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Type 2 Diabetes Mellitus is Associated with Carotid Artery Plaques in Patients with Premature Coronary Heart Disease

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ABSTRACT

Background: In subjects without a history of coronary heart disease (CHD), type 2 diabetes mellitus (T2DM) is associated with carotid artery plaques (CAP), which is a better marker than high carotid intima-media thickness (hCIMT) for predicting first or recurrent cardiovascular events. **Objective:** The objective of this study is to analyze the association of T2DM with CAP and hCIMT in premature CHD patients. **Methods:** Premature CHD was considered before the age of 55 years in men and before 65 in women. T2DM was defined according to the American Diabetes Association criteria. CAP was defined as a focal structure encroaching the arterial lumen by at least 50% of the surrounding IMT value or with a thickness > 1.5 mm. **Results:** Among 1196 patients (CHD duration 1.5 years [interquartile range: 0.4-5.6]), 37.2% had T2DM, and 97.8% were on antihypertensive, 94.4% on lipid-lowering, and 97.3% on anti-aggregate treatment. hCIMT prevalence was similar in patients with or without T2DM, whereas CAP prevalence was higher among T2DM patients (17.7% vs. 30.9%; $p < 0.001$). T2DM showed association with CAP, independently of CHD evolution and glycemic control (odds ratio: 1.57; 95% confidence interval: 1.09-2.26). **Conclusions:** T2DM has an independent association with CAP. Early detection of recurrent cardiovascular events, with CAP identification, could be useful to prevent complications in patients with CHD. (REV INVEST CLIN. 2018;70:301-9)

Key words: Coronary heart disease. Atherosclerosis. Carotid intima-media thickness. Carotid artery plaques. Diabetes mellitus.

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INTRODUCTION

Atherosclerosis is a systemic chronic inflammatory disorder involving multiple vascular territories[1,2]. High carotid intima-media thickness (hCIMT) is considered a marker of atherosclerosis in the vascular beds of the human body[3,4]. However, mean and maximal CIMT measurements have been controversially associated with cardiovascular risk[5], whereas carotid artery plaques (CAP) are closely related to the presence of coronary artery plaques[1,2]. Moreover, it has been reported that the presence of carotid plaques is better than hCIMT to predict coronary heart disease (CHD)[6-9], as well as major cardiovascular events and mortality in patients with established CHD[10].

Type 2 diabetes mellitus (T2DM) is increasing worldwide[11,12]. Macrovascular complications of T2DM are frequent causes of morbidity and mortality, and some investigations have reported that, compared to non-diabetic subjects, CHD is higher among patients with diabetes, independently of cardiovascular risk factors[13,14]. In addition, some reports have suggested that 65-80% of deaths from T2DM are due to cardiovascular or cerebrovascular complications[15].

Few studies have investigated the association of T2DM with the presence of CAP in subjects without apparent cardiovascular disease. Those reports showed that CAPs are useful for predicting the presence and extent of CHD in patients with diabetes[16,17]. Although currently, it is well known that deaths in T2DM patients are mainly due to cardiovascular or cerebrovascular complications[15]. As far as we know, no study has analyzed the association of diabetes with CAP in patients with established premature coronary artery disease. The purpose of the present study was to evaluate the association of T2DM with CAP and hCIMT in an adult population with documented premature CHD. This is important because modern cardiovascular care includes the early detection of recurrent cardiovascular events, especially in patients with premature CHD, whose identification of risk through atherosclerotic markers, such as carotid plaques, could be useful in the prevention of morbidity and mortality, besides traditional risk factors.

MATERIALS AND METHODS

Patient population

The study population was recruited from patients participating in the Genetics of Atherosclerotic Disease (GEA) study. The GEA study is a cross-sectional and observational trial designed to examine the genomic basis of CHD and to assess the relationships of traditional and emerging risk factors with clinical and subclinical atherosclerotic vascular disease in an adult Mexican population[18]. Briefly, a convenience sample of 1200 premature CHD patients aged 35-74 years was recruited from the outpatient clinic of the National Institute of Cardiology in Mexico City (July 2008-November 2012). Premature CHD was defined as a history of myocardial infarction, angioplasty, revascularization surgery, or coronary stenosis > 50% by angiography, diagnosed before age 55 in men and before 65 in women. Coronary patients and control subjects with a personal history of renal, liver, thyroid, or malignant disease, as well as those on treatment with corticosteroids, were excluded from the study. The GEA study was approved by the the Institutional Ethics Committee on research in humans at the National Institute of Cardiology and conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from each participant who was included in the study.

This study is a cross-sectional analysis of 1196 GEA patients because we excluded four patients with missing data. Trained research staff interviewed all subjects and completed questionnaires to collect information pertaining to demographic characteristics, CHD history, medication, and alcohol and tobacco use. Positive history of tobacco was considered when individuals self-reported current smoking (≥ 1 cigarette per day)[19]. Physical activity index was calculated using the Baecke questionnaire[20], and total activity was obtained from the sum of work, sport, and leisure-time activities. This questionnaire has been previously validated in an adult population and provides reliable information. All participants had a complete clinical examination. Height was measured to the nearest 1 cm using a rigid stadiometer, and weight was measured to the nearest 0.1 kg with the use of a balance scale. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Systolic and diastolic blood pressure was measured after

subjects had rested for at least 10 min, and the average of the second and third of three consecutive measurements was used for the analysis. Hypertension was defined as blood pressure > 140/90 mmHg or treatment with antihypertensive medication.

Biochemical analysis

Venous blood samples were collected from subjects after a 10 h fasting. Plasma glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured in fresh samples, using standardized enzymatic procedures in a Hitachi 902 Analyzer (Hitachi LTD, Tokyo, Japan). Accuracy and precision of lipid measurements in our laboratory are under periodic surveillance by the center for disease control and prevention (Atlanta, GA, USA). Low-density lipoprotein cholesterol (LDL-C) was estimated using the De Long et al. method[21]. Hyperlipidemia was defined as total cholesterol > 200 mg/dL or triglycerides > 150 mg/dL or use of lipid-lowering medication. The presence of T2DM was considered when fasting plasma glucose was ≥ 126 mg/dL, according to the American Diabetes Association criteria[22], and when participants reported glucose-lowering treatment or a previous diagnosis by a physician. A1C hemoglobin was measured by immunoassay method in a COBAS C501 Clinical Chemistry Analyzer (Roche Diagnostics GmbH, Mannheim, Germany). As informed, for patients with micro- or macro-vascular complications, A1C < 8% was considered a good glycemic control[22]. Total high-sensitivity C-reactive protein (hs-CRP) levels were determined by immunonephelometry on a BN Pro Spec nephelometer (Dade Behring, Marburg, Germany), according to the manufacturer's method. Interassay coefficients of variation for all assays were < 6%.

Computed tomography

Computed tomography is a validated method for measuring adipose tissue distribution[23]. Computed tomography was performed using a 64-channel multidetector helical system (Somatom Cardiac Sensation 64, Forcheim, Germany) and interpreted by experienced radiologists. Scans were read to assess and quantify total, subcutaneous, and visceral abdominal adipose tissue, as described by Kvist et al.[24]. Twenty different scans were randomly selected to evaluate the consistency of interpretation; the intraobserver correlation coefficient was 0.99 ($p < 0.001$).

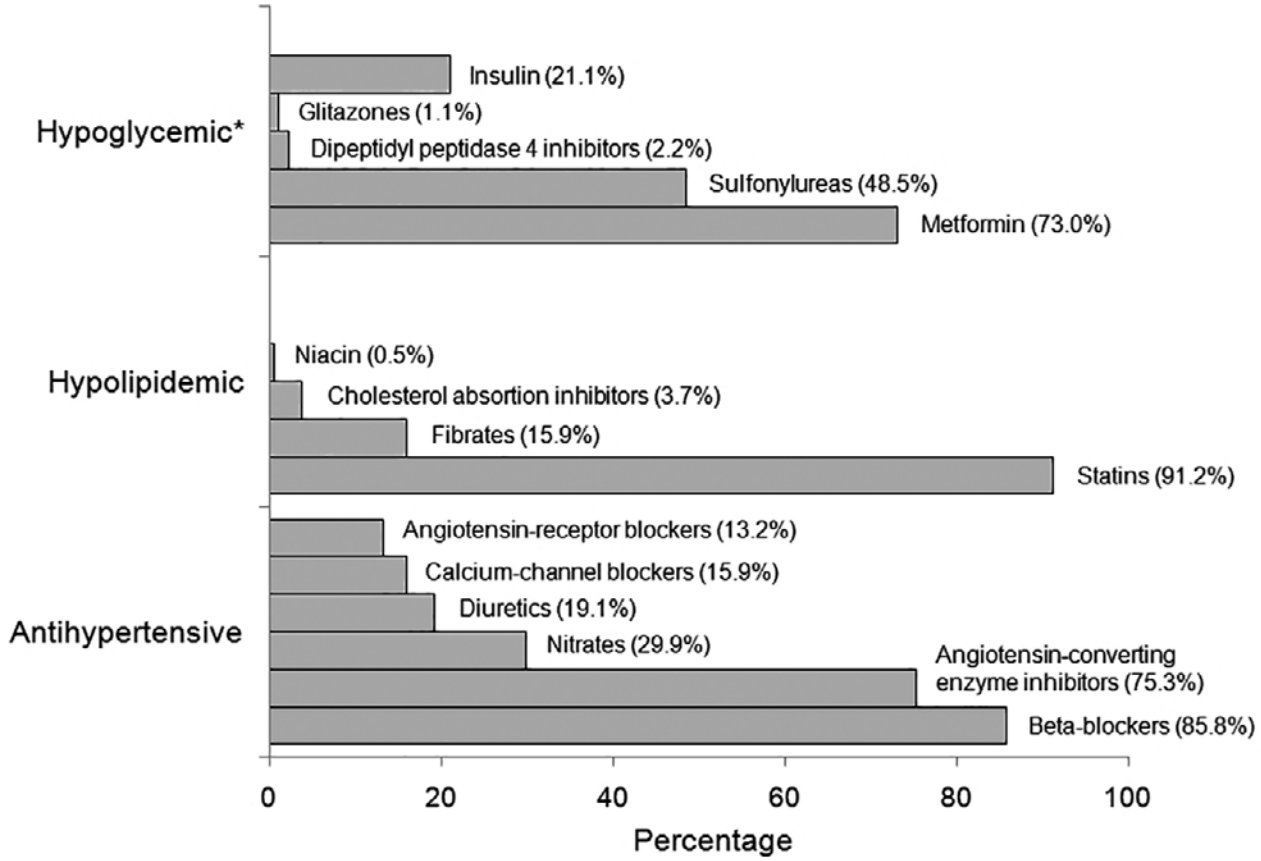
Measurement of CIMT

Carotid artery scanning was performed with a high-resolution ultrasound apparatus in B mode (Sonosite Micro Maxx), equipped with a 13-6MHz linear array transducer. The subjects were assessed in supine position, with extended neck. Measurements of common CIMT were performed in 2-cm-long segments immediately proximal to the carotid bulb bifurcation. The distance between the arterial intima-lumen interface and the media-adventitia interface of the far wall quantified the thickness of the intima-media. Five measurements were performed in the right and left carotid arteries. The CIMT was defined as the average of all measurements. A high CIMT was defined using the 75th percentile, according to age group and gender[25]. If a carotid plaque was present, CIMT was measured in a contiguous segment without plaque. Carotid plaque was defined as a focal structure encroaching the arterial lumen by at least 50% of the surrounding IMT value or with a > 1.5 mm thickness[25]. The bilateral common carotid, internal carotid, and bulb were scanned to evaluate the presence of plaque. One, especially, trained radiologist, who was unaware of the studied subject's clinical and angiographic information, performed all ultrasonographic examinations. Reproducibility of measurements was assessed with 5% of the cohort, obtaining an intraobserver correlation coefficient of 0.96.

Data analysis

Variables were analyzed in the whole sample, and participants were stratified by the presence or absence of T2DM. Values are expressed as mean ± standard deviation, median (interquartile range), or number of subjects (%). Comparisons of means, medians, and frequencies were made with Student's *t,* Mann–Whitney *U,* and Chi-squared tests, respectively. Logistic regression analyses were done to evaluate the association of T2DM with carotid plaques, using hypoglycemic treatment, years of diabetes evolution, and CHD, as well as clinical or biochemical parameters that were different between subjects with or without T2DM, as independent variables. All analyses were carried out using the statistical software SPSS v. 15.0 (SPSS Chicago, Il.). All $p < 0.05$ or 95% confidence intervals (95% CI) that excluded the unit were considered statistically significant.

Figure 1. Pharmacological treatment of patients with premature coronary artery disease (n = 1196).* Only patients with type 2 diabetes mellitus (n = 445).



RESULTS

Among the 1196 patients from the GEA cohort (cardiovascular disease duration, 1.5 years [0.4-5.6]), 37.2% coursed with type 2 diabetes, 69.6% with hypertension, 20.8% with high total cholesterol levels, 56.3% with hypertriglyceridemia, and 97.8% were on antihypertensive, 94.4% on lipid-lowering, and 97.3% on anti-aggregate treatment (Fig. 1). Compared with non-diabetes patients, a higher prevalence of female sex (26.5% vs. 15%; $p < 0.001$) and hypertension (78.0% vs. 64.7%; $p < 0.001$) was found in diabetes subjects, as well as a lower index of total physical activity (7.5 [6.7-8.6] vs. 8.0 [6.9-9.4]; $p < 0.001$). As shown in table 1, diabetes patients were also characterized by having higher values in age, BMI, total and visceral adipose tissue, systolic blood pressure, triglycerides, glucose, and hs-CRP ($p < 0.05$, for all). LDL-C was significantly lower in diabetes patients, and there were no differences between the groups regarding cardiovascular disease duration, hyperlipidemia, pharmacological treatment, smoking status, subcutaneous adipose tissue, diastolic blood pressure, and HDL or non-HDL cholesterol.

Among the 445 patients with diabetes, 92.8% were on hypoglycemic treatment (Fig. 1). According to their A1C hemoglobin, target was achieved in 58.2% of the patients with diabetes. This prevalence was inversely related with diabetes duration: < 1 year, 84.6%; 1-5 years, 77.2%; 6-10 years, 52.5%; and > 10 years, 37.8% (p trend < 0.001). Except for stable angina prevalence, clinical characteristics of CHD were similar in patients with or without diabetes (Table 2). Although the prevalence of hCIMT was greater than that of CAP, the first was similar between groups, whereas carotid plaque prevalence was significantly higher among patients with diabetes (Fig. 2).

To know whether diabetes is independently associated with the presence of carotid plaques, a logistic

Table 1. Demographic, adipose, and biochemical characteristics of patients with coronary heart disease.

	Total (n = 1196)	Diabetes (–) (n = 751)	Diabetes (+) (n = 445)	*p**
Age (years)	54 ± 8	53 ± 8	56 ± 8	< 0.001
Female sex (%)	19.3	15.0	26.5	< 0.001
Positive tobacco history (%)	11.7	12.5	10.3	0.257
Body mass index (Kg/m^2)	28.9 ± 4.3	28.7 ± 4.1	29.3 ± 4.6	0.030
Total adipose tissue (cm^2)	429 (340-531)	421 (335-519)	444 (358-554)	0.001
Subcutaneous adipose tissue (cm^2)	249 (194-319)	244 (192-313)	252 (201-330)	0.130
Visceral adipose tissue (cm^2)	170 (130-218)	163 (125-209)	182 (139-238)	< 0.001
Systolic blood pressure (mmHg)	119 ± 19	117 ± 17	123 ± 21	< 0.001
Diastolic blood pressure (mmHg)	72 ± 10	72 ± 10	73 ± 10	0.223
Total cholesterol (mg/dL)	166 ± 48	167 ± 45	165 ± 51	0.459
LDL-cholesterol (mg/dL)	96 ± 39	98 ± 39	92 ± 39	0.015
Non-HDL-cholesterol (mg/dL)	120 (93-151)	121 (95-151)	118 (89-153)	0.234
HDL-cholesterol (mg/dL)	37 (32-44)	37 (31-44)	37 (32-44)	0.936
Triglycerides (mg/dL)	162 (118-220)	160 (116-212)	166 (124-231)	0.026
Glucose (mg/dL)	112 ± 44	91 ± 10	148 ± 54	<0.001
hs C-reactive protein (mg/L)	1.2 (0.6-2.7)	1.12 (0.59-2.42)	1.36 (0.74-3.10)	0.002

Data are expressed as mean ± SD, median (interquartile range) or percentage. *p values comparing non-diabetes (–) versus diabetes (+) patients by unpaired-t, Mann–Whitney U, or Chi-squared test, LDL: low- density lipoprotein, HDL: high-density lipoprotein and hs: high sensitivity.

Table 2. Cardiovascular diagnoses of patients with coronary heart disease.

	Total (n = 1196)	Diabetes (–) (n = 751)	Diabetes (+) (n = 445)	*p**
Coronary heart disease evolution (years)	1.50 (0.40-5.60)	1.53 (0.41-5.58)	1.44 (0.46-5.56)	0.985
Acute myocardial infarction (%)	88.5	88	89.2	0.531
Unstable angina (%)	15.3	16	14.2	0.401
Stable angina (%)	29.4	27.3	32.9	0.042
Coronary percutaneous intervention (%)	47.8	48.5	46.7	0.563
Stent (%)	45	45.2	44.7	0.853
Cardiac revascularization (%)	10	9.6	10.8	0.505
High CIMT (%)	46.5	44.2	47.7	0.316

Data are expressed as median (interquartile range) or percentage. *p values compared non-diabetes (–) versus diabetes (+) patients by Mann–Whitney U or Chi-square test. CIMT: carotid intima-media thickness.

regression analysis was performed including therapy and clinical or biochemical characteristics as covariates. As shown in figure 3, age was associated with CAP (odds ratio [OR]: 1.10; 95% confidence interval [CI]: 1.07-1.13), but it was lower than that observed for diabetes, which showed a stronger association with the presence of CAP (OR: 1.57; 95% CI: 1.09-2.26).

Figure 2. Carotid intima-media abnormalities in patients with premature coronary artery disease. Prevalence of high carotid intima-media thickness (hCIMT; according to age and sex) and carotid plaque presence in patients with premature coronary artery disease and absence (–) or presence (+) of type 2 diabetes mellitus. *Chi-square test.

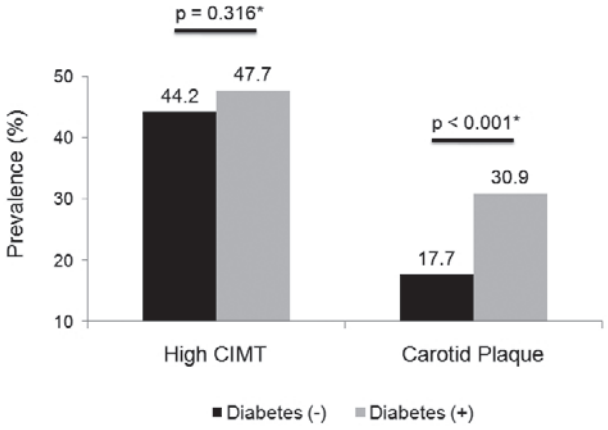
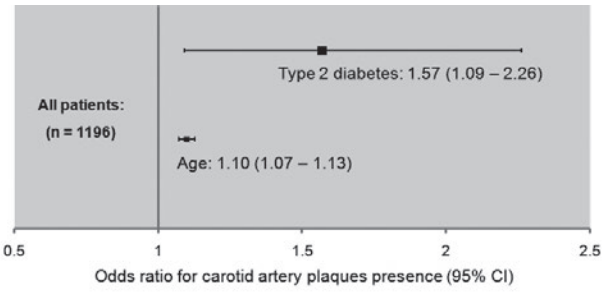


Figure 3. Association of type 2 diabetes mellitus with carotid artery plaque presence in patients with premature coronary artery disease. Multiple logistic regression analysis was carried out in the whole studied population. Type 2 diabetes mellitus, age, sex, visceral adipose tissue, systolic blood pressure, low-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein, physical activity, coronary heart disease, and type 2 diabetes mellitus years of evolution, as well as hypoglycemic treatment, were included as independent variables in the model.



DISCUSSION

Patients with established CHD are at an increased risk of total and cardiovascular mortality[26] and have been established as a top-priority group for prevention in clinical practice[27]. In this regard, some studies have suggested that, rather than CIMT, the presence of carotid artery plaque could strongly predict mortality and major cardiovascular events, even in patients with established CHD[6-10]. In line with this, results of the present study show that, compared with premature CHD patients without diabetes, those with T2DM have a more adverse cardiovascular risk profile, but it does not identify a higher prevalence of elevated CIMT. Moreover, our main finding indicates that T2DM has a strong association with the presence of CAP, independently of CHD evolution and glycemic control. This is relevant because the presence of CAP could be useful for the early detection of recurrent cardiovascular events and to promote prevention programs, which are the goals of modern cardiovascular care, especially in patients with established premature cardiovascular damage, whose accelerated progression of CHD is significant, regardless of their different clinical profile. In addition, these patients do not frequently have traditional CHD risk factors and are overlooked and misdiagnosed[28,29].

Coronary artery disease remains the major cause of morbidity and mortality around the world. Currently, subjects within the age group of 40-60 years are more susceptible to CHD due to the current pandemic of metabolic disorders associated with obesity, such as hypertension, dyslipidemia, or diabetes[30]. Results of the present study, which include subjects with CHD diagnosed before age 55 in men and before 65 in women, show that compared to non-diabetes patients, those with diabetes were older and had higher general and central adiposity, hypertension, and carotid artery plaque prevalence. Similar to this, three previous studies that investigated mortality in cardiac patients showed a trend of high prevalence of CAP among patients with diabetes[8,10 28]. To be noted, only one of these studies[10] showed a prevalence of CAP (36.4%) similar to that observed in our diabetes cohort (23.1%). The other two studies found carotid plaques in 75%-80% of the CHD patients with diabetes. These differences can be primarily explained by the differences in the ethnic group as well as the higher age and CHD evolution time, poor pharmacological treatment, or higher hypertension, dyslipidemia, and smoking prevalence in those studies[8,28].

The two most widely used protocols for evaluating carotid abnormalities are the mean common and mean maximum intima-media thickness measurements[5,31]. Nevertheless, CAP presence has been shown to be more closely associated with incidence or recurrence of major cardiovascular events, in

healthy or CHD subjects[7-10]. Results of the present study indicate that, although almost half (45.6%) of the included CHD patients had elevated CIMT, there are no differences in the elevated CIMT prevalence between patients with and without diabetes mellitus. Moreover, the data show that, compared to CHD patients without diabetes, those with diabetes had almost twice the prevalence of CAP (17.7% vs. 30.9%; $p < 0.001$). This information suggests that patients with diabetes and presence of carotid plaques could have a worse cardiovascular prognosis, which is supported by the fact that unlike hCIMT, carotid plaque presence represents predominantly intimal thickening with foam cells, smooth muscle cells, macrophages, lipid core, and fibrous cap, depending on the stage of plaque development[32].

In addition to the different pathophysiology that underlies the development of CIMT and CAP, carotid plaques seem to be more strongly determined by common CHD risk factors, such as age, sex, smoking, adiposity, hypercholesterolemia, hypertension, or diabetes[33]. In the present study, most of the patients were not currently smokers (88.3%) and were under pharmacological treatment (> 90%). Nevertheless, we cannot rule out the possibility of a history of smoking exposure or low compliance with drugs therapy, which could mask the increases in CHD and lead patients to different clinical profiles, as shown in table 1. In spite of this, multivariate logistic analysis showed that T2DM accounts for 57% of the carotid plaque presence, independently of cardiovascular risk factors, CHD or diabetes evolution time, and glycemic control. In contrast, a recent study showed that carotid plaques were not associated with T2DM[34]. However, compared with our sample, that study included a population 10 years older (only 10% with cardiovascular disease), with lower T2DM prevalence (11% vs. 37.2%) and without pharmacological treatment. Our findings are in agreement with those of Spagnoli et al.[35], who reported that, in 180 subjects (62.6 ± 7.4 years of age) with transient CHD, age and diabetes were correlated with carotid fibrous plaques. The authors highlighted the fact that atherosclerotic plaques of diabetes patients were very rich in collagen fibers and suggest that this may be influenced by inflammation factors. This is supported by more recent findings, which indicate that the pathophysiology of T2DM is characterized by increases in oxidative stress, soluble advanced glycation end products, and lipid peroxidation products. The latter are key activators of upstream kinases that lead to endothelial dysfunction and expression of inflammatory genes[15]. This information encourages our hypothesis that premature CHD patients with diabetes and carotid plaques have an increased risk of recurrent cardiovascular events and may be supported by previous data, showing that CHD-symptomatic individuals had carotid plaques with a thin fibrous cap infiltrated by macrophages and T cells expressing human leukocyte antigen-DR[36].

This study has several strengths. First, the number of well-characterized subjects allowed us to analyze the relationship between T2DM and the presence of CAP, adjusted by traditional and emergent cardiovascular risk factors. In addition, the fact that a single-trained specialist sonographer performed all carotid measurements ensured minimum intraobserver variability. A limitation of our study is that findings may not be fully representative of the entire CHD population due to the specific selection bias. However, patients with premature established CHD are a top-priority group for prevention in the clinical practice because they are at increased risk of total and cardiovascular disease mortality[26,27]. Second, the hCIMT definition applied in this report differs from other studies and could explain some differences in differences in hCIMT prevalence. Although other definitions include a CIMT, i.e., > 1 standard deviation from the mean, CIMT at the upper quartile or tertile, or absolute CIMT values ≥ 0.9 or ≥ 1 mm, the American Society of Echocardiography consensus statement recommends the use of CIMT greater than the 75th percentile specific for age, ethnicity, and sex as being abnormal[25]. Third, the association found in the current study should be interpreted with caution, and causality cannot be determined due to the cross-sectional nature of the study design. Follow-up studies are needed to analyze the real contribution of T2DM on plaque's incidence as well as the long-term impact of CIMT and carotid plaques on morbidity and mortality of patients with premature CHD. Finally, no information was collected on compliance with drug therapy, which may lead to an underestimation of the drug effects on T2DM and carotid plaque association. However, we could

adjust for CHD and diabetes clinical evolution, as well as biochemical parameters, which are metabolic markers of disease status.

In conclusion, although the prevalence of hCIMT was higher than that of CAP, the latter was strongly and independently associated with T2DM in this studied cohort of patients with established premature CHD. Given that carotid and coronary arteries are common involved sites of atherosclerosis, the identification of carotid plaques with a noninvasive, sensitive, and reproducible method, such as B-mode ultrasound, could be useful to evaluate the risk of recurrent cardiovascular events, reduce their prevalence, and improve the prognosis among young CHD patients with T2DM.

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