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Role of endogenous androgens on carotid atherosclerosis in non-obese postmenopausal women

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Abstract *Background:* Recent randomized trials on hormone replacement therapy in postmenopausal women raised many doubts about their role in cardiovascular disease prevention. Therefore the role of other sex hormones needed to be investigated. In particular androgens seem to have a protective role on atherosclerosis. The present study was performed to assess the role of endogenous sex hormones on carotid atherosclerosis in postmenopausal women.
Methods and results: We consecutively enrolled 101 postmenopausal women aged 45–75 (mean age 57.4) years referred to our University hospital menopausal health-screening clinic. The subjects underwent a medical history, a physical examination and biochemical analysis. Extracranial carotid arteries were assessed by ultrasound. Fifty percent of our sample had carotid plaques. On the multivariate logistic regression analysis age, glycaemia (positively) and testosterone (negatively) ($P = 0.02$) were significantly correlated to carotid atherosclerosis. In non-obese subjects we found that participants in the third tertile had a significantly lower prevalence of carotid atherosclerosis ($P = 0.02$) compared to those in the first tertile of testosterone.
Conclusions: These results suggest a possible protective role of endogenous androgens at least on carotid atherosclerosis. Of course these preliminary results should be supported by prospective studies. Also the different role of these hormones on obese and non-obese subjects needs to be clarified.

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Cardiovascular disease is the leading cause of human deaths, at least in western countries and the male to female ratio is usually greater than 2 [1]. This gender gap has been interpreted mainly in favour of a protective role of oestrogen against atherogenesis. But placebo-controlled, randomized clinical trials (RCT) showed no cardiovascular benefits of combined oestrogen/progestin therapy in menopausal women [2,3]. These unexpected results require exploration of the effects of other sex hormones on the cardiovascular system. In particular the role of androgens needs to be clarified. In fact, in observational case–control studies in men [4,5], androgens were inversely correlated to cardiovascular disease, but longitudinal studies contradicted this finding [4–6]. Moreover interventional studies have showed beneficial cardiovascular effects of exogenous androgen administration [7,8], but this is evidently an unnatural condition. Of course these data are probably not relevant in women since the existing difference between androgen levels by gender. Unfortunately data pertaining to the role of this hormone in cardiovascular disease in women are scarce. In two studies [9,10] testosterone was inversely correlated to carotid intima media thickness.

Therefore to further investigate the influence of endogenous sex hormones, especially the androgens, on atherosclerosis, we evaluated, in apparently healthy postmenopausal women, the relationship between carotid plaques, a well-known marker of atherosclerosis [11] and endogenous sex hormones. We aimed also to evaluate this relationship according to body mass index (BMI), since increased androgen levels were associated with insulin resistance and to obesity in women [12,13].

Methods

We consecutively enrolled 101 postmenopausal women aged 45–75 years referred for menopause health-screening tests to our University Hospital. All the participants were Caucasian and were in postmenopausal status defined as no natural menses for at least one year and serum FSH level was more than 40 IU/L. Data were collected by a standardized questionnaire, administered to obtain information about current and past medication use, smoking habits, age at menopause and presence of cardiovascular diseases. Anthropometric measurements of height and weight were determined with calibrated scales; the subjects were without shoes and with indoor clothing. Body mass index (BMI) was then calculated as weight (in kg) divided by square of height (in m). Systolic (SBP) and diastolic (DBP) blood pressures were measured twice on both arms using a calibrated aneroid sphygmomanometer after the subject had been resting in supine position for at least 5 min, to minimize alerting reaction evoked by the clinical visit; the average of two measurements was used in analysis.

Venous blood was collected into vacutainer tubes (Becton & Dickinson) after overnight fasting and centrifuged within 4 h. Serum glucose, total cholesterol, HDL cholesterol and triglyceride levels were measured by standard laboratory techniques (automatic analyzer MONARCH 2000-IL); follicle-stimulating hormone (FSH), 17β-estradiol (Diasorin S.p.A., Italy), androstenedione (Adaltis, Italy), and testosterone (Adaltis, Italy) were performed by radio immuno-assays; LDL cholesterol was calculated by Friedewald formula. Quality control assessment was performed daily for all determinations.

The following criteria were used for classification of the cardiovascular risk factors: diabetes: fasting blood glucose equal to or more than 7 mmol/L or antidiabetic treatment [14], hyperlipidemia: total cholesterol more than 5.17 mmol/L and/or triglycerides more than 2.26 mmol/L or lipid lowering drugs use; hypertension: systolic blood pressure 140 mmHg, diastolic blood pressure 90 mmHg, or use of antihypertensive medication. [15,16] Smoking: present smokers. Obesity: body mass index more than 29.9 kg/m^2 [17].

Vascular ultrasound

Evaluation of the extracranial carotid arteries was performed by B-mode ultrasonography with the use of a duplex system (a high resolution ultrasound instrument ATL, HDI 5000 with a 5- to 12-MHz linear array multifrequency transducer). The same ultrasonographer blinded to clinical information carried out all the examinations. The right and left common (CCA) and internal carotid arteries (including bifurcations) were evaluated with the subjects in supine position, with the head turned away from the sonographer and the neck extended with mild rotation. The intima media thickness (IMT), defined as the distance between the intima-luminal interface and the media-adventitial interface, was measured as previously described [18]. Briefly, in a posterior approach and with the sound beam set perpendicular to the arterial surface, 1 cm from the bifurcation, three longitudinal measurements of IMT were completed on the right and left CCAs far wall, at sites free of any discrete plaques. The mean of the three right and left longitudinal CCA-IMT measurements was then calculated. Plaque, detected in longitudinal and