Body composition, fat distribution and metabolic characteristics in lean and obese women with polycystic ovary syndrome

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ABSTRACT. The polycystic ovary syndrome (PCOS), characterized by chronic anovulation and hyperandrogenism, has many features of metabolic syndrome and can be considered a metabolic disease. Approximately 50% of patients with PCOS are overweight or obese with abdominal fat accumulation. Some metabolic alterations and abdominal fat distribution have also been reported in lean women with PCOS. The aim of this study was to evaluate the effect, if any, of obesity on metabolic features, body composition and fat distribution in patients with PCOS. Body composition and abdominal fat distribution (evaluated by DEXA), waist circumference, blood pressure, lipid profile, glucose tolerance and homeostasis model assessment index were determined in 23 lean [mean age 23±5 yr, mean body mass index (BMI) 22±2 kg/m^2] and 27 overweight-obese (mean age 21±5 yr, mean BMI 32±5 kg/m^2) patients with PCOS and in 20 age- and weight-matched eumenorrhoic women. Patients exhibited slight but non-significant differences in metabolic parameters, waist circumference, blood pressure and total and abdominal fat content compared with weight-matched controls. None of the lean subjects suffered from metabolic syndrome according to the National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATPIII) criteria as opposed to 10 overweight-obese patients and three overweight-obese control subjects (37% and 33.3% of each subgroup, respectively). Our data do not show significant metabolic alterations in lean PCOS women. Results indicate that obesity seems to underpin the metabolic alterations exhibited by the overweight-obese patients. However, since women with PCOS are at increased cardiovascular risk, further studies are needed to evaluate metabolic alterations and body composition in these patients.
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INTRODUCTION

Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders of women of reproductive age, affecting 5-10% of this population (1-4). It is characterized by hyperandrogenism of ovarian origin and chronic anovulation not connected with other causes of hyperandrogenism, such as adult-onset congenital adrenal hyperplasia, hyperprolactinemia and androgen-secreting neoplasms (5-7). Several features of metabolic syndrome (MS), particularly insulin resistance and hyperinsulinemia, are observed in most women with PCOS (8-14) and have important health implications later in life, signally an increased risk of cardiovascular (CV) and metabolic disease (15-17). Obesity is very common in women affected by PCOS: approximately 50% are overweight or obese (18) and the history of the weight gain often precedes the onset of oligomenorrhea and hyperandrogenism, suggesting a pathogenic role of obesity in the subsequent development of the syndrome (19).

Preponderant fat localization to upper body sites has been reported in overweight women with PCOS (20) and associations with glucose intolerance, insulin resistance, hypertension, atherosclerosis, and hyperlipidemia have been suggested (21-23).

Although metabolic alterations and abdominal fat distribution have also been reported in lean women with PCOS, these findings are not conclusive (24, 25).

The aim of this study was to compare the metabolic features, body composition and fat distribution in lean and overweight-obese women with PCOS and in weight-matched eumenorrhoic controls.

Key-words: Body composition, fat distribution, metabolic characteristics, lean PCOS, fat PCOS.

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MATERIALS AND METHODS

Subjects

Fifty Caucasian women with PCOS (mean age=22±5 yr) and 20 eumenorrhoic controls (mean age=26±4 yr) matched for age and body mass index (BMI) were studied. Diagnostic criteria were oligomenorrhea (≤6 menses per yr) or amenorrhea (absence of menses for ≥3 months), and hyperandrogenemia or clinical manifestations of hyperandrogenism (Ferriman-Gallway hirsutism score >8 (26), acne, alopecia). According to the National Institute of Health (NIH) criteria (5), related disorders with similar clinical presentation, such as adult-onset congenital 21-hydroxylase deficiency, hyperprolactinemia and androgen-secreting tumors, were excluded. A polycystic ovarian morphology at ultrasound was not considered a critical diagnostic criterion since this feature is found in approximately 20% of normal women (27-29). However, since it may be associated with subclinical alterations of ovarian cyclicity (30, 31), all subjects underwent ultrasound pelvic scanning; only healthy subjects with normal scans were enrolled in the study as control subjects.

Patients were subdivided into lean and overweight-obese based on BMI (≤ 25 kg/m^2 and >25 kg/m^2, respectively). Of the 50 patients, 23 were lean (l-PCOS: mean age =23±5 yr; mean BMI=22±2 kg/m^2) and 27 were overweight-obese (f-PCOS: mean age=21±5 yr; mean BMI=32±5 kg/m^2). Selection criteria of the 20 control subjects (mean BMI=27±9 kg/m^2) were regular menstrual cycles (25-35 days) and absence of hirsutism or acne. There were 12 lean (l-C: mean age=26±3 yr, mean BMI=20±1.3 kg/m^2) and 8 overweight-obese (f-C: mean age=24.7±4.8 yr, mean BMI=37±5.9 kg/m^2) controls. All the subjects enrolled in the study were in good health, had no chronic or acute diseases, and for at least 3 months had not been taking any medication known to affect sex hormone metabolism, such as oral contraceptives. All were studied in the early follicular phase (1-8 days) of the cycle or after 3 months of amenorrhea. Progesterone levels were determined in all subjects to exclude a recent ovulation.

The study was approved by the local Ethics Committee and informed written consent was obtained from each subject.

Clinical evaluation

Weight, height, waist circumference, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), and the Ferriman-Gallway score of hirsutism were determined in all subjects.

BMI was calculated using the formula: weight (kg)/height (m^2).

The waist was measured as the lowest value between the xyphoid process and the umbilicus according to WHO criteria (32). Anthropometric and blood pressure (BP) measurements were taken by the same physician and are reported in Table 1.

Biochemical measurements

Blood samples were collected in fasting condition. Total and high-density lipoprotein (HDL)-cholesterol and triglycerides were evaluated. An oral glucose tolerance test (OGTT), performed according to WHO criteria (75 g glucose), was administered to assess insulin secretion and glucose tolerance. Plasma glucose and insulin concentrations were measured at 0, +30, +60, +90, and +120 min. Insulin levels were determined using an immunometric assay (Immulite 2000; DPC, Los Angeles, CA); plasma glucose was measured by photometric determination using the glucose dehydrogenase method. Diagnosis of diabetes mellitus or glucose intolerance was made according to American Diabetes Association (33) and WHO (34) criteria.

Blood samples were collected in the early follicular phase (1-8 days) of the menstrual cycle or after 3 months of amenorrhea to evaluate free testosterone, androstenedione and dehydroepiandrosterone-sulphate (DHEA-S). Free testosterone was measured using RIA commercial kits (Free Testosterone Bridge, Adaltis, Italy), even though their accuracy has come under the criticism of some researchers (35, 36). Androstenedione levels were measured with a RIA commercial kit (RADIM, Italy). DHEA-S concentrations were determined using a commercial competitive immunoassay kit (Immulite 2000; DPC, Los Angeles, CA).

Insulin sensitivity

Although the hyperinsulinemic euglycemic glucose clamp technique is the best accepted method for estimating insulin sensitivity, it is invasive, time-consuming, expensive, and rather complex. Recently, however, various simple indexes of insulin sensitivity, derived from an oral glucose tolerance test (37, 38) or based on fasting glucose and insulin levels (39, 40), have been seen to well correlate with it. We used the fasting serum insulin concentration and the homeostasis model assessment index (HOMA) (39), which was calculated as follows:

[fasting plasma glucose (mmol/l) x fasting insulin (mU/l)] / 22.5

Body composition

Fat mass and lean tissue were measured using total-body DEXA scanner (DPX Lunar Radiation, Madison WI; software version 3.61) to study total body and three standard regions: trunk (chest, abdomen and pelvis), arms and legs. Abdominal fat between L2 and L4 vertebrae, an area shown by the magnetic resonance imaging (MRI) to exhibit a relatively high visceral and low subcutaneous fat content, was also measured by DEXA (standard software option). To exclude some subcutaneous fat, the lateral margins of the abdominal regions were aligned with the outer edge of the ribcage (41, 42). Unlike the computerized tomography (CT), the DEXA-measured fat mass does not include only adipose tissue, but it is the sum of all soft tissue fatty elements. Despite this, measures of total (visceral plus anterior and posterior subcutane-

Table 1 - *Clinical and metabolic parameters in 50 patients with polycystic ovary syndrome (PCOS) - 23 lean (l-PCOS) and 27 overweight-obese (f-PCOS)- and 20 eumenorrhoic control - 12 lean (l-C) and 8 overweight-obese (f-C).*

	l-PCOS	f-PCOS	l-C	f-C
Age (yr)	23±4.9	21±4.8	26±3	24.7±4.8
BMI (kg/m^2)	22±2	32.6±5.3	20±1.3	37±5.9*
Waist (cm)	68.8±2.7	98.3±9.9	69±3.7	102±11.7
SBP (mm Hg)	112±10	123±17	115±14	125±13
DBP (mm Hg)	73±9	80±10	125±13	79±6
Tot Chol (mg/dl)	183±28	177±49	180±28	168±36
HDL (mg/dl)	56±17	42±7	56±13	45±17
TG (mg/dl)	52±21	89±60	63±24	93±34
Glucose 120′ (mg/dl)	95±32	116±21	109±18	106±19
Insulin (μU/ml)	9±6	17±14	7±3	16±6
HOMA	1.6±0.9	3.7±3.4	1.4±0.7	3.4±1.3§

Values are expressed as mean±SD. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; Tot Chol: total cholesterol; TG: tryglycerides; *p<0.05 overweight-obese subgroups vs lean subgroups; §p<0.05 f-C vs lC.

ous fat) and abdominal fat made with DEXA correlate highly with intra-abdominal fat as determined by CT (42, 43) and MRI (44, 45). DEXA scans require about 30 min and have 2-3% precision for soft tissue (46). Subjects, wearing light clothing, were weighed and measured without shoes. The entire body was scanned, beginning from the top of the head. Different scan modes were adopted for different body sizes. Total body scans were done and analyzed by the same physician.

Statistical analysis

Data are expressed as mean±SD. Comparisons between patients and controls were made using Student's unpaired t-test, and between subgroups using Student's unpaired t-test with Bonferroni's correction. Significance was set at $p<0.05$. Statistical analyses were performed using the Statview 4.1 package (Abacus Concepts Inc., CA).

RESULTS

Endocrine evaluation

Serum androstenedione and DHEA-S levels were significantly higher in lean patients than in weight-matched controls ($p<0.05$) (Table 2). Free testosterone levels were slightly but not significantly higher in patients than in weight-matched controls.

Blood pressure

Mean BP values did not differ significantly between patients and weight-matched controls (Table 1). Only 1 patient had hypertension (aged 35, BMI=31 kg/m^2).

Lipids

Differences in total and HDL cholesterol and triglycerides between patients and control subjects were not significant, HDL levels being slightly higher and triglycerides slightly lower in both lean subgroups (Table 1).

Glucose metabolism

None of the subjects had diabetes mellitus. OGTT indicated that 4 obese subjects (3 patients and 1control) had glucose intolerance.
Fasting insulin levels and HOMA index did not show significant differences between patients and weight-matched controls, whereas HOMA was significantly higher in f-C than in l-C subjects ($p<0.05$) (Table 1).

Table 2 - *Hormonal parameters in 50 patients with polycystic ovary syndrome (PCOS) - 23 lean (1-PCOS) and 27 overweight-obese PCOS women (f-PCOS) - and 20 eumenorrhoic women - 12 lean contols (l-C) and 8 overweight-obese controls (f-C).*

	l-PCOS	f-PCOS	l-C	f-C
Free Test. (pg/ml)	1.7±0.98	2.7±2.2	0.7±0.6	1.4±1
Androstenedione (ng/ml)	3.2±1.6*	2.7±1.5	1.5±0.7	1.6±0.7
DHEA-S (µg/ml)	2.8±0.7*	2.7±1.3	1.6±1.1.	1.7±0.6

Values are the mean±SD. *$p<0.05$ l-PCOS *vs* l-C.

Waist circumference

Values for this parameter were not significantly different between patients and weight-matched controls (Table 1).

Body composition

Body composition and abdominal fat content (L2-L4) did not differ significantly between patients and weight-matched controls (Fig. 1).

Metabolic syndrome

None of the lean subjects suffered from MS according to the National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATPIII) criteria (47) as opposed to 10 overweight-obese patients and 3overweight-obese control subjects (37% and 33.3% of each subgroup, respectively), albeit this difference was not significant.

DISCUSSION

In this study we compared metabolic parameters, DEXA-measured body composition and fat distribution in lean and overweight-obese PCOS patients and in weight-matched controls.
The metabolic data (blood pressure, lipid pattern, fasting glucose and insulin) did not exhibit significant differences between patients and weight-matched controls.
Metabolic features have extensively been studied in relation to CV risk, and significant differences have been reported between PCOS patients and controls (15-17, 48-51). However, although most authors report an increased risk of cardiovascular disease in PCOS patients, not all studies make a distinction between the effect of obesity and the effect of the syndrome on metabolic parameters.
Investigations comparing patients based on BMI reported differences between PCOS and control subjects only for some CV risk indicators (52). Holte et al. (48) found higher insulin resistance indices (calculated with the hyperinsulinemic euglycemic clamp) and free fatty acids levels in PCOS than in eumenorrhoic subjects. In obese patients with PCOS the sum of truncal-abdominal skinfolds was also greater than in control subjects with the same BMI. The authors explain the absence of other alterations of the lipid profile with the interaction of diverse factors including hyperandrogenism, hyperestrogenism due to peripheral androgen aromatization, low levels of SHBG and progesterone deficiency.

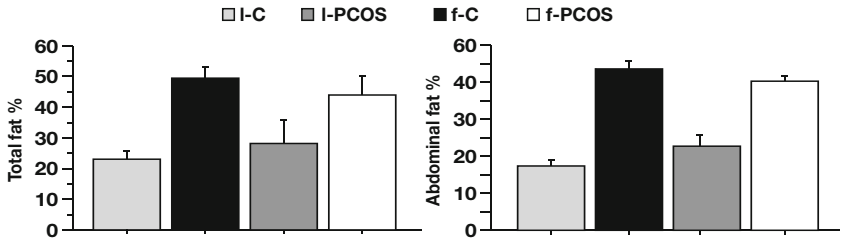

Fig. 1 - *Body composition and fat distribution measured by DEXA in 50 patients with polycystic ovary syndrome (PCOS) -23 lean (l-PCOS) and 27 overweight-obese (f-PCOS)- and in 20 eumenorrhoic subjects -12 lean (l-C) and 8 overweight-obese (f-C) controls.*

Although our data did not evidence significant differences in the metabolic parameters investigated, the overweight-obese subjects with and without PCOS shared a high incidence of metabolic syndrome; by contrast, none of the lean patients nor, as expected, any lean control subject, had metabolic syndrome. In our patients obesity, rather than PCOS, thus seems to be a critical factor in determining MS. Obesity, which is associated with an increased incidence of arterial hypertension, glucose intolerance, diabetes mellitus, and dyslipidemia (53-55), is an important risk factor for CV diseases. This is particularly true of central obesity, indeed waist circumference is among the simplest and most reliable indicators of CV risk. Although waist-hip ratio (WHR) is the most common method to identify subjects at increased risk of CV, recent studies indicate that measurement of waist circumference is sufficient and that it is more strongly related to the health risks associated with obesity (56).

The absence of significant metabolic alterations in our patients may also be due to their young age and thus to short disease duration, although significant metabolic alterations and increased CV risk have been reported in adolescents with PCOS; some studies include only overweight-obese adolescents (15, 57).

We found no significant differences in body composition and fat distribution between patients with PCOS and weight-matched controls.

The literature is not conclusive in this respect, some studies reporting a greater amount of abdominal fat in both lean and obese PCOS patients than in eumenorrhoic controls (24), others finding no differences in central adipose mass between lean patients with PCOS and weight-matched controls (25), and others still reporting a smaller amount of fat and a greater amount of muscle tissue - connected with hyperandrogenism - in lean PCOS patients (58).

The different results obtained, compared with other studies may depend on sample characteristics as well as on methodological differences in the evaluation of central fat content. Indeed, in addition to the composition of the whole body, we also determined abdominal fat content in L2-L4, a region with a greater content of visceral than subcutaneous fat, thus a better index of visceral fat. Although DEXA allows to determine total as well as regional body composition, especially at the abdominal level (41, 42), it cannot distinguish subcutaneous fat in the intra-abdominal adipose tissue. However, a recent study has suggested that central fat distribution measured with DEXA is a useful marker of insulin sensitivity in healthy subjects, and that a simple measurement of the total (visceral plus anterior and posterior subcutaneous fat) abdominal adipose mass is highly predictive of health risks and may be as valuable as measuring intra-abdominal fat depots (59). A strong correlation between DEXA-measured central abdominal fat and visceral fat measured by CT (43) or MRI (44) has recently been described. Our data are in line with those of Remsberg et al. (52), who studied body fat distribution in PCOS and healthy women using DEXA and CT, and demonstrated no significant difference in visceral fat content between PCOS women and BMI-matched eumenorrhoic controls.

In conclusion, overweight-obese women with and without PCOS included in the present study exhibited both a large amount of total and abdominal body fat and metabolic alterations compatible with MS. These data point to a greater role for obesity, rather than PCOS, in determining the endocrine-metabolic alterations affecting overweight-obese patients with PCOS and the attendant increased CV risk. Based on these data, it may be hypothesized that, like several other endocrine disorders such as diabetes mellitus, PCOS is a heterogeneous disease underpinned by multiple pathogenic mechanisms. Genetic studies of PCOS patients have evidenced varied polymorphisms and genetic alterations. Diverse deficits probably underlie the development of PCOS, and different genotypes are likely to lead with time to expression of similar phenotypes. Obese PCOS patients frequently exhibit the features of metabolic syndrome, but it is unclear at present whether PCOS precedes obesity, insulin resistance and the other endocrine-metabolic abnormalities or rather whether insulin resistance and obesity have a role in its onset. In lean PCOS patients the effects of hyperandrogenism, which involves anovularity and hirsutism, probably prevail but, although our lean patients did not exhibit metabolic alterations, they have been reported in other studies (47,

60). Further investigations with long-term follow-up are thus required to monitor the evolution of the metabolic pattern in patients with PCOS, especially lean ones.

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