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Gender-specific differences in carotid intima-media thickness and its progression over three years: A multicenter European study

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Abstract *Background and aims:* This multicentre European study evaluated, in a young-to-middle-aged healthy population without carotid atherosclerosis, the gender-related differences in carotid intima-media thickness (IMT) and its short-term (3-year) progression, and whether these differences are related to different vascular ageing rate, cardiovascular risk profile or different susceptibility to family predisposition to cardiovascular diseases (CVD).
Methods and results: 366 men and 422 women (age between 30 and 60 years) underwent B-mode carotid ultrasound at baseline and after 3-year follow-up period. IMT in 3 carotid segments was higher in men than in women ($p < 0.0001$ for all segments). When evaluated according to age decade, differences between men and women disappeared in the 6th decade, as in this decade a 3-year IMT progression rate accelerated in women ($p < 0.05$ as compared to the 4th and 5th age decade). Age was a major determinant of baseline all-segment IMT in women; in men all-segment IMT was influenced by age and LDL-cholesterol. IMT progression did not correlate with established cardiovascular risk factors, their short-term changes or family predisposition to CVD. Yet, a 3-year IMT progression in common carotid artery (CCA)

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was higher in men ($p = 0.01$) and women ($p < 0.01$) in whom relative Framingham risk increased during the corresponding period.
Conclusion: This study provides reference values on IMT and its short-term progression in healthy young-to-middle-aged population, and demonstrates gender-related differences in the susceptibility of carotid wall to ageing and LDL-cholesterol. Increase in Framingham risk accelerated a short-term CCA IMT progression rate in both genders, whereas family predisposition to CVD did not influence carotid IMT.

Introduction

Structural and functional changes in carotid arteries are used as tissue biomarkers of cardiovascular risk and atherosclerosis, and their associations with established and emerging risk factors are intensively studied. Age and male gender are acknowledged as major "unmodifiable" risk factors. It is well known that advancing age increases the incidence of hypertension, coronary heart disease (CHD) and stroke [1,2], and that in women the cardiovascular morbidity and mortality is lower and occurs 5—10 years later as compared to men [3,4]. Furthermore, age influences the endogenous levels of sex hormones that are supposed to trigger the gender-related differences in cardiovascular risk [4,5]. Advancing age and male gender lead to similar changes in carotid arteries, i.e. to luminal dilation, diffuse intimal and medial thickening and increased stiffness [2,6,7].

In the present study, we aimed to evaluate, in a selected population of apparently healthy subjects without carotid atherosclerosis, the gender-related differences in carotid intima-media thickness (IMT) and its short-term (3-year) progression rate, and whether these differences might be explained by a different rate of vascular ageing, differences in cardiovascular risk factors or different susceptibility to family predisposition to cardiovascular diseases [8]. Baseline IMT and its progression were assessed in different carotid segments, as each carotid segment has its distinct anatomy and haemodynamic pattern [2,9].

Methods

Study design

The design and the protocol of the RISC (Relationship between Insulin Sensitivity and Cardiovascular risk) Study (www.egir.org), a European multicenter study, has been reported elsewhere [10]. Briefly, more than 1400 apparently healthy Caucasian subjects were recruited between 2002 and 2005 in 19 centres in 14 European countries. The inclusion criteria were age between 30 and 60 years, and blood pressure (<140/<90 mmHg), plasma cholesterol (<7.8 mmol/L), triglycerides (<4.6 mmol/L), fasting and 2-h glucose (<7.0 and 11.1 mmol/L) within established limits. Exclusion criteria were the presence of chronic and overt cardiovascular disease, calcified carotid plaques, carotid stenosis >40% and treatment for hypertension, obesity, diabetes or dyslipidemia. Local ethics committee approval was obtained by each centre, and written consent was obtained from all participants.

A standardized examination protocol [10] included anthropometry, brachial blood pressure (BP) measurements, resting ECG, a fasting blood test, an oral glucose tolerance test, a euglycemic hyperinsulinemic clamp, a high-resolution ultrasound of extra-cranial carotid arteries. Information regarding menopausal status, medical history, drug use, alcohol and cigarette consumption and a family history of coronary heart disease and stroke in any first-degree family member was collected using standardized questionnaires. Clinical cardiovascular disease was excluded on the basis of medical history and resting ECG. A relative risk for CHD over a 10-year period was estimated from the Framingham Heart Study risk score sheets and graded as low, below average, average, above average or high [11]. All above listed measurements and examinations, except a euglycemic hyperinsulinemic clamp, were repeated during the follow-up after 3 years.

Population of the present study

Out of 1210 subjects who satisfied inclusion criteria and completed all baseline examinations, 882 subjects repeated carotid ultrasound after 3 years. For the purpose of this study we further excluded 58 subjects with carotid plaques and 36 postmenopausal women with hormone replacement therapy (HRT). Therefore, the final population included 788 apparently healthy subjects (366 men and 422 women), free of carotid atherosclerosis, without HRT (menopausal women) and with a 3-year follow-up.

Measurements

Body weight and fat free mass were measured by electrical bioimpedance (Body Composition Analyser Model TB-300, TANITA, Tokyo, Japan); fat mass was obtained as the difference between body weight and fat free mass. Brachial BP was measured by a digital electronic tensiometer (Omron, model 705cp, Kyoto, Japan) in subject seated for at least 10 min.

Laboratory examinations

A 2-h, 75-g oral glucose tolerance test and a euglycaemic hyperinsulinaemic clamp were performed on separate days, within 1 month, following previously described procedures standardized across centres [10]. Plasma glucose was measured centrally by the glucose oxidase technique (Glucose Analyser, Beckman, Fullerton, CA, USA), and the serum concentration of insulin was measured by