Morphologic and functional vascular alterations in patients with polycystic ovary syndrome

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Summary

Background: We aimed to investigate morphologic and functional alterations of common carotid arteries (CCA) and femoral arteries and the anteroposterior diameter of the abdominal aorta in patients with polycystic ovary syndrome (PCOS). *Materials and Methods:* Fifty consecutive females with the complaint of oligoamenorrhea, infertility or hirsutismus, diagnosed with PCOS and 50 healthy females admitted to the Department of Gynecology and Obstetrics, Ergani State Hospital between January 2010 and January 2011 were included in the study. *Results:* The mean BMI of 50 patients with PCOS was higher than control subjects (CS) (25.89 ± 3.3 vs 22.52 ± 2.7 kg/m^2, $p < 0.0001$). The mean arterial blood pressure was 88.93 ± 6.4 mmHg in the patient group and was it 85.73 ± 7.6 mmHg in CS ($p = 0.02$). The mean plasma glucose level (74.04 ± 6.7 vs 70.5 ± 6.4 mg/dl), total cholesterol level (167.88 ± 30.1 vs 153.38 ± 27.8 mg/dl), low density lipoprotein level (101.28 ± 27.0 vs 79.56 ± 25.5 mg/dl) and triglyceride level (121.22 ± 49.2 vs 102.54 ± 36.6 mg/dl) were higher; also the mean high density lipoprotein level (44.56 ± 8.1 vs 50.90 ± 12.3 mg/dl) was lower in patients with PCOS than CS ($p = 0.009$, $p = 0.014$, $p < 0.0001$, $p = 0.034$ and $p = 0.003$, respectively). CCA-IMT (0.63 ± 0.2 vs 0.52 ± 0.1 mm), and CCA-PI (1.44 ± 0.3 vs 1.28 ± 0.22) were higher in patients with PCOS ($p = 0.018$ and $p = 0.005$, respectively). Femoral-IMT (0.62 ± 0.6 vs 0.41 ± 0.1 mm) and anteroposterior diameter of the infrarenal aorta (12.34 ± 1.5 vs 11.4 ± 1.0 mm) were higher in patients with PCOS ($p = 0.024$ and $p = 0.001$, respectively). *Conclusion:* The present study showed that IMT and PI of CCA, and anteroposterior diameter of the infrarenal abdominal aorta and femoral-IMT were higher in patients with PCOS. These results are probably related with increased androgens, their effects on insulin resistance and lipid profile, increased BMI and blood pressure. Detection of these functional and/or structural abnormalities are important in predicting prognosis. Larger scale prospective studies are needed to determine the effects of PCOS on the mortality and morbidity, and to clarify the relation between the duration of the disease and development of these alterations.

Key words: Polycystic ovary syndrome; Vascular alterations; Vascular dysfunction.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies, affecting 5%-10% of women in reproductive age [1]. It is characterized by chronic anovulation, hyperandrogenism, insulin resistance, obesity, infertility, and an increased risk of spontaneous abortion [2]. Although it is important to recognize and address these clinical problems, attention has also turned to the risk of diabetes and cardiovascular disease due to central obesity, dyslipidemia (low high-density lipoprotein [HDL] and high cholesterol and triglyceride levels), hypertension, endothelial dysfunction, and insulin resistance [3-11]. It has been reported that women with clinical features of PCOS have five years lower cardiovascular event-free survival due to hemodynamic changes related to hormonal disturbances and their metabolic effects [12].

The intima-media thickness (IMT) of the arteries has proven to be a good marker for both the presence of early arteriosclerosis and degree of arteriosclerosis [13-18]. Prospective studies have shown a positive correlation between increased common carotid artery (CCA) IMT and risk for cardiovascular mortality [19-21]. The resistive index (RI) is not a morphological but a hemodynamic parameter that can be easily determined by Doppler ultrasound (US). It reflects local wall extensibility and the related vascular resistance. There is a clear correlation between increasing RI values and arteriosclerosis risk factors and manifestations [13, 14, 22-24].

Many vascular abnormalities have been demonstrated in women with PCOS by using Doppler US. In particular, several studies found increased CCA-IMT and/or IMT of the internal carotid arteries [25-27], and some studies found increased anteroposterior diameter of the infrarenal abdominal aorta in women affected by PCOS [4].

In the present study we aimed to investigate whether the IMT and flow parameters of CCA and femoral arteries would be higher in women with PCOS than in those without this disease control subjects (CS) and if the anteroposterior diameter of the abdominal aorta would differ between the two groups.

Patients and Methods

Fifty consecutive females complaining of oligo-amenorrhea, infertility or hirsutismus, diagnosed with PCOS according to Rotterdam criteria [28] and 50 healthy females (CS) admitted to the Department of Gynecology and Obstetrics, Ergani State

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Hospital between January 2010 and November 2010 were included in the study. Patients and controls with diabetes mellitus, metabolic syndrome, dyslipidemia, hypertension, Cushing syndrome, hyperprolactinemia, thyroid dysfunction, coronary or chronic liver or kidney diseases, with a history of thromoembolic diseases, smoking, drug usage which might affect hormonal or biochemical tests or endothelial functions which might effect imaging studies of arteries (oral contraceptives, glucocorticoids, antiandrogens, or insulin sensitizers) were excluded. The study was conducted in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki. Informed written consent was obtained from all participants.

Blood pressure (BP) of all participants was measured at rest in a climatized room at 22°C. Body mass index (BMI) of patients was calculated as kg/m^2. Serum and plasma samples were collected from patients between 08:00 and 10:00 a.m., after an overnight fast of at least 12 hours during the early follicular phase of the menstrual cycle, or on random days in amenorrheic patients on the same day of US. Luteinizing hormone (LH), follicle stimulating hormone (FSH), estrodiol, prolactin and total testosterone were determined by using an ADVIA Centaur XP Immunoassay System (Siemens Healthcare Diagnostics, NY, USA). Glucose, total cholesterol, HDL, low-density lipoprotein (LDL) cholesterol, and triglycerides were measured by enzymatic colorimetric assay, using Ortho Clinical Diagnostics, Johnson & Johnson VITROS products 5.1 FS Chemistry System (Johnson & Johnson, NY, USA), and its original reagents.

Ultrasound and Doppler analyses were performed by the same physician for all women during the follicular phase of the menstrual cycle (between the third and fifth day) after resting a minimum of 15 min in a quiet room. US studies of CCA and femoral arteries were performed bilaterally. The value of CCA and femoral arteries considered for statistical analyses was the mean of the right and left measurements for each artery. All studies were performed with a SDU-2200 pro (SDU-2200 Pro, Shimadzu, Korea) using a 5-10 MHz high-resolution probe.

IMT was defined as a low-level echo grey band that does not project into the arterial lumen. It was measured during end-diastole as the distance from the leading edge of the second echogenic line of the far walls of the distal segment of the CCA, the carotid bifurcation, and the initial tract of the internal carotid artery on both sides, and similarly of the distal segment of the common femoral artery on both sides. Measurements were performed 0.5, 1, and 2 cm below the bifurcation (three measurements on each side) for the carotid, and 0.5, 1, and 2 cm below the femoral (profunda and superficial; three measurements on each side), and the average measurement was taken as the IMT. IMT measurements were always performed in plaque-free arterial segments. The peak systolic velocity, end-diastolic velocity and mean velocity of eveluated arteries were measured, then RI and pulsative index (PI) values calculated [29]; as RI = (peak systolic velocity – end-diastolic velocity)/peak systolic melocity and PI = (peak systolic velocity – end-diastolic velocity)/mean velocity. Evaluation of the infrarenal abdominal aorta was performed in the supine position; an electronic probe was placed 1 cm left of the umbilicus. The best image in long axis projection of the abdominal aorta was then obtained. The anteroposterior diameter of the aorta was defined as the maximal external cross-sectional measurement. It was calculated as the distance between the near and the far walls of the abdominal aorta. Measurements were performed at 0.5, 1, and 2 cm above the umbilicus and expressed in centimeters [4].

Statistical analysis: Results are presented as mean and standard deviation (SD) for all parameters. Statistical significance was determined by the t-test. All tests were performed using the SPSS statistical package version 11; p values ≤ 0.05 were considered significant.

Results

There was no statistically significant difference between mean age of patients with PCOS and CS (24.76 ± 5.2 and 23.94 ± 4.8 years, respectively). Mean BMI of the patient group was higher than CS (25.89 ± 3.3 vs 22.52 ± 2.7 kg/m^2, $p < 0.0001$). Mean systolic BP was 116.0 ± 8.3 mmHg in the patient group and 110.4 ± 9.6 mmHg in CS; mean diastolic BP was 75.4 ± 7.8 mmHg in the patient group and 73.4 ± 7.9 mmHg in CS; and, the mean arterial pressure was 88.93 ± 6.4 mmHg in the patient group and 85.73 ± 7.6 mmHg in CS. The systolic and mean arterial BP were significantly higher in patients with PCOS than in CS ($p = 0.003$ and $p = 0.02$, respectively). The mean diastolic BP was also higher in the patient group but this difference was not statistically significance.

The mean fasting plasma glucose level (74.04 ± 6.7 vs 70.5 ± 6.4 mg/dl), total cholesterol level (167.88 ± 30.1 vs 153.38 ± 27.8 mg/dl), LDL level (101.28 ± 27.0 vs 79.56 ± 25.5 mg/dl) and triglyceride level (121.22 ± 49.2 vs 102.54 ± 36.6 mg/dl) were higher, and mean HDL level (44.56 ± 8.1 vs 50.90 ± 12.3 mg/dl) was lower in patients with PCOS than CS ($p = 0.009$, $p = 0.014$, $p < 0.0001$, $p = 0.034$ and $p = 0.003$, respectively).

There were no statistically significant differences between the groups in terms of FSH, estradiol and prolactin levels. However, mean LH level (8.23 ± 5.6 vs 5.8 ± 2.7 IU/l) and mean total testosterone level (70.38 ± 20.7 vs 52.98 ± 17.9 ng/dl) were higher in patients with PCOS ($p = 0.008$ and $p < 0.0001$, respectively).

CCA-IMT (0.63 ± 0.2 vs 0.52 ± 0.1 mm), and CCA-PI (1.44 ± 0.3 vs 1.28 ± 0.22) were higher in patients with PCOS ($p = 0.018$ and $p = 0.005$, respectively). There was no statistically significant difference between patients and controls in terms of CCA-RI (0.71 ± 0.1 vs 0.70). Femoral-IMT (0.62 ± 0.6 vs 0.41 ± 0.1 mm) and anteroposterior diameter of the infrarenal aorta (12.34 ± 1.5 vs 11.4 ± 1.0 mm) were higher in patients with PCOS ($p = 0.024$ and $p = 0.001$, respectively). Results are shown in Table 1.

Discussion

In this study we aimed to investigate the alterations in IMT (as a morphologic parameter) and functional flow parameters (RI) of CCA and femoral arteries in 50 consecutive women with PCOS. The patients with PCOS had a signicantly higher mean BMI, systolic blood and mean arteriel pressure, plasma glucose, total cholesterol and LDL levels and lower HDL levels than controls. Some hormonal differences were also detected in patients with PCOS. LH and total testosteron levels were higher in patients with PCOS as expected. In addition, we found some vascular morphologic and functional alterations (CCA-IMT, Ci CA-PI, femoral-IMT and anteroposterior diameter of the infrarenal aorta were higher) in patients with PCOS.

Table 1. — *Comparison of biochemical and hormonal parameters and imaging studies of patients with PCOS and CS.*

	PCOS (n = 50)	CS (n = 50)	*p*
Age (years)	24.76 ± 5.2	23.94 ± 4.8	NS
BMI (kg/m²)	25.89 ± 3.3	22.52 ± 2.7	< 0.0001
Systolic blood pressure (mmHg)	116 ± 8.3	110.4 ± 9.6	0.003
Diastolic blood pressure (mmHg)	75.4 ± 7.8	73.4 ± 7.9	NS
Mean arterial pressure (mmHg)	88.93 ± 6.4	85.73 ± 7.6	0.02
Glucose (mg/dl)	74.04 ± 6.7	70.5 ± 6.4	0.009
Total cholesterol (mg/dl)	167.88 ± 30.1	153.38 ± 27.8	0.014
LDL (mg/dl)	101.28 ± 27.1	79.56 ± 25.5	< 0.0001
HDL (mg/dl)	44.56 ± 8.1	50.9 ± 12.3	0.003
Triglyceride (mg/dl)	121.22 ± 49.2	102.54 ± 36.6	0.034
FSH (IU/l)	4.12 ± 1.4	4.56 ± 1.6	NS
LH (IU/l)	8.23 ± 5.6	5.84 ± 2.7	0.008
Estradiol (pg/ml)	55.8 ± 12.8	54.95 ± 14.4	NS
Prolactin (ng/ml)	9.64 ± 5.1	10.4 ± 5.3	NS
Total testosterone (ng/dl)	70.38 ± 20.7	52.98 ± 17.9	< 0.0001
Common Carotid artery IMT (mm)	0.63 ± 0.2	0.52 ± 0.4	0.018
Common Carotid RI	0.71 ± 0.1	0.7 ± 0.1	NS
Common Carotid PI	1.44 ± 0.3	1.28 ± 0.2	0.005
Femoral arterial IMT (mm)	0.62 ± 0.6	0.41 ± 0.1	0.024
AP diameter of infrarenal aorta (mm)	12.34 ± 1.5	11.41 ± 1.1	0.001

NS: non significant.

It is known that cardiovascular disease (CVD) risk factors such as obesity, dyslipidemia, glucose intolerance diabetes and hypertension are encountered more frequently in patients with PCOS and the mortality rate are higher in these patients related to CVD [30]. Similar to previous reports, we found that mean BMI, blood pressure and glucose levels of patients were higher in patients with PCOS. This study showed again that these patients have a tendency for hypertension, obesity and glucose intolerance. Hyperinsulinemic insulin resistance is a cardinal finding in the pathophysiology of PCOS, and hyperinsulinemia plays a key role by circulating ovarian androgen concentrations as we also demonstrated. Hyperinsulinemia may also be used for dyslipidemia related to decreased activity of lipoprotein lipase and lipoproteins received by adiposis. In addition to the vasoconstructive effects of androgenes, endothelial dysfunction and increased arterial stiffness were also detected in insulin resistance and hyperlipidemia, and both may play a role in vascular morphologic alterations [2].

IMT, measured by B-image technology, is a morphological parameter and represents the histologically verified IMI segment of the vascular wall [31]. The RI is instead based on Doppler technology, calculated by using Pourcelot's formula as shown above, and relates to the elasticity or extensibility of the vessel and its vascular resistance. Both are clearly correlated with age and other CVD factors [13, 32-34]. As demonstrated in many previous reports, CCA-IMT and RI are surrogate markers for the degree of atherosclerosis in an individual patient [13]. In this study, we showed that CCA-IMT and PI were higher in the study group. CCA-RI of patients with PCOS was also higher, however this difference was not statistically significant. Staub and collegues [13] showed a similar result in their study; however, Lakhani *et al.* [3] found decreased PI in their study group. It is not known definitely why the carotid-PI was lower in the study of Lakhani *et al.* but the authors postulated that the high estrodiol levels of their study group might have been responsible for these results. It was previously demonstrated that decreased estradiol levels in postmenopausal women caused a decrement in PI [3]. The higher levels of CCA-IMT and PI that were detected in our study are probably the result of increased androgens associated with insulin resistance and deteriorated lipid profile, increased BMI and blood pressure. Before the appearance of morphological alterations that are detectable from the thickening of the IMT complex, the early form of atherosclerosis leads to functional abnormalities that are associated with increased cardiovascular mortality. Detection of these firstly functional and lately structural abnormalities is important in predicting the mortality of these patients. It is not clearly known what the effects of PCOS are on mortality, and larger scale prospective studies are needed to determine the effects of PCOS and confounding CVD factors that may be related to prognosis.

Ciccone *et al.* [4] studied the vascular effects of PCOS in a young patient group aged between 17 and 27. They did not find a statistical difference between femoral-IMT of patients and controls, but detected a larger anteroposterior diameter of the infrarenal abdominal aorta. They suggested that the similarity between femoral-IMT but not between diameter of the infrarenal aorta may be related to the younger ages of patients, and they postulated that the earliest vascular alteration in patients with PCOS is increased diameter of the abdominal aorta. Similar to Ciccione *et al.* we found that the mean anteroposterior diameter of the infrarenal abdominal aorta was higher in these patients. In addition, we found a higher femoral IMT in our study group. The mean age of our patients was higher (24.7 ± 5.2; range 18-33 years), and the difference we found between IMT of the arteries might be related with longer duration of the disease, as Ciccone *et al.* suggested. Indeed, the alterations in IMT may be detected in longer duraton of the disease. However, larger scale studies that classify patients according to age are needed to clarify the relation between ages, duration of the disease and development of these alterations.

In conclusion, in this study we showed that CCA-IMT and PI, anteroposterior diameter of the infrarenal abdominal aorta and femoral-IMT were higher in patients with PCOS. These results are probably related to increased androgen levels, their effects on insulin resistance and lipid profile, increased BMI and blood pressure. Detection of these functional and/or structural abnormalities are important in predicting the mortality and morbidity of these patients. Larger scale prospective studies are needed to determine the effects of PCOS on mortality and

to clarify the relation between the duration of the disease and development of these alterations.

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