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POLYCYSTIC OVARY SYNDROME AND INSULIN RESISTANCE

Evaluation of body fat distribution in PCOS and its association with carotid atherosclerosis and insulin resistance

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***Objective*: The aim of this study was to compare body fat distribution in PCOS with healthy controls and to investigate the factors associated with carotid artery intima media thickness (IMT) and insulin resistance. *Subjects and Methods*: A case control study was conducted in 46 women with PCOS and 43 age matched controls. Anthropometrical measurements, hormonal levels, lipid and glucose profile were evaluated. Body fat thickness in four regions and carotid IMT were measured. Body fat distribution was compared between groups. Correlation of these parameters with carotid artery IMT and insulin resistance was investigated. *Result(s)*: Visceral and subcutaneous fat thickness and the mean carotid artery IMT were significantly higher in PCOS subjects ($p < 0.01$). In correlation analysis, age, body mass index (BMI) and waist hip ratio (WHR) showed correlation with carotid artery IMT ($r = 0,55$, $p < 0,001$; $r = 0.41$, $p < 0.008$ and $r = 0.34$ $p = 0.03$, respectively), whereas visceral fat thickness presented a correlation with HOMA-IR index as a sign of insulin resistance. *Conclusion(s)*: Fat accumulation is more prominent in visceral and subcutaneous regions in PCOS. Increased BMI and abdominal type of obesity are closely related to the increased carotid artery IMT and insulin resistance. Weight control and regional weight loss are important part of the treatment for the future health of women with PCOS.**

Keywords: Insulin resistance, polycystic ovary syndrome, body mass index, hirsutismus

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in reproductive age women with a prevalence of 5–8% and usually characterized by chronic anovulation, hyperandrogenism, hyperinsulinemia, and obesity [1–3]. It is associated with a broad spectrum of endocrine and metabolic disturbances, such as dyslipidemia, insulin resistance and hypertension predisposing to increased cardiovascular disease and type-2 diabetes [4]. Carotid artery intima media thickness (IMT), a preceding indicator of potential stroke and myocardial infarction, has also been shown to be increased in PCOS patients compared to age matched controls [5–9]. Despite studies investigating visceral fat accumulation, little is known about regional distribution of fat in PCOS patients. In this study, we aimed to compare the body fat distribution at abdominal and mid-thigh region in PCOS patients with those of healthy controls, and to investigate the association of these measurements with Carotid artery IMT and insulin resistance.

Materials and methods

This prospective study was carried out between September 2009 and September 2010. Study population was most probably drawn from the patients who attended the outpatient clinic of gynecology of Denizli State Hospital. Rotterdam criteria (Rotterdam ESHRE-ASRM sponsored PCOS consensus workshop group-2004) were used for selection of PCOS patients. Patients with the presence of two of the folowing criteria with the exclusion of related disorders were accepted as having PCOS; clinical findings of amenorrhea or oligomenorrhea, clinical or laboratory signs of hirsutismus (Ferriman–Gallwey score ≥ 8 or increased total testosterone levels), appearance of polycystic ovaries on ultrasonography. Patients with type-2 diabetes, hyperprolactinemia, hypogonadotrophic hypogonadism, thyroid disease, congenital adrenal hyperplasia, androgen secreting tumors and Cushing's syndrome were ruled out by appropriate laboratory work up, and smoking patients were excluded. The patients diagnosed as PCOS on admission, and did not take any treatment previously constituted the study group. Overall 46 patients met the inclusion criteria for PCOS group. A control group consisted of 43 consecutive non-smoker patients with regular menses, without signs of hirsutismus, normal hormonal status and sonographic examination, who were matched for age and BMI.

Initial physical examination included weight, height, hip and waist circumference (WC) to calculate waist to hip ratio (WHR) and body mass index (BMI). Fasting glucose, triglyceride, total cholesterol, HDL cholesterol levels were measured by photometric assay. Low density lipoprotein (LDL) level was calculated via Friedewald Formula (LDL cholesterol = total cholesterol– (HDL cholesterol + (triglyceride/5)). Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Estradiol (E2), total Testosterone, dehydroepiandrosterone sulfate (DHEA-S), insulin, and homocysteine levels were measured by chemiluminescent immunoassay. Homeostatic model assessment was applied by using the Formula "HOMA Insulin Resistance (HOMA-IR = Fasting blood glucose (mg/dl)/18 x Fasting insulin (IU/L)/22.5[10]".

Sonographic measurements were performed with a properly calibrated ultrasound (Acuson Antares, Siemens, Erlangen, Germany) on day three of the cycle by an experienced sonographer, who was unaware of the diagnosis of the patients. Carotid

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artery IMT was measured as defined previously by Pignoli et al. [11] via 5–13 MHz broadband linear transducer. Estimation of body fat distribution was performed with measurements taken from abdominal subcutaneous, preperitoneal and mid-thigh regions via a 4–9 MHz linear probe, and from visceral region via 2–4 MHz convex probe. Visceral fat thickness was measured 1 cm above the umbilicus on the xypho-umbilical line between internal face of the rectus abdominis muscle and the anterior wall of the aorta [12]. Preperitoneal fat thickness was measured longitudinally. Subcutaneous fat thickness was measured with the same transducer transversely placed perpendicular to the skin in the midline of abdomen, between the xyphoid process and umbilicus. Mid-thigh fat thickness measurement was performed on the medial side of the middle of the thigh on both sides and the mean value was taken for the evaluation.

Statistical analysis

Continuous variables were reported as the mean ± SD and compared using student *t*-test and Mann–Whitney *U* test between the groups. Categorical data were reported as percentages. Kolmogorov Simirnov-Z test was used to analyze the normal distribution of investigated parameters. Correlation analysis was performed via Pearson correlation test for continuous variables with normal distribution.

All analysis was run by using SPSS Statistical Package Program 10.0 (SPSS Inc. Chicago, IL).

Results

The clinical characteristics and steroid hormone levels of the study population were presented in Table 1. The subjects in both groups were similar for age, BMI, and WHR ($p > 0.05$). Ferriman–Gallwey score ($p = 0.0001$), LH, and testosterone levels ($p = 0.01$ and $p = 0.0001$, respectively) were significantly higher in PCOS group. The fasting glucose, fasting insulin, HOMA-IR index, homocysteine and lipid profiles were tabulated in Table 2. Fasting insulin levels and HOMA-IR index were significantly higher in PCOS group ($p = 0.003$ and $p = 0.0001$, respectively). The criteria of insulin resistance or decreased insulin sensitivity such as HOMA-IR >2.5 was significantly more frequent in the PCOS group compared to the controls ($p < 0.001$). Total cholesterol, triglyceride and LDL levels were significantly higher, whereas HDL cholesterol level was significantly lower in subjects with PCOS compared to healthy controls. Consequently, total cholesterol/HDL ratio which was accepted as a risk factor for the assessment of coronary heart disease was significantly higher in PCOS group ($p = 0.0001$).

Table 1. Comparison of selected patient characteristics in subjects with and without PCOS.

Variable	PCOS ($n = 46$)	Control ($n = 43$)	p
Age (years)	25.9 ± 5.5	25.2 ± 5.0	NS
BMI (kg/m^2)	27.5 ± 3.9	26.6 ± 3.8	NS
Waist/hip ratio	0,82 ± 6.45	0,79 ± 7.41	NS
Ferriman–Gallwey score	11,8 ± 3.6	3.4 ± 2.3	<0.01[a]
FSH (mIU/ml)	5.99 ± 2.04	5.44 ± 1.14	NS
LH (mIU/ml)	8,49 ± 4.90	4.80 ± 1.98	<0.01[a]
E2 (pg/ml)	58.46 ± 26.44	47.41 ± 28.45	NS
Testosterone (ng/ml)	0.78 ± 0.29	0.64 ± 0.17	<0.01[a]
DHEA-S (μg/dl)	213.54 ± 92.29	192.53 ± 97.71	NS

Variables are expressed as means ± SD.
[a]Student's *t*-test.
DHEA-S=dehydroepiandrostenedione sulphate; BMI=body mass index; NS=nonsignificant.

The fat partitioning of the body and carotid artery IMT were significantly different between two groups (Table 3). Carotid artery IMT, visceral and subcutaneous fat thicknesses were higher in subjects with PCOS ($p < 0.01$). However, there was no difference in the preperitoneal and mid-thigh fat thicknesses ($p > 0.05$) between two groups.

Carotid artery IMT significantly correlated with age, BMI and WHR was in PCOS patients ($r = 0.55$, $p < 0.001$; $r = 0.41$, $p < 0.008$; $r = 0.34$, $p = 0.03$, respectively). A significant correlation was also detected between HOMA-IR index and visceral fat thickness in the PCOS group ($r = 0.364$, $p = 0.018$).

Discussion

Polycystic ovary syndrome is a unique disorder associated with metabolic, cardiovascular and endocrine problems. Our findings suggest that, despite similar age and body mass indexes, body fat was mainly accumulated in visceral and subcutaneous compartments in patients with PCOS. Studies on fat distribution of PCOS yielded conflicting results. In one study, increased body fat accumulation in upper half of body was detected using skin thickness measurements [13]. Increased visceral and preperitoneal fat thickness was also detected in another study [14]. On the other hand, Barber et al. [15] found no difference in regional fat distribution between PCOS cases compared to BMI-matched controls. In our study, although case and control groups had similar age, BMI, and WHR, the visceral and subcutaneous fat accumulations were significantly higher in PCOS subjects, which may be due to larger sample size of this study compared to the former. Ultrasonographic investigation of carotid artery is being undertaken increasingly to assess cardiovascular risk [16]. Sonographic detection of elevated carotid IMT has been shown to precede carotid artery plaque formation and appears to be a useful marker of atherosclerosis [17]. Increased carotid artery IMT has been shown to be associated with age, obesity, hypercholesterolemia, diabetes, and smoking in previous studies [18–20], indicating increased cardiovascular events. In our study, all patients were under thirty five years old, and patients with known diabetes, hypercholesterolemia, and

Table 2. Fasting glucose, fasting insulin, HOMA-IR index and lipid profiles in women with and without PCOS.

Variable	PCOS ($n = 46$) (Mean ± SD)	Control ($n = 43$) (Mean ± SD)	p
Fasting glucose (mg/dl)	94.0 ± 8.3	91 ± 8.02	NS
Fasting insulin (μ IU/ml)	11.96 ± 4.91	8.57 ± 3.52	0.003
HOMA-IR	2.8 ± 1.37	1.5 ± 0.44	0.0001
Total cholesterol	178.4 ± 26.88	156.75 ± 24.29	0.01
Triglyceride	125.19 ± 59.63	68.32 ± 30.7	<0.01
LDL	104.52 ± 21.97	86.04 ± 21.84	0.02
HDL	48.88 ± 10.87	55.72 ± 21.84	0.015
Total cholesterol/HDL ratio	3.61 ± 0.93	2.87 ± 0.83	<0.01
Homosistein (umol/L)	9.04 ± 4.19	8.91 ± 3.39	NS

Table 3. Distribution of body fat and carotid artery IMT in patients with and without PCOS.

Variable	PCOS ($n = 46$) (Mean ± SD)	Control ($n = 43$) (Mean ± SD)	p
Subcutaneous fat thickness (mm)	25.86 ± 9.03	18.83 ± 8.45	0.01
Preperitoneal fat thickness (mm)	18.37 ± 7.34	13.91 ± 5.37	N S
Visceral fat thickness (mm)	57.67 ± 26.2	38.24 ± 14.7	<0.01
Midtigh fat thickness (mm)	29.06 ± 7.03	25.73 ± 8.29	NS
Carotid intima media thickness (mm)	0.53 ± 0.10	0.45 ± 0.19	<0.01

history of smoking were excluded in order to increase the power of the study. We found that the mean carotid artery IMT was significantly higher in PCOS cases compared to control group, and the mean values both for PCOS and control groups were comparable with previous studies [5,21,22]. However, Vural et al. [7] detected higher carotid artery IMT in a study involving mainly PCOS patients in early adulthood. Although age, BMI and WHR were lower and the mean Ferriman–Gallwey score was similar between two studies, they detected higher values. This discrepancy may be due to the smokers they included in their study.

In this study, not only body weight, but also BMI, WHR and WC were similar between PCOS and control groups in order to avoid confounding factor of WC and obesity. Janssen et al. [23] suggested that WC is more informative than BMI in indicating cardiovascular risk factor and for a given body mass index, patient with greater WC have higher obesity related risk. For all these reasons, WC and WHR may be valuable parameters in daily practice in the assessment of metabolic risks in PCOS. One of the major findings of this study is that carotid artery IMT was significantly correlated with age, BMI and WHR in PCOS patients, whereas no correlation was detected in the control group. The most likely explanation is that, altered hormonal milieu and lipid profile trigger the events leading to increased carotid artery IMT in PCOS, and increasing age, BMI and abdominal fat deposition play important role in the progression of atherosclerosis. Since it is not possible to modify the age, control of BMI and WHR are important for the cardiovascular health of PCOS patients.

A common feature of obesity and PCOS is the insulin resistance. The problems related to glucose metabolism and insulin resistance were shown to be seen in different rates in PCOS patients [24–26]. In this study, we detected significantly higher fasting insulin levels and insulin resistance as estimated by HOMA-IR in the PCOS patients. Is it related to PCOS or the obesity? Since, age and body mass indexes were similar, it is likely to be related to PCOS. However, visceral fat which was shown to be well correlated with HOMA-IR index was measured thicker in PCOS group. In studies including lean PCOS patients, slight or no increase in glucose intolerance was detected [27,28]. Therefore risk factor for insulin resistance may be neither the presence of PCOS nor the obesity, but the abdominal fat accumulation itself. Since all these problems are closely interrelated, larger controlled studies with subjects having not only similar age and weight, but also similar fat distribution are needed. Whatever the reason is, PCOS patients seem to have increased risk for both cardiovascular disease and insulin resistance. Obesity is probably both a triggering factor and the result in the pathophysiology of PCOS, and weight control should be encouraged in addition to medications.

There were a few limitations in our study. First, it was a hospital based study with a relatively small sample size. The second, we used ultrasonography in the measurement of fat thickness because it was defined as the best cost effective method at the moment [29]. Although computerized tomography and magnetic resonance imaging are more accurate methods in the measurement of the fat thickness, exposure to ionizing radiation in the former and the high cost in the later limit their usage.

In conclusion, PCOS patients show different fat partitioning compared to normal subjects. Fat accumulation is more prominent in visceral and subcutaneous regions. Increased BMI, WHR and abdominal type of obesity are closely related to the increased carotid artery IMT. Increased visceral type of obesity in PCOS is the most important factor for the insulin resistance. Since the risk of cardiovascular disease is increasing with age, weight control and regional weight loss are important part of the treatment for the future health of women with PCOS.

***Declaration of interest*:** The authors declared no conflict of interest.

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