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Carotid atherosclerosis severity in relation to glycemic status: A cross-sectional population study

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ABSTRACT

Objective: Intima-media thickness (IMT) is increased in subjects with prediabetes or newly diagnosed diabetes. However, no previous studies have evaluated the relationship between the severity of carotid atherosclerosis, assessed by the presence of carotid plaques or stenosis, and the glycemic status, assessed either by fasting glucose, an oral glucose tolerance test (OGTT) or A1C levels.
Methods: Cross-sectional analysis of 1475 subjects (mean age 62 years, 44% males), randomly selected from the population. A fasting blood sample was obtained to determine glucose, lipids, and A1C levels. An OGTT was performed in non-diabetic subjects. Carotid atherosclerosis was evaluated by echo-doppler.
Results: A 10.5% of the population had a previous diagnosis of diabetes. Of the 1320 non-diabetic participants, 349 (26.4%) had normal fasting glucose, normal glucose tolerance and A1C < 5.7%, and were considered controls. Prediabetes was diagnosed in 850 subjects (64.4%), and diabetes was newly diagnosed in 121 (9.2%). The prevalence of patients with carotid plaques was 34.2% in controls, 45.1% in prediabetics, 64.2% in newly diagnosed diabetics, and 72.9% in established diabetic patients. These numbers were 0.3%, 1.1%, 5.0% and 7.7% for carotid stenosis, respectively. In multivariate analysis, glycemic status remained significantly associated with the prevalence of carotid plaques after adjusting for age, sex, statin treatment, and cardiovascular risk factors.
Conclusions: Glycemic status is associated with all grades of carotid atherosclerosis, from early signs, as demonstrated by the IMT, to intermediate degrees, as demonstrated by the presence of carotid plaques, to advance atherosclerosis, as established by the presence of carotid stenosis.

Subjects with diabetes have a high incidence of cardiovascular morbidity and mortality [1]. For that reason, early detection and treatment of diabetes is crucial with the aim of reducing their risk of developing micro and macrovascular complications. Also, an early diagnosis of prediabetes has been recommended, in order to establish lifestyle habits to help prevent the progression to diabetes, and to decrease the cardiovascular risk [2,3]. Although different criteria for the diagnosis of prediabetes have been proposed, with good predictive values for the development of type-2 diabetes [4], there are scarce and conflicting data as to which one is the best for predicting cardiovascular disease [5–7].

Carotid atherosclerosis, i.e. increased intima-media thickness (IMT), carotid plaques or carotid stenosis, has long been associated with a greater risk of cardiovascular complications [8]. Consequently, it has been considered a cardiovascular risk equivalent by different guidelines [9,10]. The relation between IMT, carotid plaques and incident cardiovascular disease, has been previously described in both, diabetic and non-diabetic individuals [11,12]. Although not consistently observed, carotid plaques predict the risk of subsequent cardiovascular events better than an increased IMT [13].

While many studies have demonstrated that IMT is increased in subjects with prediabetes and diabetes compared to

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normoglycemic individuals [5–7,14], the prevalence of patients with carotid plaques or carotid stenosis according to the glycemic status has not been previously investigated. The demonstration that subjects with prediabetes have a higher proportion of carotid plaques or stenosis would be relevant, as it could recommend a higher intensity cardiovascular risk factor modification strategy in this population, with the aim of reducing their chances of having a cardiovascular event.

The objective of the present study was to determine the prevalence of patients with carotid plaques and carotid stenosis, according to the presence of normoglycemia, prediabetes or newly diagnosed diabetes in a broad population sample, and to evaluate which test for defining prediabetes and diabetes, either fasting glucose, an OGTT or A1C levels, better identifies an increased atherosclerotic burden.

1. Patients and methods

The **S**creening **PRE**-diabetes and type 2 **DIA**betes (SPREDIA-2) study, is a population-based, prospective cohort study, with baseline screening, in the Region of Madrid (Spain). A random sample of urban subjects, between 45 and 74 years, living in the northwest metropolitan area of Madrid (Spain) was selected for the study. In the reference population there are approximately 183,000 persons of this age. Pregnant women, subjects with severe chronic or terminal illnesses, institutionalized subjects or those chronically treated with steroids or antipsychotic drugs were excluded.

A total of 2553 subjects were contacted for the study, of whom 1592 accepted to participate (62.4%). Of them, 1475 had a valid carotid ultrasound and were the ones selected for the present analysis.

Participants were scheduled in the outpatient clinic of the Hospital Carlos III after an overnight fast. Upon arrival, and after signing a consent form, a fasting blood analysis was obtained for measuring the blood levels of glucose, creatinine, A1C, and lipids and lipoproteins. Immediately after blood sampling, all subjects without a previous diagnosis of diabetes had an OGTT with 75 g of anhydrous glucose in a total fluid volume of 300 ml. A second blood sample was obtained 2 h later.

Sociodemographic variables (date of birth, gender, nationality, and educational level), family history of prevalent diseases (diabetes, coronary heart disease, cerebrovascular disease), self-reported cardiovascular risk factors (smoking habit, hypertension, alcohol ingestion), comorbidities, and current treatments, were recorded in all individuals. Patients were considered current smokers if they had regularly smoked during the past 6 months. All participants had a physical examination with the determination of height, weight, waist circumference (midway between the lowest rib and the iliac crest), and blood pressure (the mean of the last 2 measurements after 3 determinations 5 min apart).

An eco-doppler of both carotids was performed with a 7.5 mHz probe (Sonosite Micromaxx Ultrasound, Sonosite Inc, Bothell, Wash, USA). Patients laid in the supine position with the neck rotated to the opposite site of the examination. One centimeter images were obtained from the distal wall of the common carotid artery proximal to the bifurcation, in three different angle views. IMT was obtained with an automated software (Sonosite, Sonocalc IMT Software, Sonosite Inc, Bothell, Wash, USA), and the maximal region and the overall mean IMT values for each of the 6 segments analyzed (3 angles in 2 territories), was calculated. IMT values for the 3 different projections and for right and left carotid arteries were averaged to obtain the maximum-CCA-IMT and the mean-CCA-IMT. Carotid plaques were defined as a local thickening of the intima >1 mm or a thickening of >50% of the surrounding IMT value. Carotid stenosis was determined according to the presence of lumen narrowing and flow velocities. A less than 50% stenosis was considered when internal carotid artery peak systolic velocity (ICA PSV) was less than 125 cm/s; a 50–69% stenosis when ICA PSV was 125–230 cm/s; and a ≥70% stenosis to near occlusion was diagnosed when ICA PSV was more than 230 cm/s [15].

The diagnosis of pre-diabetes and diabetes was performed according to the ADA criteria [16]. Prediabetes was defined as not having previous diabetes, but having a fasting plasma glucose between 100 and 125 mg/dL, or A1C levels between 5.7 and 6.4%, or a 2h-OGTT plasma glucose between 140 and 199 mg/dl (impaired glucose tolerance; IGT). Newly diagnosed diabetes was defined as not having previous diabetes, but having a fasting plasma glucose ≥126 mg/dL, or A1C levels ≥6.5%, or a 2-h OGTT plasma glucose ≥200 mg/dl. All subjects with normal fasting plasma glucose, normal glucose tolerance and A1C <5.7% were considered controls in the present analysis.

1.1. Laboratory methods

Glucose was measured by the glucose oxidase method. Creatinine, cholesterol and triglycerides were determined by standard methods. LDL cholesterol was calculated according to the Friedewald formula (LDL cholesterol = total cholesterol − (HDL cholesterol + triglyceride/5), in subjects with triglycerides below 400 mg/dL. HDL-cholesterol was measured after precipitation of apo-B lipoproteins. HbA1c was measured by a high-performance liquid chromatography (HPLC) method, using the National Glycohemoglobin Standarization Program, standardized to the Diabetes Control and Complications Trial [17].

1.2. Statistical analysis

The quantitative variables are presented as means with standard deviations or, when indicated, by the standard error of the mean (SEM). The qualitative variables are presented as percentages. Quantitative variables were compared by ANOVA, and qualitative variables by the χ^2 test. Logistic regression analysis were performed to evaluate the independent contribution of the different cardiovascular risk factors and the glycemic status to the presence of carotid plaques and carotid stenosis. Variables were introduced using the "enter" method based on the statistical significance in the univariate analysis ($p < 0.10$), and trying to avoid overadjusting. The magnitude of the associations was expressed using the odds ratio. Multivariate linear regression analysis was used to assess the independent contribution of age, sex, glycemic status and traditional risk factors, to the mean and maximum carotid IMT.

Statistical processing of the data was performed with SPSS for windows, v.19.0; IBM Corp, Armonk, New York, USA.

1.3. Ethical considerations

The study protocol was approved by the Research Ethics Committee of the Carlos III Hospital in Madrid. The study complied with the International Guidelines for Ethical Review of Epidemiological Studies (Geneva, 1991). All patients signed an informed consent form.

2. Results

Of the 1475 participants, 155 (10.5%) had a previous diagnosis of diabetes, with a reported median duration of 7 years. Of the 1320 non-diabetic participants, 47.2% had a fasting glucose <100 mg/dl, 48.6% had impaired fasting glucose (IFG) and 4.3% a fasting plasma glucose ≥ 126 mg/dL. After an oral glucose tolerance test, 74.7% had normal glucose tolerance, 19.5% IGT and 5.8% were diagnosed with