hounsfield units (HU). The Agatston score was calculated by multiplying the area of each lesion by a weighted CT attenuation score, depending on the maximal CT attenuation (HU) within the lesion. The cardiologist reading the CT scans was unaware of the clinical data.

### Statistical analysis

The Student *t*-test and the  $\chi^2$  test were used to compare clinical and laboratory data and Pearson correlation was determined. Data with a normal distribution are reported as means  $\pm$  SD, and quantitative variables without a normal distribution (UAER, triglycerides, CAC score, and eGDR) are reported as median and range and were log transformed before analysis. The CAC score was added to the number 1 and then log transformed [ $\log(\text{CAC} + 1)$ ]. Models of multiple logistic regression analysis were used with the presence of CAC ( $>0$ ) as the dependent variable and age (at 10-year intervals), gender and eGDR as independent variables. P values  $<0.05$  (two-tailed) were considered to be significant.

### Results

Of 100 patients evaluated, 31 were CAC-positive. Clinical and laboratory data are described in Table 1. CAC-positive patients were older, had a longer duration of diabetes and were more frequently hypertensive. CAC-positive women had a higher waist/hip ratio (WHR), an association that was not observed among men. The eGDR was lower among CAC-positive patients compared to CAC-negative patients, suggesting an increased insulin resistance in subjects with CAC. Lipid profile, glycemic control and the mean dose of insulin did not differ between the two groups.

In the univariate analysis, the proportion of patients with CAC did not differ between men ( $21/58 = 36\%$ ) and women ( $10/42 = 24\%$ ;  $P = 0.20$ ) nor did the amount of CAC ( $P = 0.22$ ). Among 31 CAC-positive patients, 9 had CAC  $>100$  HU and 22 had CAC between  $>0$  and  $\leq 100$  HU. In patients with the presence of CAC, the amount of calcium in the coronaries had a significant positive correlation with age ( $r = 0.56$ ;  $P < 0.001$ ), diabetes duration ( $r = 0.30$ ,  $P = 0.003$ ), WHR ( $r = 0.30$ ;  $P = 0.003$ ) and a negative correlation with eGDR ( $r = -0.40$ ;  $P < 0.001$ ) and eGFR ( $r = -0.20$ ;  $P = 0.04$ ). UAER, BP values and lipid profile did not correlate with the extent of CAC.

To analyze a possible association between cardiovascular risk factors and the presence of CAC, a logistic regression model was performed with the presence of CAC as the dependent variable and age (at 10-year intervals), gender and eGDR as independent variables. Age [OR = 2.73 (95%CI = 1.53-4.86),  $P = 0.001$ ] and eGDR [OR = 0.08

(95%CI = 0.02-0.21),  $P = 0.004$ ] were associated with the presence of CAC, whereas male gender [OR = 1.20 (95%CI = 0.40-3.47),  $P = 0.76$ ] was not. Next, we tested for interaction between gender and eGDR, which was significant ( $P = 0.01$ ). There was no interaction between gender and age. For a better understanding of the interaction, we showed the odds ratio of eGDR by gender (Table 2).

Additionally, we evaluated the presence of metabolic syndrome (MetS; NCEP criteria; <http://www.americanheart.org/presenter.jhtml?identifier=4756>). Patients with MetS more frequently presented CAC [10/19 (52.6%)] than patients without MetS [21/81 (25.9%)],  $P = 0.023$ . CAC scores were higher ( $P = 0.006$ ) in patients with MetS [2.0 HU (0.0-1364),  $N = 19$ ] than in patients without MetS [0.0 HU (0.0-1410),  $N = 81$ ]. The proportion of patients with CAC did not differ between men (21/58 = 36%) and women (10/32 = 31%,  $P = 0.20$ ). In addition, we performed a logistic regression including MetS, gender and age (at 10-year intervals) as independent variables and the presence of CAC as the dependent variable. MetS and gender did not remain associated with outcome and only age [OR = 3.62 (95%CI = 2.17-6.05),  $P < 0.001$ ] was related to the presence of CAC.

## Discussion

An association between the presence of CAC and age and insulin resistance (assessed by eGDR) was observed in the present study. Additionally, we observed an interaction between insulin resistance and gender in female T1D subjects with CAC.

One third of the patients had CAC. It is known that patients with T1D have more CAC than non-diabetic patients (6) and that CAC increases with age in T1D subjects and in non-diabetic subjects (12). The odds ratio for an increase in CAC was 2.73 times for every 10 additional years of age. Insulin resistance, as assessed by eGDR, was validated by Williams et al. (16) in patients with T1D to determine the degree of insulin sensitivity. It is easy to calculate and shows a close correlation with insulin resistance determined by the clamp method (16). Moreover, eGDR has been described as a predictor of cardiovascular outcomes and microvascular complications in prospective studies with T1D (12,17,18) and has been shown to be independently associated with CAC in patients with T1D, thus possibly explaining the greater CAC seen in women than in men among T1D subjects (6). Recently, eGDR was reported to be associated with CAD only in women with T1D (11). We observed an interaction between female gender and insulin resistance index, probably because our female group with CAC had a higher WHR than the female group without CAC. Visceral obesity was an independent predictor of CAC progression in a study with older adults without known heart disease (19). Recently eGDR, as an insulin resistance marker, provided more useful information than

other classical variables such as insulin requirements, to predict vascular complications in a cohort of T1D individuals (13). In our sample, eGDR was a better predictor of the presence of CAC than the presence of MetS.

The lack of association between CAC and BP values and between CAC and UAER can be explained by the fact that these patients were taking antihypertensive medica-

**Table 1.** Clinical characteristics of patients with type 1 diabetes according to the presence of coronary artery calcification.

	CAC+ (N = 31)	CAC- (N = 69)
Age (years)	47 ± 9*	35 ± 9
Diabetes duration (years)	23 ± 11*	16 ± 7
Race (white), N (%)	28 (90.3)	60 (87.1)
Men, N (%)	21 (67.7)	38 (55.1)
Waist/hip ratio		
Men	0.86 ± 0.06	0.85 ± 0.04
Women	0.86 ± 0.06*	0.78 ± 0.05
BMI (kg/m <sup>2</sup> )	25 ± 3.5	25 ± 3.4
Systolic blood pressure (mmHg)	126 ± 17	120 ± 15
Diastolic blood pressure (mmHg)	77 ± 9	77 ± 11
Hypertension, N (%)	18 (58)*	16 (23)
Current smokers, N (%)	4 (12)	8 (12)
Insulin dose/kg (U·kg <sup>-1</sup> ·day <sup>-1</sup> )	0.69 ± 0.29	0.70 ± 0.20
eGDR (mg·kg <sup>-1</sup> ·min <sup>-1</sup> )	5.7 (3.2-10.6)*	8.7 (3.4-11.2)
UAER (µg/min)	9.7 (3.5-1251)	8.8 (0.9-476)
Total cholesterol (mg/dL)	179 ± 40	177 ± 49
HDL (mg/dL)	59 ± 21	57 ± 13
LDL (mg/dL)	100 ± 30	102 ± 44
Triglycerides (mg/dL)	89 (37-212)	68 (30-706)
A1c (%)	8.2 ± 1.6	8.6 ± 1.9
GFR (mL·min <sup>-1</sup> ·(1.73 m <sup>2</sup> ) <sup>-1</sup> )	76 ± 29	86 ± 27
Diabetic nephropathy, N (%)	12 (38)	14 (20)

CAC = coronary artery calcification measured by multidetector computed tomography; BMI = body mass index; eGDR = estimated glucose disposal rate; UAER = urinary albumin excretion rate; GFR = glomerular filtration rate. \* $P < 0.05$  CAC+ vs CAC- ( $t$ -test or  $\chi^2$  test).

**Table 2.** Odds ratio for the presence of coronary artery calcification by gender.

	OR	95%CI	P
Female patients			
Age (per 10 years)	3.78	1.38-10.36	0.009
eGDR	0.42	0.24-0.72	0.002
Male patients			
Age (per 10 years)	3.62	1.70-7.74	0.001
eGDR	0.73	1.26	0.79

eGDR = estimated glucose disposal rate.

tion and had a good BP control (126/77 vs 120/77 mmHg). Furthermore the number of patients with nephropathy was small (N = 26).

Curiously, in our study, male gender was not a risk for the presence of CAC, probably because male patients with CAC had a smaller abdominal circumference than males without CAC, a fact that could have increased their insulin sensitivity.

Small sample size is a limitation of the present study. Of note, our cohort showed that women with T1D and visceral

obesity had an additional risk for subclinical atherosclerosis and that subclinical atherosclerosis was associated with age and with insulin resistance in T1D subjects.

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