Association of Impaired Glucose Homeostasis With Preclinical Carotid Atherosclerosis in Women: Impact of the New American Diabetes Association Criteria

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The aim of this study was to determine whether impaired glucose regulation, defined according to the new American Diabetes Association (ADA) criteria, is associated with early signs of carotid atherosclerosis. We examined 310 clinically healthy women from southern Italy, aged 30 to 69 years, recruited for a prospective study, currently ongoing, on the etiology of cardiovascular disease and cancer in the female population (Progetto Atena). All subjects underwent cardiovascular risk factor assessment and high resolution B-mode ultrasound to measure intima-media thickness (IMT) of common carotid arteries and carotid bifurcations. At the time of our survey, fasting glucose levels ≥ 7.0 mmol/L had already been found in 7 women, 17 participants were diagnosed on that occasion as having new diabetes, 38 had impaired fasting glucose (IFG), and the remaining 248 presented normal fasting glucose values (NFG). Diabetic women showed a worse cardiovascular risk profile, with higher values of triglycerides, body mass index, and diastolic blood pressure than either normoglycemic or IFG subjects. The frequency of atherosclerotic plaques (IMT > 1.2 mm) increased as glucose homeostasis worsened. In multivariate logistic regression analyses, only diabetes mellitus was associated with a significantly increased risk of carotid atherosclerosis (odds ratio [OR], 11.5; 95% confidence interval [CI], 1.4 to 92.7). Our findings suggest a definite association between diabetes mellitus, as defined by the new ADA diagnostic criteria and early carotid structural changes. Furthermore, the condition of IFG does not seem to identify subjects at significantly increased atherosclerotic risk.

OVER THE LAST decade, high resolution B-mode ultrasound has proven to be a valid and reliable method to detect and monitor changes in carotid intima-media thickness (IMT), a marker of preclinical generalized atherosclerosis.[1] Increased carotid IMT is a powerful predictor of the presence of coronary atherosclerosis and its clinical sequelae[2,3] and has been found in subjects with cardiovascular risk factors, including diabetes mellitus, as diagnosed according to the World Health Organization (WHO) criteria.[4-7]

Recently, the American Diabetes Association (ADA) proposed new diagnostic criteria for diabetes mellitus.[8] These criteria were developed with the purpose to simplify the detection of diabetes; they are based mainly on fasting glucose levels, with an upper threshold for the diagnosis lowered from 7.8 mmol/L to 7.0 mmol/L, and no longer recommend the routine clinical use of the oral glucose tolerance test. Furthermore, the ADA criteria identify a new metabolic category intermediate to normal glucose homeostasis and diabetes, different from the WHO class of impaired glucose tolerance (IGT), called impaired fasting glucose (IFG), for fasting plasma glucose between 6.1 and 6.9 mmol/L.

Although the glucose levels chosen by the ADA for the diagnosis of diabetes are associated with a sharp increase in microvascular complications, ie, retinopathy, it is not yet known whether they are related with the risk of developing atherosclerotic vascular disease. Moreover, while previous studies have demonstrated that IGT identifies individuals at risk of atherosclerosis and cardiovascular events,[9-11] few data are available on IFG.

In a currently ongoing female population-based study, Progetto Atena, we evaluated whether an impaired glucose regulation, defined according to the ADA criteria, is associated with preclinical carotid atherosclerosis.

MATERIALS AND METHODS

Progetto Atena is a prospective study on the etiology of major chronic diseases in the female population.[12] The total study cohort, enrolled within a 4-year period, consisted of 5,062 clinically healthy women, aged from 30 to 69 years, living in the area of Naples, a city in southern Italy. Potential participants with previous diagnosis of myocardial infarction, stroke, and major cancers were excluded. During a 6-month period, every day the older 3 of the 10 participants were asked to undergo a free high resolution B-mode ultrasound examination of the carotid arteries; 310 women underwent this additional investigation and were included in the present analysis. After age adjustment, there were no differences in the cardiovascular risk profile between the sample of women who underwent carotid ultrasound evaluation and the remaining cohort of Progetto Atena (Table 1).

Clinical and Biochemical Assessment

Standard procedures for blood pressure measurements, training, and supervision of observers as applied to similar epidemiologic studies were used.[13] Body mass index was calculated as weight (in kilograms) divided by height squared (m^2). A standard questionnaire was used to collect information about smoking status. The average number of

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Table 1. Cardiovascular Risk Profile of Progetto Atena Remaining Cohort and High Resolution Carotid Ultrasound Subsample

	Cohort (n = 4,752)	Subsample (n = 310)
Body mass index (kg/m^2)	27.0 ± 0.1	27.2 ± 0.3
Systolic blood pressure (mm Hg)	133.9 ± 0.3	133.3 ± 1.1
Diastolic blood pressure (mm Hg)	81.4 ± 0.1	81.5 ± 0.6
Total cholesterol (mmol/L)	6.1 ± 0.02	6.1 ± 0.06
LDL cholesterol (mmol/L)	3.9 ± 0.01	3.9 ± 0.06
HDL cholesterol (mmol/L)	1.6 ± 0.01	1.6 ± 0.02
Triglycerides (mmol/L)	1.2 ± 0.02	1.3 ± 0.03
Current smokers (%)	40.1	37.2

NOTE. Age-adjusted values are mean ± SE or %.

cigarettes smoked per day was noted for each smoker and ex-smoker. The total number of years of smoking in current and ex-smokers was multiplied by the average number of packs of cigarettes smoked daily: the product was called "pack-years".

Blood specimens were collected in fasting conditions early in the morning between 8:00 and 9:30 AM to reduce the influence of circadian variation. Total cholesterol and triglycerides were measured using standard enzymatic methods.[14,15] High-density lipoproteins (HDL) were precipitated by phosphotungstate,[16] and low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula.[17] Fasting glucose levels were assessed by the hexokinase method.

Diabetes mellitus was defined if the subject reported medical history of the disease or use of antidiabetic drugs or with fasting glucose levels ≥ 7.0 mmol/L. IFG was diagnosed when fasting glucose was 6.1 to 6.9 mmol/L.

High Resolution Carotid Ultrasound

Carotid B-mode ultrasound examinations were accomplished by an internationally certified sonographer, unaware of the subjects' glycemic status, using the Biosound (Indianapolis, IN) 2000 II SA equipped with an 8 MHz annular array mechanical transducer. This system provides high resolution ultrasonic images with 0.3 mm axial resolution. Scans were performed according to a standardized protocol developed by the Division of Vascular Ultrasound Research at the Wake Forest University School of Medicine.[18] The key features of the protocol were the identification of 2 anatomical landmarks, ie, the dilation of the bulb and flow divider and the use of different scanning angles, ie, anterior, lateral, and posterior, in order to measure IMT thickness in 2 carotid segments, the distal 1 cm of the common carotid artery and the carotid bifurcation. The occurence of atherosclerotic plaques, defined as localized echo structures encroaching into the vessel lumen with an IMT greater than 1.2 mm, was used as ultrasound end-point of the study. A cutoff point of 1.2 mm for IMT was chosen, beacuse it has been previously used in randomized clinical trials[19-21] and also because it corresponded to the 90th percentile of the mean IMT of a random sample of 170 Neapolitan women. All IMT measurements were made by the sonographer at the time of the examination using the machine' s electronic caliper. In our vascular laboratory, which takes part in interventional clinical trials using ultrasound, the within-subject coefficient of variation previously reported for IMT is less than 6%.[22]

The external lumen diameter (defined as the distance between the near and far media-adventitia interfaces) and the internal lumen diameter (defined as the distance between the near and far lumen-intima interfaces) of common carotid arteries were also measured.

Statistical Analysis

All statistical analyses were performed with SPSS (SPSS Inc, Chicago, IL) for Windows 95, version 7.0. Continuous variables were described as mean and standard error, and discrete variables were reported as percentages. Logarithmic transformation of triglycerides was performed to normalize the distribution before analyses. Analysis of covariance was used to obtain age-adjusted means of variables and to compare groups. Odds ratios (OR) for the presence of atherosclerotic plaques were calculated by unconditional logistic regression and 95% confidence intervals (CI) were computed from the standard error of the regression coefficient.

RESULTS

Of the 310 participants included in the present study, 205 (66%) had atherosclerotic plaques mainly localized at the carotid bifurcation.

Seven participants had fasting glucose levels ≥ 7.0 mmol/L already at enrollment, were either on specific antidiabetic diet or taking hypoglycemic agents, and were thus considered as having established diabetes mellitus. Seventeen women without previous history of disease were classified as having diabetes on the basis of their fasting glucose concentrations, 38 met the criteria for IFG, and 248 had normal glucose values (NFG). Clinical and biochemical characteristics of the study population stratified according to the ADA fasting criteria are reported in Table 2. We grouped diabetic participants with previously and newly detected fasting glucose levels ≥ 7.0 mmol/L, because they did not differ significantly in risk factor profile. Women with type 2 diabetes were significantly older (59.1 ± 1.1 *v* 55.6 ± 1.33 for IFG and 55.3 ± 0.5 for normoglycemic subjects), more overweight, and tended to have higher values of triglycerides and diastolic blood pressure than women with either normoglycemic status or IFG. There were

Table 2. Characteristics of the Study Population Classified According to ADA Criteria

	NFG (n = 248)	IFG (n = 38)	Diabetes Mellitus (n = 24)
Body mass index (kg/m^2)	27.4 ± 0.3	28.8 ± 0.7	29.5 ± 0.9*
Waist circumference (cm)	85.9 ± 0.7	86.4 ± 1.8	86.8 ± 2.7
Hip circumference (cm)	103.4 ± 0.6	103.8 ± 1.6	103.9 ± 2.6
Waist/hip ratio	0.82 ± 0.003	0.84 ± 0.008	0.84 ± 0.009
Systolic blood pressure (mm Hg)	138.1 ± 1.2	151.5 ± 3.1	144.0 ± 4.0
Diastolic blood pressure (mm Hg)	82.4 ± 0.7	86.9 ± 1.7	87.3 ± 2.2*
Pulse pressure (mm Hg)	55.7 ± 1.0	64.5 ± 2.5	56.7 ± 3.2
Total cholesterol (mmol/L)	6.3 ± 0.1	6.5 ± 0.2	6.7 ± 0.3
LDL cholesterol (mmol/L)	4.0 ± 0.1	4.2 ± 0.2	4.3 ± 0.2
HDL cholesterol (mmol/L)	1.6 ± 0.02	1.5 ± 0.06	1.5 ± 0.1
Triglycerides (mmol/L)	1.3 ± 0.04	1.4 ± 0.1	1.9 ± 0.1†
Smoking status (%)	37.2	36.8	37.5
Cigarettes/day (no.)	14.1 ± 9.7	15.2 ± 9.1	13.1 ± 11.6
Smoking, pack-years	18.3 ± 14.7	23.8 ± 19.2	25.2 ± 19.6

NOTE. Data presented are mean value ± SE, age-adjusted by ANCOVA.

Abbreviations: NFG, normal fasting glucose; IFG, impaired fasting glucose; ANCOVA, analysis of covariance.

*$P < .05$ for trend; †$P < .01$ for trend.

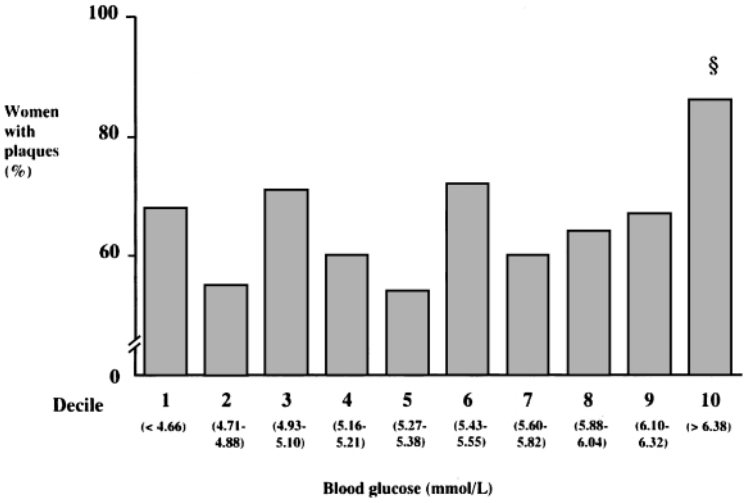

Fig 1. Increased prevalence of carotid atherosclerotic plaques in the upper decile of blood glucose compared with decile 1 to 9.

no significant differences among groups with regard to the percent of current smokers, the average number of cigarettes smoked by current and ex-smokers, and the number of pack-years.

The prevalence of carotid atherosclerosis gradually increased as glucose homeostasis worsened (64% for NFG *v* 71% for IFG *v* 94% for diabetes mellitus, $P < .01$ for trend), whereas no significant differences were observed between groups with regard to external (7.52 ± 0.87, 7.61 ± 0.72, 7.77 ± 0.74, for NFG, IFG, and diabetes mellitus, respectively) and internal lumen diameter (5.82 ± 0.71 for NFG, 5.94 ± 0.66 for IFG, 5.95 ± 0.69 for diabetes). Furthermore, when we divided subjects into deciles of blood glucose, blood glucose in the upper decile ($>$ 6.38 mmoL/L) was associated with an increased risk of carotid plaques (OR, 1.36; 95% CI, 1.17 to 1.58; $P < .006$) compared with decile 1 to 9 (Fig 1).

Age-adjusted OR of carotid atherosclerosis associated with diabetes mellitus was 9.3 (95% CI, 1.2 to 71.1); this risk did not change markedly when triglycerides or other risk factors were taken into account (Table 3). In contrast, multivariate analyses demonstrated that IFG was not independently associated with carotid plaques.

DISCUSSION

Since the proposal of new criteria for diabetes mellitus in 1997, several studies have been performed with the main purpose of assessing the diagnostic and prognostic value of ADA compared with the old WHO criteria.[23-26] The results of these studies highlight the considerable discrepancy between the 2 sets of recommendations, with individuals diagnosed as diabetic on 1 criterion, but not on the other, and, more importantly, show the prognostic usefulness of the oral glucose tolerance test to identify subjects with either isolated postchallange hyperglycaemia or IGT, both at high risk of cardiovascular disease and death.

Table 3. Adjusted OR (95% CI) From Logistic Regression Models for the Presence of Carotid Atherosclerotic Plaques

	Model 1* OR (95% CI)	Model 2† OR (95% CI)	Model 3‡ OR (95% CI)
Diabetes	9.3 (1.2-71.1)	9.6 (1.2-74.1)	11.5 (1.4-92.7)
IFG	1.4 (0.6-3.2)	1.4 (0.6-3.2)	1.4 (0.6-3.2)

Abbreviations: OR, odds ratio; CI, confidence interval.

*Includes adjustment for age; †adjusted for age and triglycerides; ‡adjusted for age, triglycerides and other risk factors (diastolic blood pressure, body mass index, total cholesterol, and cigarette smoking).

In the present study, we addressed yet another open question: whether the fasting glucose levels proposed by the ADA committee for the diagnosis of diabetes are associated with increased risk of preclinical atherosclerotic disease.

Atherosclerotic clinical manifestations, such as acute coronary syndromes, ischemic stroke, and peripheral arterial disease are known to be rather common and represent the major causes of morbidity and mortality in patients with type 2 diabetes.[27] Nevertheless, the onset of cardiovascular events in diabetics is generally preceded by asymptomatic structural and functional atherosclerotic changes, which can be accurately assessed by noninvasive ultrasonographic measurements, such as carotid IMT and brachial arterial reactivity.[28] The presence of the preclinical disease, compared with diabetes without preclinical disease, significantly increases the risk of incident coronary events and death.[29]

Our data suggest that the new ADA criteria enable an early detection of diabetic individuals with initial carotid atherosclerotic lesions and thus at high risk, in whom a strict glycemic control and an aggressive treatment of the risk factors often associated with diabetes are needed to prevent cardiovascular complications.

In our cohort of clinically healthy women coming from a huge metropolitan area, where the Mediterranean advantage has progressively disappeared, the prevalence of early arterial abnormalities was relatively high (66%). A worse cardiovascular risk profile, compared with other female populations, may account for the high presence of carotid plaques.[30,31]

In accordance with previous studies, subjects with established or newly diagnosed diabetes showed higher levels of a number of risk factors, including triglycerides, body mass index, and diastolic blood pressure, which are likely to reflect the insulin resistance commonly present in type 2 diabetics. It has been suggested that both the classical risk factors and those related to insulin resistance may mediate the association between diabetes mellitus and atherosclerotic disease or interact with hyperglycemia in accelerating atherogenesis, eg, oxidation or glycosylation of lipoproteins.[32] Because of their role in the pathogenesis of atherosclerosis in diabetics, these risk factors should not be considered as confounding variables and should not be controlled for in the analyses. However, because our interest was to assess the independent contribution of hyperglycemia to early carotid atherosclerosis, we additionally adjusted for them. Even after controlling for such risk factors, a significant relationship was found between diabetes mellitus and carotid wall thickness, suggesting that a level of glycemia consistent with overt diabetes increases itself the atherosclerotic risk.

A potential limitation is that, as in other epidemiologic analyses, the diagnosis of diabetes was based on 1 diagnostic test; the ADA criteria, instead, emphasize that, for clinical practice, the diagnosis should always be confirmed by repeating the test on another day.

Concerning the second objective of this study, we found that IFG, the new category of impaired glucose homeostasis proposed by the ADA committee, was not an independent predictor of early carotid atherosclerosis. This finding is consistent with results from the Bruneck Study showing that IFG subjects did not have an increased occurence or progression of atherosclerosis.[33] Our data are in agreement with recently published conclusions of large prospective cohort studies demonstrating a lower risk of cardiovascular disease and death for IFG than for IGT, and seem to indicate that the presence of IFG simply implies a risk for future development of diabetes, but does not increase cardiovascular risk.[25,26,34] Certainly, further studies are needed to fully clarify the prognostic significance of this condition. Furthermore, although it is now clear that IFG and IGT do not identify the same group of people with abnormal glucose regulation, the metabolic abnormalities of individuals with IFG remain to be elucidated.

In conclusion, our findings suggest that the use of ADA criteria may allow an early identification of diabetic individuals with preclinical atherosclerotic structural changes and thus at increased risk of developing cardiovascular sequelae.

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