Nutrition, Metabolism & Cardiovascular Diseases (2015) **25**, 742–748

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

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

M. Catalan [a], Z. Herreras [a], M. Pinyol [a], A. Sala-Vila [b,c], A.J. Amor [c], E. de Groot [d], R. Gilabert [e], E. Ros [b,c], E. Ortega [b,c,*]

[a] Consorcio de Atención Primaria del Eixample (CAPSE), Grup Transversal de Recerca en Atenció Primària, IDIBAPS, Barcelona, Spain
[b] Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y Nutrición (CIBERobn), Instituto de Salud Carlos III (ISCIII), Spain[1]
[c] Endocrinology and Nutrition Service, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Spain
[d] Department of Vascular Medicine and Cardiovascular Imaging, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands
[e] Vascular Unit, Centre de Diagnòstic per l'Imatge, IDIBAPS, Hospital Clínic, Barcelona, Spain

Received 4 December 2014; received in revised form 26 March 2015; accepted 26 April 2015
Available online 7 May 2015

KEYWORDS
Diabetes;
Carotid ultrasound;
Atherosclerosis;
Plaque;
Intima-media thickness

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].

* Corresponding author. Endocrinology and Nutrition Service, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain.
E-mail address: eortega1@clinic.ub.es (E. Ortega).
[1] http://www.ciberobn.es.

http://dx.doi.org/10.1016/j.numecd.2015.04.009
0939-4753/

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

with a VF 10-5 linear transducer (frequency range 5–10 MHz). Control individuals were also identified and assessed with the same protocol during the same timeframe. The same certified sonographer performed all examinations. IMTs at the common carotid artery (CCA), bulb, and internal carotid artery (ICA) were measured offline by semiautomatic software. IMT-mean and IMT-maximum from each segment was recorded. Plaques were explored by using B-mode and color Doppler and defined as a focal wall thickening encroaching into the arterial lumen by at least 50% of the surrounding IMT value or with thickness of at least 1.5 mm as measured from the media adventitia interference to the intima-lumen surface [14]. Plaque scores (sum of maximum heights of all plaques) were recorded for all study subjects. For more detailed description, see Supplemental Materials.

Statistical analyses

Data are presented as medians and 25th and 75th percentiles, mean ± SD, or n (%), as appropriate. Non-normally distributed variables were log transformed to reduce skewness. Between-group differences in clinical, anthropometric, and laboratory variables were evaluated by the chi-squared test for categorical variables, Mann–Whitney test for continuous non-normally distributed variables, or unpaired student's t-test for continuous normally distributed variables. Although by study design there were no group differences in age and sex, carotid atherosclerosis outcomes (dependent variables) were adjusted for age and sex due to its marked effect on atherosclerosis. To this aim linear regression and logistic binary regression models were built with age, sex, and GROUP as explanatory variables for IMT and plaque outcomes, respectively. To test whether group differences were modified by sex, we introduced the interaction term GROUP × SEX in these models. Age-and-sex adjusted odds ratios (OR) and 95% confidence intervals (CI) for plaque outcomes were computed by using binary logistic regression. Finally, to investigate whether group differences in preclinical atherosclerosis between new-onset T2DM patients and non-diabetic individuals could be explained by clinical and metabolic differences already present at the time of diabetes diagnosis, stepwise multiple regression models were adjusted (in addition to age, sex, hypertension, dyslipidemia, and smoking) for those variables that were different between groups, i.e., BMI, waist circumference, atherogenic dyslipidemia (HDL-cholesterol and triglycerides), LDL-cholesterol, systolic blood pressure, CRP, leukocyte count, HOMA-IR, and HbA1c.

No information on plaque prevalence in new-onset T2DM was available at the time of study design. Sample size was therefore estimated based on expected differences in CCA-IMT between individuals with and without T2DM [15]. We anticipated a mean CCA-IMT group difference of 0.12 mm (SD 0.24). A sample size of 95 subjects per group was estimated to provide 85% statistical power, assuming a 20% dropout rate. Analyses were performed with SAS software, v.9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Subject's characteristics

Per study design, new-onset T2DM and control groups did not differ by age, sex, smoking status, or prevalence of hypertension or dyslipidemia. However, new-onset T2DM patients had higher BMI, body fat, waist circumference, and prevalence of overweight and obesity. Total and LDL-cholesterol were similar between groups and mean systolic blood pressure was on average 5 mmHg higher in new-onset T2DM. As expected, diabetes-related variables (fasting glucose, HbA1c, HOMA-IR) and most laboratory variables associated with obesity or increased abdominal fat, such as triglycerides, HDL-cholesterol, and markers of chronic inflammation (leukocyte count and CRP) were also different between groups (Table 1).

Intima-media thickness and sex differences

Carotid IMT values for diabetic and control individuals are shown in Tables 2 and 3. All values were significantly higher in new-onset T2DM compared to controls, with the exception of BULB-mean and BULB-max ($p = 0.13$ and $p = 0.10$, respectively) (Table 2). We tested whether between group differences in IMT were similar in men and women and found that differences in CCA-IMT and BULB-IMT between new-onset T2DM and controls were larger (significant SEX × GROUP interactions) for women than for men (Table 3). Although this trend was also observed for ICA-IMT measurements, interactions terms did not reach statistical significance. While IMT measurements were higher in non-diabetic men compared with non-diabetic women ($p < 0.01$ all), no sex differences ($p > 0.4$ all) were found for these variables within the diabetic group (Table 3).

Carotid plaque and sex differences

Carotid plaque prevalence was associated with age (OR [95% IC] for a 5 year increment 1.40 [1.15–1.71], $p = 0.009$) and male sex (age-adjusted OR 1.80 [0.99–3.29], $p = 0.05$). Therefore, age and sex were included as covariates in statistical analyses. Carotid plaques tended to be more prevalent (72% vs. 60%, $p = 0.06$) in new-onset T2DM compared to controls, and this difference was driven by a higher prevalence of plaques at the ICA segment ($p < 0.01$), but not at the CCA or bulb. Carotid plaque burden was higher in new-onset T2DM patients compared with controls, as the former had more often ≥3 plaques (age-adjusted OR 2.86 [1.45–5.62]) or at least one plaque with ≥2.5 mm height (OR 2.44 [1.25–4.75]), and also had a higher total carotid and ICA plaque score (sum of plaque heights) (Table 4). None of the participants had carotid stenosis >50%.

Table 1 Subjects' characteristics.

	Control (n = 99)	New-onset diabetes (n = 106)	p value
Variables used to match groups			
Female sex	46 (47)	49 (46)	0.9727
Age (years)	63 (55–67)	62 (55–66)	0.7889
Smoking (current/past /never), (%)	20/30/50	20/31/49	0.9601
Dyslipidemia	37 (37)	43 (41)	0.6396
Hypertension	54 (55)	57 (54)	0.9117
General clinical and laboratory characteristics			
Systolic BP (mm Hg)	127 ± 16	132 ± 17	0.0406
Diastolic BP (mm Hg)	81 ± 9	82 ± 10	0.2055
Body mass index (kg/m^2)	27.3 (25.1–31.2)	30.2 (27–33.8)	<0.0001
BMI < 25/25–30 />30 kg/m^2, (%)	24/45/31	7/41/52	0.0004
Body fat, (%)	36.1 ± 8.7	39.3 ± 7.5	0.0042
Waist circumference (cm)	97.5 ± 12.2	104.5 ± 12.8	0.0001
Total cholesterol (mg/dl)	210 ± 35	200 ± 41	0.0726
HDL-cholesterol (mg/dl)	56 (48–67)	48 (41–55)	<0.0001
LDL-cholesterol (mg/dl)	130 ± 31	122 ± 33	0.0788
Triglycerides (mg/dl)	103 (76–132)	131 (89–172)	<0.0001
Leukocyte count (109/L)	6.3 (5.4–7.1)	6.8 (5.9–8.7)	0.0116
C-reactive protein (mg/dl)	0.19 (0.11–0.35)	0.35 (0.16–0.65)	0.0002
Diabetes related clinical and laboratory characteristics			
Hemoglobin A_{1c} (%)	5.6 (5.5–5.9)	6.7 (6.4–7.3)	<0.0001
Hemoglobin A1c (mmol/mol; IFCC)	38 (37–41)	50 (46–56)	<0.0001
Fasting glucose (mg/dl)	98 (91–105)	133 (120–150)	<0.0001
Insulin (mU/L)	10.9 (7.7–18.3)	15.3 (11–24.3)	0.0002
C-peptide (ng/mL)	2.1 (1.5–3)	2.6 (2–3.8)	<0.0001
HOMA-IR (mU/l × mmol/L)/ 22.5	2.6 (1.8–4.7)	5.1 (3.4–8.4)	<0.0001
Serum creatinine (mg/dL)	0.85 ± 0.15	0.84 ± 0.16	0.7545
MDRD4, ml/min	83 ± 13	84 ± 16	0.8439
UACR ≥ 30 mg/gr	8 (8)	11 (11)	0.5129

Data are shown as n (percentage), median (Q1–Q3), or mean ± standard deviation.
P-values for group comparisons are reported.
BP: blood pressure; BMI: Body Mass Index; HDL: high density lipoprotein; LDL: low density lipoprotein; HOMA-IR homeostasis model assessment of insulin resistance; MDRD: Modification of Diet in Renal Disease Study equation; UACR: urine albumin to creatinine ratio.

We also explored whether the new-onset T2DM vs. control differences in carotid plaque were similar in men and women. Subgroup analyses by sex showed that new-onset T2DM women had higher prevalence of carotid plaque (OR [95% IC], 3.02 [1.22–7.48]), ≥3 carotid plaques (4.62 [1.36–15.65]), and ICA plaque (5.47 [1.91–15.66]) than women without diabetes, while no differences in plaque prevalence between men with and without diabetes were observed. Also, the overall prevalence of total plaques (p = 0.01) and CCA plaques (p = 0.02) was higher in non-diabetic men compared with non-diabetic women, while no sex differences were found within the new-onset T2DM group (Fig. 1).

Factors explaining group (new-onset T2DM vs. control) differences in carotid atherosclerosis (supplementary table)

Factors contributing to differences in atherosclerosis between individuals with and without diabetes were investigated (see methods). In multiple linear (for IMT) or logistic (for plaque variables) regression models, we found that HbA1c, and triglycerides and/or HDL-cholesterol were the variables (among those that were different between groups) associated with carotid atherosclerosis. Specifically (Model 4 Supplementary Table), age, HbA1c, sex, HDL-cholesterol and LDL-cholesterol; age, sex, and triglycerides; and age, hypertension, and triglycerides were associated with CCA, BULB, and ICA-IMT, respectively. Age (OR 1.09 [1.04–1.13] for a 1 year increment), HDL-cholesterol (0.96 [0.94–0.98] for a 1 mg/dl increment), and HbA1c (1.36 [1.00–1.86] for a 1% increment), and age (1.09 [1.03–1.15]), HDLc (0.96 [0.93–0.99]), HbA1c (1.27 [1.00–1.62]), and triglycerides (1.01 [1.001–1.013] for a 1 mg/dl increment) were associated with carotid plaque and ≥3 plaques, respectively. The variable group (new-onset T2DM vs. control) was not associated with outcome variables when it was added into this full-adjusted model (Model 4 Supplementary Table).

Discussion

In this study patients with a new diagnosis of T2DM and without clinical CVD had more advanced preclinical carotid atherosclerosis than non-diabetic subjects even after controlling for traditional CVRF, such as age, sex, hypertension, dyslipidemia, and smoking. The duration of the prediabetic state and undiagnosed diabetes and the metabolic abnormalities associated with untreated hyperglycemia and insulin resistance might be responsible in part for these differences. Indeed, HbA1c and, particularly, variables defining atherogenic dyslipidemia (HDL-cholesterol, triglycerides, or both), but not BMI, inflammatory markers, or HOMA-IR, were associated with preclinical atherosclerosis in regression analyses.

To the best of our knowledge, previous information regarding carotid plaque prevalence in new-onset T2DM was limited to a single study [16], in which moderate-to-severe plaque was found in approximately 30% of newly diagnosed 61 year-old diabetic Swedish men. In 2013, while our study was ongoing, prevalence of carotid plaque was reported to be higher in a large cohort of Chinese patients with new-onset T2DM than in non-diabetic individuals, ranging from 31% to 73% in individuals aged 50 to ≥70 years [17]. More information is available regarding IMT and IMT progression at and after T2DM diagnosis,

Table 2 Carotid intima-media thickness (IMT) by group (control vs. new-onset diabetes).

	Control (n = 99)		New-onset diabetes (n = 106)		p-value[a]
	Median	Q1–Q3	Median	Q1–Q3	
CCA-mean	0.725	0.671–0.825	0.801	0.686–0.872	0.0127
CCA-max	0.808	0.765–0.936	0.907	0.762–0.983	0.0266
BULB-mean	0.976	0.845–1.148	1.028	0.882–1.249	0.1353
BULB-max	1.193	0.989–1.431	1.261	1.086–1.529	0.1003
ICA-mean	0.727	0.643–0.880	0.802	0.632–1.037	0.0354
ICA-max	0.876	0.775–1.093	1.011	0.777–1.348	0.0080

Data are shown as median (Q1–Q3).
CCA, common carotid artery; ICA, internal carotid artery; mean-values: IMT mean of mean right IMT and mean left IMT carotid (CCA, BULB, or ICA) segment; max-values: IMT mean of the maximum right and maximum left IMT (CCA, BULB, or ICA) segment.
[a] P-values for age-and-sex-adjusted group comparisons.

respectively [15,16,18]. Studies have shown that IMT values (mainly at CCA) were larger in new-onset T2DM patients compared with non-diabetic individuals [15,16,18]. We assessed IMT at different carotid sites and, to ascertain whether differences between new-onset T2DM and non-diabetic subjects were due to a higher prevalence of classical risk factors (which is usually the case for diabetic population), we not only matched cases and controls for age and sex [15,16,18], but also for additional factors associated with preclinical carotid atherosclerosis, i.e., hypertension, dyslipidemia, and smoking.

New-onset T2DM is not a benign condition. Significant morbidity is already present at clinical diagnosis, which has been estimated to be delayed at least 4–7 years after diabetes onset [19], with nearly one-half of diabetic patients being unaware of their condition [20]. Indeed, a recent report of the large SOUL-D cohort of newly diagnosed T2DM patients from different ethnic backgrounds shows that microvascular complications are not rare at this stage (26–37% with at least one complication) [21]. At this moment in the natural history of T2DM, microvascular evaluation is not based on detection of clinical events: renal failure (for diabetic kidney damage), loss of vision (for diabetic retinopathy), or presence of foot ulceration (for diabetic neuropathy). Rather, we precisely evaluate microvascular complications by repeated determinations to detect subtler alterations: urine albumin-to-creatinine ratio, digital two-field photography of retina, and vibration perception threshold or monofilament examination [22]. We have chosen this approach because both prognosis and the intensity of treatment are determined by these findings. In the SOUL-D study prevalent CVD ranged from 5% to 13% depending on ethnic background, but vascular imaging to detect atherosclerosis, the precursor of clinical disease, was not performed [21].

Albeit CVD is the leading cause of morbidity and mortality in T2DM and prevention is more efficacious at early stages of the disease [1–4], using imaging techniques to evaluate preclinical atherosclerosis in order to tailor intervention to findings is not customary in this high-risk group. Moreover, it is still common clinical practice to rely mainly on the duration of the disease to decide whether patients should be on an intensive multifactorial treatment strategy, even though at this stage prevention of CVD by intensive therapy is questionable [4]. It is possible that a CVD prevention strategy based on age, CVRF, and image biomarkers, particularly carotid ultrasound, could be useful to better identify individuals at higher risk [23]. Although more research is necessary to identify features of so-called vulnerable plaques prone to rupture (such as thin cap fibroatheroma, large lipid core, and neovascularization), information on carotid plaque presence and burden is useful in the identification of individuals at risk of future CVD [23,24]. In our study approximately one third of new-onset T2DM patients were free of carotid plaque, one third had 1–2 plaques, and one third had ≥3 plaques. Thus, fully two-thirds of new-onset T2DM patients are candidates to intensified treatment directed at CVD risk reduction. On the other hand, IMT measurements were systematically lower in controls and only 16% of them had ≥3 carotid plaques, indicating a younger vascular age compared with new-onset T2DM. Plaque

Table 3 Carotid intima-media thickness by group (control vs. new-onset diabetes) and sex.

	Women (n = 95)		Men (n = 110)	
	Control (n = 46)	New-onset diabetes (n = 49)	Control (n = 53)	New-onset diabetes (n = 57)
CCA-mean	0.701 (0.644–0.783)[a]	0.799 (0.663–0.853)	0.771 (0.698–0.883)	0.807 (0.703–0.896)
CCA-max	0.785 (0.712–0.855)[a]	0.904 (0.758–0.959)	0.846 (0.796–0.982)	0.913 (0.775–1.010)
BULB-mean	0.883 (0.758–1.107)[b]	0.981 (0.855–1.153)	1.065 (0.938–1.200)	1.052 (0.908–1.265)
BULB-max	1.103 (0.956–1.310)[b]	1.233 (1.075–1.523)	1.324 (1.065–1.514)	1.291 (1.104–1.533)
ICA-mean	0.696 (0.603–0.767)[b]	0.779 (0.637–1.037)	0.788 (0.673–0.919)	0.832 (0.629–1.022)
ICA-max	0.811 (0.725–0.980)[a]	0.998 (0.783–1.321)	0.927 (0.824–1.187)	1.014 (0.777–1.368)

Data are shown as median (Q1–Q3).
p-values for age-adjusted SEX × GROUP interactions for CCA-mean, CCA-max, BULB-mean, BULB-max, ICA-mean, and ICA-max were 0.0277, 0.0165, 0.0425, 0.0366, 0.2398, and 0.1847, respectively.
CCA, common carotid artery; ICA, internal carotid artery; mean-values: IMT mean of mean right IMT and mean left IMT carotid (CCA, BULB, or ICA) segment; max-values: IMT mean of the maximum right and maximum left IMT (CCA, BULB, or ICA) segment.
[a]$p<0.01$ and [b]$p < 0.05$ for age-adjusted differences between women with and without diabetes. No differences ($p > 0.3$) found between men with and without diabetes.

Table 4 Carotid plaque prevalence.

	Control (n = 99)	New-onset diabetes (n = 106)	p value
Carotid plaque	59 (60)	76 (72)	0.0583
Common carotid plaque	13 (13)	23 (22)	0.1093
Bulb carotid plaque	52 (53)	61 (58)	0.4561
Internal carotid plaque	20 (20)	44 (42)	0.0011
≥3 carotid plaques	16 (16)	37 (35)	0.0023
Plaque height ≥ 2.5 mm	17 (17)	35 (33)	0.0093
Plaque score (mm)	3.43 (1.73–5.16)	5.59 (3.25–7.46)	0.0003
Internal carotid plaque score (mm)	2.02 (1.73–2.75)	2.56 (1.95–4.67)	0.0243

Data are shown as n (percentage) and median (Q1–Q3).
P-values for age-and-sex-adjusted group differences are reported.
CCA, common carotid artery; ICA, internal carotid artery; Plaque score (sum of heights of all plaques).

prevalence was marginally lower (p = 0.06) in controls, but it was still high (60%), probably because, by definition of the cohort to match CVRF with the disease group, they had a high cardiovascular risk profile [25,26] (Table 1).

Male sex is a well-established cardiovascular risk factor and lifelong risk for CVD is higher in men than in women [27]. We [28] and others [29] have shown increased IMT and plaque prevalence in non-diabetic men compared to non-diabetic women. Diabetes, however, has a different impact on CVD according to sex. Compared to non-diabetic populations, diabetes increases CVD risk by 3–4 times in women but only twice in men [30,31]. Several studies have compared IMT measurements or plaque prevalence between men and women with diabetes. However, little information is available regarding preclinical atherosclerosis differences when women and men with diabetes are compared with their non-diabetic counterparts. Our results show that, similarly to what has been reported for clinical outcomes, even at this early disease stage women with diabetes disclose worse preclinical atherosclerosis

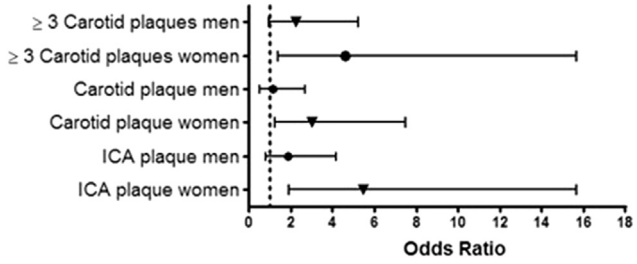

Figure 1 Carotid plaque in patients with new-onset T2DM (vs. controls) by sex. Age-adjusted odds ratios (OR) and 95% confidence intervals (95%CI) for the probability of presenting different carotid plaque variables in patients with new-onset T2DM (vs. without diabetes) separate by sex. ≥3 carotid plaques OR (95% CI) 2.26 (0.97–5.25) and 4.62 (1.36–15.65); total carotid plaque 1.15 (0.49–2.69) and 3.02 (1.22–7.48); and ICA (internal carotid) plaque 1.85 (0.82–4.17) and 5.47 (1.91–15.66), for men and women, respectively. p-values for age-adjusted SEX × GROUP interactions were p = 0.34, p = 0.13, and p = 0.11 for reported ≥3 carotid plaques, total carotid plaque, and ICA plaque, respectively.

than non-diabetic women, with ORs of 3–4 for several carotid outcomes. Moreover, preclinical atherosclerosis in women with new-onset T2DM was similar to that observed in men with new-onset T2DM, indicating that the protective effect of sex on CVD may already be lost when T2DM is diagnosed in women.

In conclusion, as determined by carotid ultrasound, preclinical atherosclerosis, the soil for cardiovascular events, is already present in a significant proportion of newly diagnosed individuals with T2DM, even after controlling for traditional CVRF. At this early stage, HbA1c and diabetic dyslipidemia explain, at least in part, between-group differences in preclinical atherosclerosis. We suggest that, similarly to how new-onset T2DM patients with microvascular complications are managed, a differential approach to diabetes management and cardiovascular prevention should be implemented at diabetes presentation with the aim of improving prognosis and preventing clinical CVD. Finally, analogous to what is known for clinical CVD risk, new-onset T2DM women show preclinical atherosclerosis of a degree that is similar to that found in diabetic men, but is worse in comparison to their respective non-diabetic counterparts.

Acknowledgments

This study was funded (PI11/01723) by the Spanish Ministry of Health (ISCIII) & FEDER. AS-V was supported by post-doctoral contract FIS CP12/03299. None of the funding sources played a role in the design, collection, analysis or interpretation of the data or in the decision to submit the manuscript for publication. This work would not have been possible without the help (physicians, nurses, and administrative personal) of the three primary care centres (CAPSE, CAP Borrell, Casanovas, and Les Corts) involved in the study. CIBERobn is an initiative of ISCIII, Spain.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2015.04.009.

References

[1] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–89.
[2] Moritz T, Duckworth W, Abraira C. Veterans affairs diabetes trial–corrections. N Engl J Med 2009;361:1024–5.
[3] Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–72.
[4] Gerstein HC, Miller ME, Byington RP, Goff Jr DC, Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–59.
[5] Hanefeld M, Duetting E, Bramlage P. Cardiac implications of hypoglycaemia in patients with diabetes – a systematic review. Cardiovasc Diabetol 2013;12:135.
[6] Ceriello A, Novials A, Ortega E, Pujadas G, La Sala L, Testa R, et al. Hyperglycemia following recovery from hypoglycemia worsens endothelial damage and thrombosis activation in type 1 diabetes

and in healthy controls. Nutr Metab Cardiovasc Dis 2014;24:116–23.
[7] Reaven PD, Moritz TE, Schwenke DC, Anderson RJ, Criqui M, Detrano R, et al. Intensive glucose-lowering therapy reduces cardiovascular disease events in veterans affairs diabetes trial participants with lower calcified coronary atherosclerosis. Diabetes 2009;58:2642–8.
[8] Del PS. Megatrials in type 2 diabetes. From excitement to frustration? Diabetologia 2009;52:1219–26.
[9] Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010;56:e50–103.
[10] Naghavi M, Falk E, Hecht HS, Jamieson MJ, Kaul S, Berman D, et al. From vulnerable plaque to vulnerable patient–part III: executive summary of the Screening for Heart Attack Prevention and Education (SHAPE) task force report. Am J Cardiol 2006;98:2H–15H.
[11] Roche MM, Wang PP. Sex differences in all-cause and cardiovascular mortality, hospitalization for individuals with and without diabetes, and patients with diabetes diagnosed early and late. Diabetes Care 2013;36:2582–90.
[12] Gomez-Ambrosi J, Silva C, Catalan V, Rodriguez A, Galofre JC, Escalada J, et al. Clinical usefulness of a new equation for estimating body fat. Diabetes Care 2012;35:383–8.
[13] Junyent M, Cofán M, Núñez I, Gilabert R, Zambón D, Ros E. Influence of HDL cholesterol on preclinical carotid atherosclerosis in familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 2006;26:1107–13.
[14] Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the advisory board of the 3rd and 4th watching the risk symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis 2007;23:75–80.
[15] Wagenknecht LE, Zaccaro D, Espeland MA, Karter AJ, O'Leary DH, Haffner SM. Diabetes and progression of carotid atherosclerosis: the insulin resistance atherosclerosis study. Arterioscler Thromb Vasc Biol 2003;23:1035–41.
[16] Sigurdardottir V, Fagerberg B, Hulthe J. Preclinical atherosclerosis and inflammation in 61-year-old men with newly diagnosed diabetes and established diabetes. Diabetes Care 2004;27:880–4.
[17] Li LX, Zhao CC, Ren Y, Tu YF, Lu JX, Wu X, et al. Prevalence and clinical characteristics of carotid atherosclerosis in newly diagnosed patients with ketosis-onset diabetes: a cross-sectional study. Cardiovasc Diabetol 2013;12:18.
[18] Temelkova-Kurktschiev TS, Koehler C, Leonhardt W, Schaper F, Henkel E, Siegert G, et al. Increased intimal-medial thickness in newly detected type 2 diabetes: risk factors. Diabetes Care 1999;22:333–8.
[19] Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care 1992;15:815–9.
[20] Soriguer F, Goday A, Bosch-Comas A, Bordiu E, Calle-Pascual A, Carmena R, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es Study. Diabetologia 2012;55:88–93.
[21] Winkley K, Thomas SM, Sivaprasad S, Chamley M, Stahl D, Ismail K, et al. The clinical characteristics at diagnosis of type 2 diabetes in a multi-ethnic population: the South London Diabetes cohort (SOUL-D). Diabetologia 2013;56:1272–81.
[22] American Diabetes Association. Standard of medical care in diabetes – 2015. Diabetes Care 2015;38(Suppl. 1):S1–94.
[23] Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol 2010;55:1600–7.
[24] Johnsen SH, Mathiesen EB, Joakimsen O, Stensland E, Wilsgaard T, Lochen ML, et al. Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromso Study. Stroke 2007;38:2873–80.
[25] López-Cancio E, Dorado L, Millán M, Reverté S, Suñol A, Massuet A, et al. The Barcelona-Asymptomatic Intracranial Atherosclerosis (AsIA) study: prevalence and risk factors. Atherosclerosis 2012;221:221–5.
[26] Betriu A, Martinez-Alonso M, Arcidiacono MV, Cannata-Andia J, Pascual J, Valdivielso JM, et al. Prevalence of subclinical atheromatosis and associated risk factors in chronic kidney disease: the NEFRONA study. Nephrol Dial Transpl Off Publ Eur Dial Transpl Assoc Eur Ren Assoc 2014;29:1415–22.
[27] Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. Circulation 2011;124:2145–54.
[28] Junyent M, Zambon D, Gilabert R, Nunez I, Cofan M, Ros E. Carotid atherosclerosis and vascular age in the assessment of coronary heart disease risk beyond the Framingham Risk Score. Atherosclerosis 2008;196:803–9.
[29] Kozakova M, Palombo C, Morizzo C, Nolan JJ, Konrad T, Dekker JM, et al. Gender-specific differences in carotid intima-media thickness and its progression over three years: a multicenter European study. Nutr Metab Cardiovasc Dis 2013;23:151–8.
[30] Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332:73–8.
[31] Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di AE, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215–22.