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Relationship between endogenous testosterone and cardiovascular risk in early postmenopausal women

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Abstract

Cardiovascular disease (CVD) is the leading cause of death among postmenopausal women. Changes in endothelial function play an important role in the pathophysiology of atherosclerosis, and evidence suggests that interventions to improve endothelial function could modify the rates of progression and the risk of cardiovascular events. In addition, a positive association between markers of endothelial dysfunction and androgenicity has been described in women with polycystic ovary syndrome, suggesting a correlation with the early-onset endothelial dysfunction found in these patients. We performed a cross-sectional study to verify whether endogenous testosterone levels are correlated with markers of inflammation and endothelial function and with anthropometric and metabolic profile in 53 postmenopausal women. Serum testosterone, sex hormone–binding globulin, C-reactive protein (CRP), fibrinogen, and plasma endothelin-1 (ET-1) were determined. Patients were stratified into 2 groups (higher or lower than the mean testosterone levels of the studied sample). Mean age was 55 years (±5), and median time since menopause was 5.5 years (interquartile range, 3-8 years). Body mass index and waist circumference were significantly higher in the group with testosterone levels ≥0.49 ng/mL. Median CRP levels were greater in the group with higher testosterone levels (1.17 [0.17-2.36] vs 0.17 [0.17-0.61] mg/L, $P = .039$). Median ET-1 levels were also higher in women with greater testosterone levels (0.84 [0.81-0.97] vs 0.81 [0.74-0.84] pg/mL, $P = .023$). An association of testosterone with CRP ($r = 0.416$, $P = .004$) and ET-1 ($r = 0.323$, $P = .031$) was observed. This association was dependent on homeostasis model assessment index for ET-1 but not CRP. Testosterone was also associated with waist circumference and blood pressure ($P = .001$). These data suggest that endogenous testosterone levels in recently postmenopausal women may be part of a proatherogenic profile. Longitudinal studies are needed to assess if androgenicity represents a risk factor for cardiovascular disease and the clinical relevance of its association with ET-1 and CRP in this population.

1. Introduction

Although much progress has been made in the prevention and treatment of cardiovascular disease (CVD), it is still the leading cause of death among postmenopausal women in developed countries [1]. Changes in endothelial function play an important role in the pathophysiology of atherosclerosis [2], and there is evidence suggesting that interventions to improve endothelial function may impact the progression and the risk of cardiovascular events [2-5].

Circulating inflammatory markers are regarded as manifestations of endothelial dysfunction and have also been linked to CVD. C-reactive protein (CRP), a reliable and easily measured marker of inflammation, has been described as a predictor of cardiovascular events in postmenopausal women [6-8]. Another inflammation marker, endothelin 1 (ET-1), a peptide isolated from endothelial cells, presents a powerful vasoconstrictor action. Increased levels of ET-1 have been observed in states of insulin resistance and in early endothelial dysfunction [9]. In addition, a positive association between ET-1 levels and androgenicity has been

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described in women with polycystic ovary syndrome (PCOS), suggesting a correlation with the early-onset endothelial dysfunction found in these patients [10].

In turn, endogenous androgens are thought to be potential mediators of cardiovascular risk in women at midlife, in addition to having been associated with CRP [11,12]. Therefore, the aim of the present study was to investigate the relationship between testosterone, CRP, and ET-1 levels and the metabolic profile in a group of postmenopausal women.

2. Patients and methods

2.1. Patients

The study was carried out with women consulting for climacteric symptoms at the Gynecological Endocrinology Unit at Hospital de Clínicas de Porto Alegre, Brazil. Fifty-three postmenopausal women fulfilling all the inclusion criteria were consecutively enrolled in the study. Inclusion criteria were as follows: (1) *menopause*, defined as last menstrual period at least 1 year before the beginning of the study plus follicle stimulating hormone (FSH) levels higher than 35 IU/L; (2) older than 40 years; (3) no use of any medication known to interfere with hormonal, glucose, or lipoprotein levels in the past 3 months; and (4) no use of steroidal or nonsteroidal anti-inflammatory drugs in the last 15 days. Diabetic patients or patients with thyroid, hepatic, or renal dysfunction were excluded. Five patients were smokers. The study protocol was approved by the local Ethics Committee, and written informed consent was obtained from every subject.

2.2. Study protocol

Anthropometric measurements included body weight, height, waist circumference (waist measured at the midpoint between the lower rib margin and the iliac crest), hip circumference (recorded at the level of the greater trochanter), waist-to-hip ratio, and body mass index (BMI; current measured weight in kilograms divided by height in square meters), as previously reported [13]. Blood pressure was measured in the supine position after a 10-minute rest. The same calibrated mercury manometer attached to a 12.5 × 23-cm inflatable cuff was used in all patients by the same operator, who adopted the fifth Korotkoff sound to determine diastolic pressure. *Hypertension* was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive drugs [14].

After the patients were submitted to a 3-day, 300-g–carbohydrate diet, 2 blood samples were drawn from an antecubital vein for determination of plasma glucose and insulin: one after overnight fasting and another 2 hours after the ingestion of 75 g of glucose. The FSH, luteinizing hormone (LH), estradiol, total testosterone (TT), sex hormone–binding globulin (SHBG), dehydroepiandrosterone sulfate, fibrinogen, ET-1, CRP, total and high-density lipoprotein (HDL) cholesterol, and triglycerides were also determined using the fasting blood sample. All samples were obtained between 8 AM and 10 AM.

2.3. Assays

Total cholesterol, HDL cholesterol, triglycerides, and glucose were determined by colorimetric-enzymatic methods using the Bayer 1650 Advia System (Mannheim, Germany). Low-density lipoprotein (LDL) cholesterol was determined indirectly using the formula LDL = total cholesterol − HDL − triglycerides/5. Serum LH and FSH were measured by electrochemiluminescence immunoassay (ECLIA), with intra- and interassay coefficients of variation (CVs) of 1.8% and 4.8%, respectively, for LH and 1.8% and 3.3%, respectively, for FSH. The sensitivity of the assays was 0.12 IU/L for LH and 0.05 IU/L for FSH. The TT levels were measured with the radioimmunoassay method (ICM, Costa Mesa, CA), with an assay sensitivity <0.2 ng/mL and intra- and interassay CVs of 10% and 11.3%, respectively. Estradiol was measured by ECLIA (Roche Diagnostics, Mannheim, Germany), with an assay sensitivity of 5.0 pg/mL and intra- and interassay CVs of 5.7% and 6.4%. Sex hormone–binding globulin was measured by chemoluminescence enzyme immunoassay (DPC, Los Angeles, CA), with an assay sensitivity of 0.2 nmol/L and intra- and interassay CVs of 6.1% and 8.0%, respectively. Serum insulin levels were measured using ECLIA (Roche Diagnostics), with a sensitivity of 0.200 μIU/mL and intra- and interassay CVs of 2.0% and 4.3%, respectively. Dehydroepiandrosterone sulfate (DHEAS) was measured by ECLIA (Roche Diagnostics), with a sensitivity of 0.10 μg/dL and intra- and interassay CVs of 2.8% and 6.5%, respectively. Fibrinogen was measured by the coagulometric method (Diagnostica Stago, Asnières, France), with a sensitivity of 4 seconds and intra- and interassay CVs of 3.3% and 10.0%, respectively. Ultrasensitive CRP was assayed using stored specimens, with a validated high-sensitivity nephelometric method (Dade Behring Marburg, Marburg, Germany). Sensitivity was 0.17 mg/L; and intra- and interassay CVs were 4.4% and 5.7%, respectively. For data analysis, individual results below the limit of sensitivity were considered as equal to 0.17 mg/L. Endothelin-1 was assayed using a luminoimmunoassay (R&D Systems, Minneapolis, MN) in stored EDTA plasma samples, with sensitivity of 0.5 pg/mL in our laboratory and intra- and interassay CVs of 4.6% and 6.5%, respectively. Free androgen index (FAI) was estimated by dividing TT (in nanomoles per liter) by SHBG (in nanomoles per liter) × 100. Homeostasis model assessment (HOMA) was calculated by multiplying insulin (in micro–international units per milliliter) by glucose (in millimoles per liter) and dividing this product by 22.5 [15], as previously reported [16].

2.4. Statistical analysis

Results are expressed as means ± SD or median and interquartile range. Comparisons between the 2 group means were

analyzed by Student *t* test; comparisons between median values were analyzed with Mann-Whitney *U* test. Spearman rank or Pearson correlation coefficient was calculated between variables using a 2-tailed significance test for variables with a Gaussian or non-Gaussian distribution, respectively. Partial correlations of TT with ET-1 and CRP were calculated after adjustment for HOMA index. Comparisons between ratios were carried out using the χ^2 test. All analyses were performed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL). Data were considered to be significant at $P < .05$. Calculation of the sample size was based on the higher ET-1 levels observed in the pilot study in women with circulating TT ≥0.49 pg/mL. The sample had a power of 90%, with a significance level of 0.05.

3. Results

The mean age of participants was 55 (±5) years, the age at menopause was 48 (±3) years, and the median time since menopause was 5.5 (3-8) years. *Metabolic syndrome*, as defined by the National Cholesterol Education Program–Adult Treatment Panel III criteria [17,18], was diagnosed in 7 patients (13.2%). Twelve (21%) had mild hypertension.

The distribution of anthropometric, metabolic, and hormonal variables and markers of inflammation and endothelial function was analyzed in relation to the mean level of TT (<0.49 ng/mL) in these early postmenopausal women (Table 1). The groups (TT <0.49 ng/mL or ≥0.49 ng/mL) were similar regarding age and time since menopause and regarding the distribution of individuals with metabolic syndrome (3 [5.7%] vs 4 [7.5%], $P = .27$), history of smoking (5 [9.4%] vs 3 [5.7%], $P = .67$), and hypertension (5 [9.4%] vs 7 [13.2%], $P = .12$). Glucose, lipid levels, and HOMA index were also similar. The group with TT ≥0.49 ng/mL had greater FAI, systolic pressure, BMI, and waist circumference than the group with TT <0.49 ng/mL. Whereas fibrinogen was similar, CRP and ET-1 were significantly higher in the group with TT ≥0.49 ng/mL.

Table 1
Distribution of anthropometric, hormonal, metabolic, and hemostatic variables and markers of inflammation and endothelial function according to testosterone levels

Variable	Testosterone levels		*P*
	<0.49 (n = 32)	≥0.49 (n = 21)	
Age (y)	55 ± 5	54 ± 5	.846
Time since menopause[a]	6 (3-8)	5 (3-9)	.908
BMI (kg/m^2)	25 ± 3	27 ± 2	.005
Waist circumference (cm)	84 ± 7.9	92 ± 7	.002
Systolic pressure (mm Hg)	124 ±9	134 ± 17	.024
Diastolic pressure (mm Hg)	78 ± 8	85 ± 13	.056
Fasting glucose (mg/dL)	92 ± 11	95 ± 9	.288
Fasting insulin (μIU/mL)	7.6 ± 3	8.2 ± 4	.599
Total cholesterol (mg/dL)	218 ± 34	224 ± 42	.608
HDL-C (mg/dL)	58 ± 10	56 ± 9	.597
LDL-C (mg/dL)	138 ± 27	145 ± 36	.475
Triglycerides (mg/dL)	110 ± 48	118 ± 46	.575
Testosterone (pg/mL)	0.34 ± 0.08	0.69 ± 0.18	<.001
FAI[a]	2.5 (1,5-3.2)	5.3 (3.39-6.8)	<.001
HOMA[a]	1.57 (0.94-2.51)	1.67 (1.58-2.14)	.594
SHBG (nmol/L)[a]	53 (38-76)	44 (31-73)	.273
Fibrinogen (mg/dL)	323 ± 122	350 ± 134	.469
CRP (mg/L)[a]	0.17 (0.17-0.61)	1.17 (0.17-2.36)	.039
ET-1 (pg/mL)[a]	0.81 (0.74-0.84)	0.84 (0.81-0.97)	.023

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Student *t* test (mean ± SD) or [a]Mann-Whitney *U* test (median and interquartile range: 25%-75%).

Table 2
Correlation between testosterone and waist circumference, BMI, blood pressure, ET-1, and CRP levels

	Testosterone (pg/mL)			
	r	*P*	*r*[b]	*P*[a]
ET-1 (pg/mL)[a]	0.323	.031	0.286	.101
CRP (mg/L)[a]	0.416	.004	0.626	<.001
Waist circumference	0.516	<.001		
BMI	0.522	<.001		
Systolic pressure	0.475	.001		
Diastolic pressure	0.334	.019		

Pearson correlation coefficient or [a]Spearman correlation.
[b]Correlation of testosterone with ET-1 and CRP levels after adjustment by HOMA index.

As shown in Table 2, positive correlations were observed between TT levels and waist circumference, BMI, and systolic and diastolic pressure. Total testosterone was significantly associated with CRP and ET-1. However, whereas the association of TT with CRP remained significant, the correlation with ET-1 was lost after adjustment by HOMA index.

4. Discussion

In the present study, a significant association between endogenous testosterone and ET-1 was found in postmenopausal women. To our knowledge, this is the first time this association is described in early postmenopausal women. The proinflammatory marker CRP was also found to be associated with testosterone levels in this population.

Evidence suggests that sex hormones may modulate plasma ET-1 levels. Webb et al [19] found that 17β-estradiol decreased ET-1 levels in the coronary circulation of postmenopausal women. More recently, Silvestri et al [11] also showed a reduction of ET-1 levels in postmenopausal women under oral hormone therapy. In turn, high levels of ET-1 were described by Polderman et al [12] in a study with female-to-male transsexuals treated with testosterone.

Orio et al [20] have recently described early impairment of endothelial function in young normal-weight PCOS patients without metabolic or cardiovascular disease. The patients presented a significant increase in carotid intima-media wall thickness, a decrease in flow-mediated dilation, and an increase in ET-1 levels [20]. Moreover, the use of the

insulin sensitizer metformin in patients with PCOS has been shown to promote overall improvement in androgenic profile, insulin resistance, and ET-1 levels, without requiring concomitant changes in body weight [21]. In the present study, a positive association was observed between TT and ET-1; and this association was shown to be dependent on HOMA index. This observation suggests that the increased ET-1 may be the result of a modulation exerted by slight insulin sensitivity changes in postmenopausal women with androgen levels in the superior limit of the reference range. If that is the case, it is possible that these patients could potentially benefit from treatment with insulin-sensitizing drugs such as metformin to reverse this proatherogenic profile. Further studies are needed to specifically test this hypothesis.

Fibrinogen has been suggested to be an independent risk factor for CVD. Framingham Study data indicate that increases in fibrinogen impose an independent increment on cardiovascular risk in both sexes [22]. In addition, androgens have been associated with some hemostatic factors [23]; but there is controversy concerning the relationship between androgens and fibrinogen [24,25]. In our study, fibrinogen levels were similar in the 2 groups stratified by testosterone levels. Taken together, these data support the notion that fibrinogen is more related to BMI [26] and lipoprotein levels than to menopausal status [27], at least when postmenopausal women without clinical disease are considered.

In the present study, TT was associated with CRP, independently of HOMA. C-reactive protein is considered an independent predictor of CVD in both men and postmenopausal women [8,28]; but the direction of causality has not yet been determined in the postmenopausal population. Our data confirm the results of a recently published cross-sectional study in which CRP was negatively associated with SHBG and positively associated with bioavailable testosterone after adjustment for age, BMI, physical activity, alcohol consumption, and tobacco use [29]. Folsom et al [25], analyzing a subsample of the Atherosclerosis Risk in Communities study (n = 57), showed that, after adjustment for age, race, and case-control status, mean CRP was 2-fold greater in the highest vs lowest quartiles of estrone and androstenedione, and CRP was 2-fold lower across quartiles of SHBG. However, because of the sample size, not all these associations reached statistical significance [25].

Conversely, a few studies disconfirm the association between androgenicity and CRP in specific postmenopausal subpopulations such as older patients referred to coronary angiography, stratified by the presence or absence of coronary artery disease [30]. Joffe et al [31] found CRP to be negatively and independently correlated with SHBG and testosterone in menopausal women who subsequently developed clinical CVD, but the negative correlation between CRP and testosterone was not present in those who remained CVD-free. However, the patients in that study were older than our patients; and around 20% were smokers. In addition, a positive association between CRP and FAI was found when the entire group of women not using hormonal therapy was analyzed. Therefore, it is possible that the association between testosterone and CRP is not linear across the range of CRP values, appearing only with lower CRP levels, as suggested by Crandall et al [29].

Although time since menopause was not controlled in the present study, the patients included were in the early years of menopause. Along with the low levels of CRP, this profile may also partially explain the low prevalence of metabolic disturbances such as insulin resistance and dyslipidemia. In contrast, at least 2 criteria for metabolic syndrome, waist circumference and blood pressure, were more prevalent in postmenopausal women with higher testosterone levels. We have found an association between insulin resistance and androgenicity in a previous study [32]. However, in that study, patients were older and more obese than those in the present study.

In conclusion, the present results suggest that testosterone levels in recently postmenopausal women may indicate a proatherogenic profile. Longitudinal studies are needed to determine if androgenicity represents a risk factor for CVD and to establish the clinical relevance of the association between testosterone, ET-1, and CRP in postmenopausal women.

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