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Early Impairment of Endothelial Structure and Function in Young Normal-Weight Women with Polycystic Ovary Syndrome

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The aim of this study was to evaluate the presence of early vascular damage in young normal-weight women with polycystic ovary syndrome (PCOS).

Thirty young normal-weight women with PCOS, who had no additional metabolic or cardiovascular diseases, and 30 healthy women (controls) matched for age and body mass index were studied. A complete hormonal assay was performed in each subject. Serum insulin and glucose levels were measured at baseline and after the oral glucose tolerance test. Plasma endothelin-1 levels and serum lipid profile were also assessed. The endothelial function was studied by flow-mediated dilation on the brachial artery, and arterial structure was evaluated by intima-media thickness measurement using Doppler ultrasound of both common carotid arteries.

A significant ($P < 0.05$) difference in flow-mediated dilation (14.3 ± 1.9% *vs.* 18.1 ± 2.0% for PCOS patients and controls, respectively) and in intima-media thickness (0.53 ± 0.09 mm *vs.* 0.39 ± 0.08 mm for PCOS patients and controls, respectively) was found between PCOS and control subjects. Serum endothelin-1 levels were also significantly ($P < 0.05$) higher in PCOS patients compared with controls (1.1 ± 0.4 pmol/liter *vs.* 0.5 ± 0.2 pmol/liter for PCOS patients and controls, respectively).

In conclusion, our data show that young, normal-weight, nondyslipidemic, nonhypertensive women with PCOS have an early impairment of endothelial structure and function. (*J Clin Endocrinol Metab* 89: 4588–4593, 2004)

POLYCYSTIC OVARY SYNDROME (PCOS) is a common endocrine-metabolic disease that occurs in up to 10% of reproductive-age women (1, 2). PCOS is considered not only a reproductive endocrinopathy but also a metabolic disorder associated with long-term health risks, including diabetes mellitus (3–5) and coronary artery disease (6–8). In particular, insulin resistance, hyperandrogenemia, and dyslipidemia are likely the major risk factors for the occurrence of cardiovascular disease (CVD) in PCOS (9–11). These cardiovascular risk factors are often evident at an early age (12, 13), suggesting that women with PCOS represent a large group of women at increased risk for developing early-onset CVD.

One of the early signs of cardiovascular lesions is the endothelial injury (9, 14, 15). Several authors (16–18) have reported precocious anatomical and functional arterial changes in PCOS women. The insulin resistance could play a key role in the development of endothelial damage (16, 19–22), which represents an early sign of atherosclerosis (15, 23).

Vascular changes can be noninvasively examined by the intima-media thickness (IMT) of carotid arteries and by flow-mediated dilation (FMD) of brachial arteries. IMT of the common carotid artery is a morphological marker of precocious atherosclerosis (24–26), and it has been associated with both elevated androgen levels and insulin resistance (27, 28). In addition, the assessment of FMD of the brachial artery has been widely used as method of determining endothelial function (29).

Among the several circulating endothelium-derived vasoactive molecules, endothelin (ET)-1 is considered one of the best known markers of abnormal vascular reactivity (30, 31). Elevated serum levels of ET-1 have been reported in some insulin-resistant states (32, 33) and recently also in PCOS (34).

At present, no data are available on either the functional or biochemical evaluation of endothelium in women with PCOS. Therefore, the aim of the present study was to investigate the endothelial function, arterial structure, and serum ET-1 levels in a population of young PCOS women.

Subjects and Methods

Subjects

Thirty young normal-weight women with PCOS and 30 age- and body mass index (BMI)-matched controls were enrolled in this study.

Abbreviations: Δ4-A, Androstenedione; AUC, area under the curve; BMI, body mass index; CV, coefficient of variation; CVD, cardiovascular disease; DBP, diastolic blood pressure; DHEA-S, dehydroepiandrosterone sulfate; ET, endothelin; FAI, free androgen index; FMD, flow-mediated dilation; Hcy, homocysteine; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; SBP, systolic blood pressure; T, testosterone; TC, total cholesterol; TG, triglycerides; TV-USG, transvaginal ultrasonography; WHR, waist to hip ratio.

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A BMI between 18 and 25 was considered as the index of normal weight (35).

The diagnosis of PCOS was made by anovulatory infertility (confirmed by luteal progesterone assay) and normal serum FSH levels (normal range, 1.0–10.0 IU/liter) and at least two of the following features: hirsutism (Ferriman-Gallwey score > 8) (36), elevated serum androgen levels [total testosterone (T) > 2 nmol/liter, and/or androstenedione (Δ4-A) > 15 nmol/liter, and/or dehydroepiandrosterone sulfate (DHEA-S) > 10 μmol/liter], LH to FSH ratio greater than 2, and polycystic ovaries identified by transvaginal ultrasonography (TV-USG) examination (37). All the patients achieved National Institute of Child Health and Human Development criteria for PCOS (38). Table 1 shows the clinical and biochemical diagnostic features of the women with PCOS.

The control group consisted of healthy volunteer females who had regular menstrual cycles (defined as 26–32 d in length). Their healthy state was determined by medical history, physical and pelvic examination, and complete blood chemistry. The normal ovulatory state was confirmed by TV-USG and plasma progesterone levels during the luteal phase of the cycle.

Exclusion criteria for all subjects included age less than 18 or greater than 25 yr, pregnancy, hypothyroidism, hyperprolactinemia, Cushing's syndrome, nonclassical congenital adrenal hyperplasia, and current or previous (within the last 6 months) use of oral contraceptives, glucocorticoids, antiandrogens, ovulation induction agents, antidiabetic and antiobesity drugs, or other hormonal drugs. Women with clinical and/or biochemical hyperandrogenism alone were excluded from the control group.

PCOS and control women with glucose intolerance, as assessed by World Health Organization criteria (39), were excluded from the study.

None of the subjects were affected by any neoplastic, metabolic, hepatic, and cardiovascular disorder or other concurrent medical illness (*i.e.* diabetes, renal disease, and malabsorptive disorders). All subjects were nonsmokers and had a normal physical activity level; none drank alcoholic beverages.

Study protocol

The procedures used were in accordance with the guidelines of the Helsinki Declaration on human experimentation. The study was approved by the Institutional Review Board of the University "Federico II" of Naples. The purpose of the protocol was explained both to the patients and control women, and a written consent was obtained from them before beginning the study.

At study entry, all subjects had venous blood drawn to perform the genetic study and to evaluate the complete hormonal assays, lipid profile, and ET-1, glucose, insulin, and homocysteine (Hcy) levels. Glucose and insulin values were detected also after oral glucose tolerance tests (OGTT). To evaluate the hyperandrogenetic state, free androgen index (FAI) was also calculated (40). During the same visit, all subjects underwent TV-USG, anthropometric measurements, cardiovascular assessment, and echocolor-Doppler evaluation.

The anthropometric measurement included height, weight, BMI (kg/m^2), and waist to hip ratio (WHR). BMI was measured as the ratio between the weight and the square of the height. WHR was calculated as the ratio between the smallest circumference of the torso (between the twelfth rib and the iliac crest) and the circumference of the hip (considered as the maximal extension of the buttocks). All measurements were performed when the patients were in standing position with relaxed abdomen, arms at sides, and joined feet (41).

TABLE 1. Clinical and biochemical diagnostic features of the 30 PCOS women studied

Features	No. of women	%
Anovulatory infertility	30	100
Normal FSH levels	30	100
Oligo/amenorrhea[a]	30	100
Clinical hyperandrogenism[a]	27	90
Hirsutism[b]	27	90
Acne	7	23.3
Biochemical hyperandrogenism[a]	11	36.7
T > 2 nmol/liter	9	30
Δ4-A > 15 nmol/liter	8	26.7
DHEA-S > 10 μmol/liter	8	26.7
LH/FSH ratio > 2	28	93.3
Polycystic ovary at TV-USG	23	76.7

[a] National Institutes of Health PCOS criteria.
[b] As evaluated by Ferriman-Gallwey score.

Measurements of heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were evaluated by standard methods. SBP and DBP were measured in the right arm, with the subjects in a relaxed sitting position. The average of six measurements (three measurements taken by each of two examiners) with a mercury sphygmomanometer was used (42).

A semiquantitative questionnaire was used to evaluate patients' daily physical activities, jobs, and daily activities. Physical activity was expressed as a score ranging from 1 to 3. A score of 3 was assigned to women who exercised regularly (high physical activity); a score 2 of was assigned to women who did not exercise regularly but who participated daily in activities like house cleaning, climbing stairs, or walking to work, to the bus stop, or to a restaurant (moderate physical activity); a score of 1 was assigned to women who did not participate in any of above-mentioned activities (low physical activity) (43).

The data regarding the echocardiographic assessments will be shown elsewhere.

Biochemical assays

All blood samples were obtained in the morning between 0800 h and 0900 h after an overnight fast and when the subject was resting in bed during the early follicular phase (d 2–5) of the spontaneous or progesterone-induced menstrual cycle. Blood samples (5 ml) were collected in tubes containing EDTA after a 12-h fast and a 30-min resting period in the supine position. The samples were immediately centrifuged at 4 C for 20 min at 1600 × *g*, and plasma samples were stored at −20 C.

Plasma LH, FSH, prolactin, estradiol, progesterone, 17-hydroxyprogesterone, T, Δ4-A, and DHEA-S were measured by specific RIA as previously reported (44–49). SHBG levels were measured using an immunoradiometric assay (48). Serum insulin was measured by a solid-phase chemiluminescent enzyme immunoassay using commercially available kits (Immunolite Diagnostic Products Co., Los Angeles, CA) (48).

Glucose and insulin concentrations were also measured 30 min after insertion of the iv catheter to detect the fasting levels (time 0) before OGTT. Successively, each subject received an oral 75-g glucose load. Further blood samples (10 ml each) were obtained at 30-min intervals for the following 3 h during the infusion period (times 30, 60, 90, and 120), and glucose and insulin concentrations were determined. Blood glucose levels were determined by the glucose oxidase method (45). The glucose and insulin response to OGTT was also analyzed by calculating the area under the curve (AUC). The $AUC_{glucose}$ to $AUC_{insulin}$ ratio was also calculated in each subject (50).

The serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) levels were measured with an autoanalyzer (Monarch 1000; Instrumentation Laboratory, Milan, Italy) using commercial kits (IL TEST; Instrumentation Laboratory) (51). The LDL-C was evaluated using the following formula: TC − HDL-C − 1/5 TG.

Serum ET-1 was measured by ELISA (Biomedica Gesellschft, Wien, Austria), with a sensitivity of 0.05 pmol/liter and intra- and interassay coefficients of variation (CV) of 4.5 and 6.9%, respectively. Normal ET-1 levels ranged between 0.2 and 0.7 pmol/liter, and the recovery measured with two levels of synthetic ET-1 was 95% in samples with 0.5 pmol/liter and 104% in samples with 2 pmol/liter. The cross-reactivity with ET-3 and Big ET was estimated as less than 5% and less than 1%, respectively.

Serum Hcy levels were measured by HPLC as previously described (49).

Brachial artery study

Vascular reactivity was assessed using brachial artery ultrasound. A 7.5-MHz linear phased array ultrasound transducer (Vingmed System Five; GE, Horten, Norway) was used to image the dominant brachial artery longitudinally just above the antecubital fossa (41).

Subjects were asked to fast for at least 8–12 h and to refrain from physical activity for at least 4–6 h before the examination. All hemodynamic measurements were obtained with the subjects in a supine comfortable position in a quiet, temperature-controlled room. In all studies, blood pressure in the contralateral brachial artery was recorded at regular intervals, and the electrocardiogram was monitored continuously. After baseline images of brachial arterial diameter were obtained, limb flow occlusion was produced by inflating a standard sphygmomanometry cuff on the upper arm to 40 mm Hg above SBP for 4 min. This caused ischemia and consequent dilatation of downstream resistance vessels. Subsequent cuff deflation induced a brief high-flow state through the brachial artery (reactive hyperemia) for the release of endothelial nitric oxide to accommodate the dilated resistance vessels. The brachial artery diameter was measured at 30 sec, and 1, 2, 3, and 4 min after ischemia (41).

All images were recorded on videotape for subsequent off-line analysis. FMD of the brachial artery was expressed as the percentage change in the arterial diameter from baseline to 4 min after deflation cuff. The FMD was used as a measure of endothelium-dependent vasodilatation. In our studies, the intra- and interobserver CV for the repeated measurements of resting arterial diameter were 2.3 and 5.6%, respectively.

Carotid artery study

Longitudinal ultrasonographic scans of the carotid artery were obtained on the same day as the studies of brachial artery reactivity. All women were examined in the supine position, with the head hyperextended and turned away from the side being scanned. Scans were performed by an experienced ultrasonographer (B.D.S.), who was blinded to clinical data, using a color Doppler (Vingmed System Five; GE) with a high-resolution 10-MHz linear probe. The sonographer scanned the right and left common carotid artery and the carotid bifurcation-bulb area from multiple planes (lateral, anterior oblique, and posterior oblique). Images were obtained from the distal portion of both common carotid arteries, 1–2 cm proximal to the carotid bulb and immediately proximal to the origin of the bifurcation. To simplify the scanning procedure and because of the lesser stability of measurements of the internal and external carotid artery, these segments were not taken into consideration in the present study (52, 53). The IMT of the posterior (far) wall of both common carotid arteries was measured as the distance between the junction of the lumen and intima and the junction of the media and adventitia (24, 53, 54).

The IMT was measured at the end-diastole from the B-mode screen. The mean IMT for each side was calculated as the average of 10 measurements made in the right and left carotid arteries using electronic calipers. Ambient light and temperature were controlled throughout the procedure. In our studies, the intra- and interobserver CV for the repeated measurements of IMT were 7.0 and 12.0%, respectively.

Statistical analysis

Continuous data were expressed as mean ± SD. A $P < 0.05$ was considered statistically significant. The SPSS 11.0 (SPSS Inc., Chicago, IL) package was used for statistical analyses.

The comparisons among controls and patients in demographic and biochemical data were performed by the Student's *t* test for unpaired data. All parameters were adjusted for chronological age, BMI, WHR, smoking status, glucose and insulin levels, FAI, lipid profile, Hcy concentrations, and SBP and DBP.

Stepwise multiple linear regression analysis was performed to test separately each of the primary end points (FMD, IMT, and ET-1) against the independent variables of chronological age, BMI, WHR, $AUC_{glucose}$ to $AUC_{insulin}$ ratio, Hcy levels, FAI, lipid concentrations, and SBP and DBP.

Results

Patient characteristics and hormonal profile are presented in Table 2. The groups were adequately and closely matched for age and BMI. The Ferriman-Gallwey scores were significantly ($P < 0.05$) higher in PCOS patients than in the control group. A significant ($P < 0.05$) difference was observed for LH, progesterone, 17-hydroxyprogesterone, T, Δ4-A, DHEA-S, and SHBG. The FAI was also significantly higher in PCOS group than in control group ($P < 0.05$; Table 2).

TABLE 2. Clinical and biochemical data of women with PCOS and controls

	Women with PCOS (n = 30)	Controls (n = 30)
Age (yr)	22.2 ± 2.5	22.6 ± 2.3
BMI (kg/m^2)	22.4 ± 2.1	22.1 ± 1.8
WHR	0.77 ± 0.4	0.72 ± 0.3
Ferriman-Gallwey score	12.1 ± 1.3[a]	4.5 ± 0.9
Physical activity score[b]	2.0 ± 0.3	2.1 ± 0.4
FSH (IU/liter)	10.5 ± 1.2	8.8 ± 1.3
LH (IU/liter)	24.6 ± 3.7[a]	11.6 ± 1.5
PRL (ng/ml)	11.5 ± 1.9	10.8 ± 1.3
E2 (pmol/liter)	117.9 ± 28.1	109.8 ± 31.3
P (nmol/liter)	1.2 ± 0.5[a]	1.9 ± 0.7
17-OHP (nmol/liter)	1.9 ± 0.2[a]	0.7 ± 0.1
T (nmol/liter)	2.6 ± 0.4[a]	1.0 ± 0.2
Δ4-A (nmol/liter)	5.18 ± 0.7[a]	2.14 ± 0.5
DHEA-S (μmol/liter)	4535 ± 527[a]	2988 ± 311
SHBG (nmol/liter)	28.1 ± 5.1[a]	50.5 ± 8.6
FAI	14.6 ± 7.6[a]	3.2 ± 1.6

Data are expressed as mean ± SD. PRL, Prolactin; E2, estradiol; P, progesterone; 17-OHP, 17-hydroxyprogesterone.
[a] $P < 0.05$ *vs.* control group.
[b] Physical activity score: 1, low; 2, moderate; 3, high.

TABLE 3. Metabolic assessment in women with PCOS and controls

	Women with PCOS (n = 30)	Controls (n = 30)
Vitamin B_{12} (ng/ml)	375.4 ± 113.9	392.1 ± 135.1
Folate (nmol/ml)	8.4 ± 2.2	8.6 ± 2.3
Hcy (μmol/liter)	10.4 ± 2.7	10.2 ± 2.5
Fasting glucose (mmol/liter)	6.1 ± 2.1	5.4 ± 1.9
Fasting insulin (μU/ml)	18.8 ± 5.5[a]	6.9 ± 2.0
OGTT		
$AUC_{glucose}$	1109 ± 531	1093 ± 449
$AUC_{insulin}$	5404 ± 1227[a]	2278 ± 496
$AUC_{glucose}$ to $AUC_{insulin}$ ratio	0.21 ± 0.31[a]	0.48 ± 0.37
TC (mmol/liter)	3.96 ± 0.12	3.94 ± 0.12
LDL-C (mmol/liter)	1.79 ± 0.16	1.78 ± 0.14
HDL-C (mmol/liter)	2.85 ± 0.23	2.81 ± 0.20
TG (mmol/liter)	1.23 ± 0.20	1.22 ± 0.19

Data expressed as mean ± SD.
[a] $P < 0.05$ *vs.* control group.

Table 3 shows the metabolic data of women with PCOS and controls. Serum vitamin B_{12}, folate, and Hcy concentrations were similar between the two groups (Table 3). In addition, no differences were detected in fasting glucose and in $AUC_{glucose}$ levels between the groups; however, fasting insulin levels, $AUC_{insulin}$, and $AUC_{glucose}$ to $AUC_{insulin}$ ratio were significantly ($P < 0.05$) higher in PCOS patients than in control women (Table 3). No differences in serum TC, LDL-C, HDL-C, and TG levels were detected between the PCOS and control groups (Table 3).

No difference was observed in heart rate, SBP, and DBP between PCOS patients and control women (Table 4). Moreover, artery diameters at baseline (3.24 ± 0.3 mm *vs.* 2.96 ± 0.4 mm for PCOS patients and controls, respectively) and after reactive hyperemia (3.7 ± 0.3 mm *vs.* 3.5 ± 0.2 mm for

TABLE 4. Structural and functional parameters of cardiovascular assessment in women with PCOS and controls

	Women with PCOS (n = 30)	Controls (n = 30)
HR (bpm)	78.3 ± 3.9	76.2 ± 4.2
SBP (mm Hg)	111.3 ± 8.2	113.2 ± 6.7
DBP (mm Hg)	74.2 ± 4.7	71.4 ± 4.3
Baseline artery diameter (mm)	3.24 ± 0.3[a]	2.96 ± 0.4
Diameter after reactive hyperemia (mm)	3.7 ± 0.3[a]	3.5 ± 0.2
FMD (%)	14.3 ± 1.9[a]	18.1 ± 2.0
IMT (mm)	0.53 ± 0.09[a]	0.39 ± 0.08
ET-1 (pmol/liter)	1.1 ± 0.4[a]	0.5 ± 0.2

All data (expressed as mean ± SD) were adjusted for chronological age, BMI, WHR, smoking status, glucose and insulin levels, FAI, lipid profile, Hcy concentrations, and SBP and DBP. HR, Heart rate.

[a] $P < 0.05$ *vs.* control group.

TABLE 5. Final models of stepwise multiple linear regression analysis in PCOS patients to test separately each of our primary end points against the main independent variables

Variable	Coefficient	β	P
FMD			
$AUC_{glucose}$ to $AUC_{insulin}$ ratio	4.179	0.449	0.013
Constant	13.419		
IMT			
FAI	0.004	0.369	0.045
Constant	0.469		
ET-1			
$AUC_{glucose}$ to $AUC_{insulin}$ ratio	−1.254	−0.638	<0.001
SBP	0.021	0.432	0.001
Constant	−0.978		

PCOS patients and controls, respectively) were significantly ($P < 0.05$) different between the PCOS and control groups.

A significant ($P < 0.05$) difference in FMD (14.3 ± 1.9% *vs.* 18.1 ± 2.0% for PCOS patients and controls, respectively) and IMT (0.53 ± 0.09 mm *vs.* 0.39 ± 0.08 mm, for PCOS patients and controls, respectively) was found between PCOS and control women (Table 4). Serum ET-1 levels were also significantly ($P < 0.05$) higher in PCOS patients when compared with controls (1.1 ± 0.4 pmol/liter *vs.* 0.5 ± 0.2 pmol/liter, respectively; Table 4).

In women with PCOS, stepwise multiple linear regression analysis showed a direct relationship between FMD and $AUC_{glucose}$ to $AUC_{insulin}$ ratio ($P = 0.013$), IMT and FAI ($P = 0.045$), and ET-1 and SBP ($P = 0.001$; Table 5). An inverse linear relationship was found between ET-1 and $AUC_{glucose}$ to $AUC_{insulin}$ ratio ($P < 0.001$; Table 5). No relationship was found in controls.

Discussion

PCOS is characterized by several metabolic alterations that could increase the risk of CVD (9, 55, 56), and one of the early signs of cardiovascular lesions is the endothelial injury (24). This study was carried out to clarify the exact relationships between vascular damage and PCOS. In fact, here we investigate the functional and structural vascular damage in PCOS by serum ET-1 assay and both carotid IMT and brachial artery FMD evaluation.

Our data demonstrated that women with PCOS had higher ET-1 levels and IMT than controls, whereas they showed reduced FMD values.

Some authors (57, 58) have postulated that ET-1, as a precocious marker of CVD, could contribute to the atherosclerotic process. In addition, circulating ET-1 levels have been shown to be increased in patients with obesity (59, 60), atherosclerosis (57, 58), myocardial infarction (57, 61), diabetes mellitus (33, 60), and, more recently, PCOS (34).

Specifically, hyperinsulinemic women with PCOS have a significant risk of early CVD (22, 23), and this risk seems to be further increased by the stimulating effects of insulin on ET-1 secretion (32). Furthermore, ET-1 is considered as an additional risk factor in nonobese hypertensive subjects with metabolic abnormalities (24), and PCOS women represent an intriguing biological model that can illustrate metabolic and hormonal effects on the endothelium without overt cardiovascular risk factors.

According to Diamanti-Kandarakis *et al.* (34), we found that serum ET-1 levels were significantly higher in normalweight women with PCOS than in BMI-matched healthy controls, suggesting that increased ET-1 concentrations are a feature of PCOS independent of obesity. A putative cause of the increased ET-1 levels in PCOS could be the insulin resistance. In fact, it was considered a prominent abnormality in both obese and lean patients with hyperandrogenism and PCOS (62). In support of our hypothesis, several studies (7, 20) have shown that hyperinsulinemia is a predictor of coronary artery disease and that insulin stimulates secretion of ET-1 *in vivo* and *in vitro* (32).

Recently, Migdalis *et al.* (63) investigated the possible relationship between ET-1 and arterial wall thickness in diabetic subjects and revealed not only that elevated ET-1 levels are present in patients with increased IMT but also that ET-1 is the main associate of the change of IMT value (64).

At present, IMT is the best-studied ultrasonographic marker for early atherosclerotic vascular wall lesions (24, 25, 65). A direct correlation between IMT and the risk of myocardial infarction and stroke in patients without a history of vascular disease has been shown (66). Several metabolic alterations, such as obesity (67, 68), insulin resistance (28, 69), and hyperandrogenism (70), have been widely accepted as risk factors for increased IMT.

IMT has been already considered a potential marker of risk for CVD in women with PCOS (17). In particular, Talbott *et al.* (17) showed an association between PCOS and premature carotid atherosclerosis in middle-aged women, demonstrating a BMI-independent difference in carotid IMT between middle-aged women with PCOS and controls, but not in younger women. Conversely, our data show an increased IMT even in young women with PCOS and demonstrate that, in PCOS, the increased IMT is not due to a prolonged exposure to an adverse cardiovascular profile.

Our study population was not only young women, but it also included women who were of normal weight, nondyslipidemic, and nonhypertensive. A significant difference in insulin resistance and in androgen levels was observed between PCOS patients and controls, suggesting an important role for the exposure of androgens or insulin in the most precocious development of atherosclerosis. Previous studies (66, 70–72) have demonstrated the importance of sex hor-

mones in contributing to carotid arterial wall thickness. Hyperandrogenemia in women with PCOS may result in a male pattern of lipoproteins, suggesting an increased atherogenic potential in PCOS patients (73). In addition, Lakhani *et al.* (74) evidenced impaired carotid viscoelastic properties in PCOS women, providing additional evidence of vascular dysfunction in women with this syndrome (75).

Data regarding endothelial dysfunction in PCOS patients are poor and contrasting (16, 18, 75). Mather *et al.* (75) showed no difference in FMD between PCOS patients and controls, despite the hyperandrogenism and insulin resistance of PCOS patients. Conversely, Paradisi *et al.* (18) showed markedly diminished endothelium-dependent and insulin-mediated flow responses in the femoral artery of women with PCOS. Recently, Kelly *et al.* (16) demonstrated an increased vascular stiffness and a functional defect in the vascular action of insulin in PCOS patients.

In conclusion, our data show that young, normal-weight, nondyslipidemic, nonhypertensive women with PCOS have altered endothelial function and increased IMT and serum ET-1 values, suggesting early functional, structural, and biochemical preatherosclerotic vascular impairment.

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