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Subclinical cardiovascular disease in postmenopausal women with low/medium cardiovascular risk by the Framingham risk score

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ABSTRACT

Objectives: To evaluate the prevalence of subclinical cardiovascular disease (CVD) and its association with clinical and hormone variables in postmenopausal women from Southern Brazil.
Study design: Cross-sectional study.
Main outcome measures: Coronary artery calcification (CAC) assessed by electron-beam computed tomography. Carotid intima–media thickness (IMT) and atheromatous plaques assessed using B-mode ultrasound. IMT was measured at three segments. Subclinical CVD was defined as the presence of plaque and/or IMT >0.9 mm.
Results: Ninety-seven postmenopausal women (mean age 55 ± 5 years, median duration of menopause 5.8 [3–10] years) were studied. A low/medium Framingham risk score (FRS) was present in 97.9% of participants; 35.1% had subclinical CVD on carotid ultrasound, and 24.7% had the presence of plaque. Seven women had a CAC score ≥100, and two had a score ≥200. CAC score ($p < 0.001$) and FRS ($p = 0.013$) were higher in patients with subclinical atherosclerosis. Positive correlations were found between IMT and age (rs = 0.293 $p = 0.004$), duration of menopause (rs = 0.237, $p = 0.020$), and CAC score (rs = 0.468, $p < 0.001$). Common carotid IMT (IMT-CC) was negatively associated with estradiol levels ($\beta = -0.237$, $p = 0.018$) and positively with age ($\beta = 0.210$, $p = 0.033$), and BMI ($\beta = 0.260$, $p = 0.010$). However, correlations with estradiol and age did not remain significant when adjusted for systolic blood pressure and LDL-cholesterol levels.
Conclusion: A high prevalence of subclinical atherosclerosis was detected in this sample of postmenopausal women with low/medium CV risk by the FRS. The association between IMT-CC and age or endogenous estrogen levels was dependent of blood pressure and LDL-cholesterol in these postmenopausal women from Southern Brazil.

1. Introduction

Menopause has been associated with increased risk of atherosclerosis, and postmenopausal women experience an upward transition of cardiovascular (CV) risk, possibly in association with changing hormonal status and aging [1,2]. While clinical manifestations of atherosclerosis arise only in middle age, the process of atherosclerosis and the development of vascular changes begin earlier in life, and have been associated with an increase in CV risk factors [3–5].

The decline in endogenous estrogen production during the menopausal transition has been associated with CV risk factors and higher prevalence of subclinical cardiovascular disease (CVD), such as atherosclerosis, in postmenopausal women [6–9].

Some non-invasive procedures are able to detect and measure different stages of atherosclerosis, even in its subclinical form. B-mode ultrasound is commonly used to assess brachial artery flow-mediated dilation (FMD), carotid intima-media thickness (IMT), and carotid plaques, while the coronary artery calcification (CAC) score can be derived through electron-beam or multislice computed tomography (CT) scanning. Adverse FMD results, increased IMT, and the presence of carotid plaques or CAC have

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been associated with higher CV risk that is independent of other conventional risk factors [10–12].

Within this context, the aim of this study was to estimate the prevalence of subclinical CVD and its associations with endogenous estradiol levels and demographic, anthropometric, and metabolic variables in postmenopausal women.

2. Methods

2.1. Patients

This cross-sectional study was carried out on a sample of women presenting with climacteric symptoms at the Gynecological Endocrinology Unit of Hospital de Clínicas de Porto Alegre, Brazil. Volunteers were also consecutively recruited through advertisements placed in a local newspaper and radio station. The inclusion criteria were as follows: (1) menopause, defined as a last menstrual period at least 1 year before the beginning of the study plus follicle-stimulating hormone (FSH) levels above 35 IU/L; (2) age between 45 and 65 years; and (3) no use of hormone therapy in the past 3 months. The exclusion criteria were diabetes, current smoking, or prior diagnosis of CVD. The study was approved by the local Research Ethics Committee, and written informed consent was obtained from each participant.

2.2. Study protocol

Anthropometric measurements included body weight, height, waist circumference (WC) (measured at the midpoint between the lower rib margin and the iliac crest), and body mass index (BMI, calculated as the latest measured weight in kilograms divided by the height in meters squared). Blood pressure was measured with participants in the seated position, with feet on the floor, and the arm supported at heart level after a 10-min rest. Two measurements were obtained, 10 min apart, using an automatic blood pressure monitor (HEM-742INT; Omron, Rio de Janeiro, Brazil). Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥90 mmHg, or current use of antihypertensive drugs [13].

The presence of CV risk factors and of the metabolic syndrome were defined as recommended by the Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity [14]. Increased WC was defined by the cutoff ≥88 cm. The Framingham General Cardiovascular Risk Score (10-year risk) (FRS) was computed, using lipids, through the online interactive risk score calculator available on the Framingham Heart Study website [15].

2.3. Biochemical and hormone assays

Serum FSH and estradiol (E2) levels, as well as glucose and lipid profile (triglycerides, total cholesterol, and high-density lipoprotein [HDL] cholesterol) were determined in a 12-h fasting blood sample. All samples were obtained between 8 and 10 a.m. Glucose and lipid profile were determined by colorimetric–enzymatic methods (Bayer 1800 Advia System, Mannheim, Germany), with a coefficient of variation <3.4%. Low-density lipoprotein (LDL) cholesterol was estimated indirectly using the Friedewald formula [16]. FSH was measured with chemiluminescent immunoassays (Centaur XP, Roche Diagnostics, Mannheim, Germany) with a sensitivity of 0.3 IU/L and intra- and interassay coefficients of variation of 2.9% and 2.7%, respectively. Estradiol was measured by ECLIA (Roche Diagnostics, Mannheim, Germany), with an assay sensitivity of 5.0 pg/mL and intra- and interassay coefficients of variation of 5.7% and 6.4%, respectively.

2.4. Measurement of carotid intima–media thickness

Carotid IMT (C-IMT) was assessed bilaterally by B-mode ultrasonography (Xsario, Toshiba) by a single operator (an expert sonographer), using a standardized protocol. A 7.5-MHz, fixed-angle, multi-frequency linear array probe was used. The right and left carotid arteries were scanned to obtain a total of nine images, of the far wall of the common carotid (1 cm proximal to the carotid bulb), of the carotid bulb (1 cm proximal to the flow divider), and of the proximal internal carotid arteries (1 cm distal from the flow divider) [17,18]. In each segment, three measurements of maximum IMT were obtained. Subsequently, the average IMT of the three segments was calculated for each of the two carotid arteries [10]. Subclinical atherosclerosis was defined as IMT >0.9 mm and/or the presence of atherosclerotic plaque in any of the studied segments [9]. Plaque was defined by at least two of the following three criteria: C-IMT >1.5 mm; shape abnormalities such as protrusion into the lumen or loss of alignment with adjacent arterial wall boundary; the presence of brighter echoes than adjacent boundaries [10].

2.5. Coronary artery calcification assessment

CAC was assessed by chest CT, using a 64-slice multidetector system (LightSpeed VCT, GE Healthcare). All participants were scanned by certified technologists. Sixty-four contiguous images were acquired, beginning at the carina and proceeding caudally during a single breath-hold at 40% or 65% of the *R–R* interval, depending on heart rate. A radiologist read all scans. The reader-work station interface identified and quantified CAC from images calibrated according to calcium phantom readings. Total coronary calcium was quantified as proposed by Agatston et al. [19].

2.6. Statistical analysis

All descriptive data were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). The Student's *t* test was used for comparisons between group means, and the Mann–Whitney *U* test for comparisons between median values. Spearman rank or Pearson correlation coefficients were calculated between variables using a two-tailed significance test for variables with a Gaussian or non-Gaussian distribution, respectively. The regression model was used to estimate independent associations between common carotid IMT (IMT-CC) and age, BMI, and estradiol levels. Adjustments were made according to systolic blood pressure and LDL-cholesterol levels. IMT-CC values were log-transformed for multiple regression analysis. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 16 (SPSS Inc., Chicago, IL, USA). Findings were deemed significant at $p < 0.05$.

3. Results

The distribution of clinical, biochemical, and hormonal variables is shown in Table 1. The mean age of participants was 55.5 (±5) years, and the median (IQR) duration of menopause was 5.8 (3–10) years. A low/medium FRS was present in 97.9% of participants. Using the atherosclerotic cardiovascular disease (ASCVD) risk estimator 56.6% of participants presented a risk lower than 7.5% and all other had an intermediate risk. Hypertension was present in 38 participants (39.2%), all of whom were on antihypertensive drugs and 26 participants (26.8%) had metabolic syndrome. LDL cholesterol