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Prevalence by sex of preclinical carotid atherosclerosis in newly diagnosed type 2 diabetes

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Abstract *Background and aims:* There is clinical trial evidence that only early, intensive risk factor control can reduce cardiovascular disease (CVD) morbidity and mortality in type 2 diabetes (T2DM). However, there is little information regarding preclinical atherosclerosis at diabetes diagnosis. We assessed carotid atherosclerosis in new-onset T2DM and control individuals without prior CVD.
Methods and results: In a cross-sectional case–control study, we determined intima-media thickness (IMT) and plaque (IMT $\geq$1.5 mm) by ultrasound at all carotid sites in new-onset T2DM patients and controls. We assessed 106 T2DM patients, median age 62 years, 46% women, 19% smokers, 54% with hypertension, and 41% with dyslipidemia and 99 non-diabetic subjects matched by age, sex, and cardiovascular risk factors. Compared to controls, T2DM patients had higher common carotid artery (CCA)-IMT (median 0.725 vs. 0.801 mm, $p = 0.01$), bulb-IMT (0.976 vs. 1.028 mm, $p = 0.12$), and internal carotid artery (ICA)-IMT (0.727 vs. 0.802 mm, $p = 0.04$). The prevalence of total plaque (60% vs. 72%, $p = 0.06$), ICA plaque (20% vs. 42%, $p < 0.01$), and harboring $\geq$3 plaques (16% vs. 35% $p < 0.01$) was also higher in T2DM. Plaque score (sum of maximum plaque heights) was also higher ($p < 0.01$) in T2DM. Diabetic women showed more advanced carotid atherosclerosis than diabetic men when they were compared with their respective non-diabetic counterparts.
Conclusions: There is a high prevalence of preclinical atherosclerosis (carotid plaque presence and burden) in new-onset T2DM subjects, especially in women. Early, still reversible, preclinical atherosclerosis may explain in part why early intervention is effective to prevent CVD in this patient population.

Introduction

Based on clinical trial evidence, it has been suggested that only early intervention can prevent cardiovascular disease (CVD) morbidity and mortality in patients with type 2 diabetes (T2DM) [1–3]. Intensive glucose control at advanced disease stages may not necessarily improve cardiovascular outcomes and may even be detrimental [4].

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Whether this differential impact on CVD is due to the different drugs used for glycemic control, rates of hypoglycemia [5] or glucose variability [6], preexisting CVD [4,7], or diabetic neuropathy, is still a matter of debate [8].

These findings may also imply that atherosclerosis at diabetes diagnosis is at an early, still modifiable disease stage in which intensive glycemic control may modify its natural history and thus be worth pursuing [1]. However, sparse information is available regarding atherosclerosis prevalence and its characteristics when diabetes is diagnosed. Furthermore, although CVD prevention is one of the major goals of treatment in T2DM, risk assessment tools, mostly based on traditional cardiovascular risk factors (CVRF), lack adequate specificity to identify individuals with diabetes at higher risk. Therefore, non-invasive testing for preclinical vascular disease, such as carotid ultrasound or coronary artery calcium by computerized tomography, have been recommended to better define cardiovascular risk in selected groups of individuals, including those at intermediate risk or with T2DM [9,10].

This clinical study aimed to improve knowledge on the natural history of CVD in subjects with new-onset T2DM by investigating whether carotid intima-media thickness (IMT) and plaque differed in new-onset T2DM free of CVD compared with non-diabetic controls. Furthermore, given the evidence that diabetes is a stronger risk factor for CVD in women [11], we investigated whether potential differences in preclinical atherosclerosis were similar in men and women at this early diabetes stage when they were compared with their respective non-diabetic counterparts.

Methods

The DIABIMCAP Study (Carotid Atherosclerosis in Newly Diagnosed Type 2 Diabetic Individuals, ClinicalTrials.gov Identifier: NCT01898572) is an observational study aiming to investigate preclinical carotid atherosclerosis in this population. Briefly, participants are evaluated twice, at baseline and after 18 months of follow-up, during which they are followed and treated by their primary care physicians according to current clinical practice guidelines in Spain. Here we report cross-sectional data at baseline. Primary care teams from 3 primary care centers in Barcelona were invited to identify patients with new-onset T2DM between January 2012 and June 2013. Individuals meeting inclusion criteria and willing to participate were enrolled after signing an informed consent to a protocol approved by the institutional review board. The study protocol was conducted according to the principles of the Declaration of Helsinki. Subjects from our Public Health System with clinical (lack of autoimmune diabetes or anti-glutamic acid decarboxylase negativity in suspicious cases) and laboratory (fasting glucose and/or HbA1c, 1999 WHO criteria) evidence of type 2 diabetes were identified. They were considered new-onset T2DM and included in the study if they were diagnosed within the previous year of our recruiting period. In each patient an earlier diagnosis of T2DM was ruled out on the basis of the personal clinical history and after careful review of electronic clinical and laboratory (fasting glucose and HbA1c levels) records available at primary care centers since the year 2001. Because diabetic patients usually have a high prevalence of CVRF, new-onset T2DM were matched to non-diabetic controls for age ($\pm$5 years) and sex as the main determinants of atherosclerosis, but also for traditional CVRF, namely treated hypertension and dyslipidemia, and current smoking habit. Exclusion criteria for both new-onset T2DM and control individuals were: prior history of CVD, cancer, chronic renal failure (serum creatinine $>$1.5 mg/dl) or chronic liver disease, congestive heart failure (NYHA Class III-IV), history of alcohol or drug abuse or dependence, major psychiatric illness, debilitating chronic illness, or short life expectancy.

Clinical and laboratory determinations

Participants were invited to attend a first visit at their primary health care center for physical examination and ascertainment of inclusion and exclusion criteria. Age, sex, smoking habits (current vs. nonsmoker), first-degree family history of diabetes and CVD, and personal history and treatment for hypertension and dyslipidemia were recorded. Weight, height and waist circumferences were measured by using standard methods. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Percentage body fat was calculated by a validated equation based on BMI, sex, and age, as previously described [12]. Blood pressure was measured using a blood pressure monitor (Omron HEM-7223-E; Hoofddorp, The Netherlands) after a few minutes at supine position on the day when carotid ultrasound study was performed. A fasting blood and spot first morning urine samples were collected and biochemical measurements were analyzed in a single laboratory (Biomedical Diagnostic Center, Hospital Clinic, Barcelona) using standardized assays to measure glucose, glycosylated haemoglobin (HbA1c), the lipid profile (including total cholesterol, HDL-cholesterol, LDL-cholesterol by the Friedewald formula, and triglycerides), alanine transaminase, aspartate aminotransferase, gamma-glutamyl transpeptidase, uric acid, high sensitivity C-reactive protein (CRP), white blood cell count, insulin, c-peptide, creatinine, and the albumin-to-creatinine ratio. The Modification of Diet in Renal Disease (MDRD-4) Study equation was used to estimate glomerular filtration rate. The homeostasis model assessment of insulin resistance (HOMAIR) index was calculated as fasting serum insulin (mU/ml) $\times$ fasting plasma glucose (mmol/l)/22.5.

Carotid ultrasound

In a second visit, bilateral carotid artery B-mode ultrasound imaging to evaluate intima-media thickness (IMT) and plaque presence was performed according to a standardized protocol, as previously described [13]. Briefly, within 1–3 months of clinical diagnosis, all new-onset T2DM patients underwent sonographic assessment with an Acuson X300 ultrasound system (Siemens) equipped