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Original Article

Polycystic ovary syndrome patients with high BMI tend to have functional disorders of androgen excess: a prospective study

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Abstract

Biochemical or clinical changes of hyperandrogenism are important elements of polycystic ovary syndrome (PCOS). There is currently no consensus on the definition and diagnostic criteria of hyperandrogenism in PCOS. The aim of this study was to investigate the complex symptoms of hyperandrogenic disorders and the correlations between metabolism and hyperandrogenism in patients with PCOS from an outpatient reproductive medicine clinic in China. We conducted a case control study of 125 PCOS patients and 130 controls to evaluate differences in body mass index (BMI), total testosterone (TT), modified Ferriman–Gallwey hirsutism score, sex hormone binding globulin (SHBG), homeostasis model assessment-estimated insulin resistance (HOMA-IR) and free androgen index (FAI) between PCOS patients and controls and subgroups of PCOS. The prevalence of acne and hirsutism did not differ significantly between the hyperandrogenic and non-hyperandrogenic subgroup. Patients with signs of hyperandrogenism had significantly higher BMI ($P < 0.05$), but differences in TT, SHBG, FAI and waist/hip ratio were insignificant. The odds ratio of overweight was calculated for all PCOS patients. Our results suggest that PCOS patients with high BMI tend to have functional disorders of androgen excess; therefore, BMI may be a strong predictor of hyperandrogenism in PCOS.

Keywords: polycystic ovary syndrome, diagnostic criteria, obesity, reproductive health, long-term weight

Introduction

Polycystic ovary syndrome (PCOS), a heterogeneous condition associated with irregular menstrual cycles and androgen excess, is a common gynecological endocrine disorder affecting 6%-12% of premenopausal women[1]. Since the National Institutes of Health (NIH) sponsored conference on PCOS in 1990, it has become appreciated that the syndrome encompasses a broader spectrum of signs and symptoms of ovarian dysfunction than those defined by the original diagnostic criteria[2]. The 2003 Rotterdam consensus workshop concluded that PCOS is a syndrome of two of three criteria: oligo- or anovulation; clinical and/or biochemical signs of hyperandrogenism; polycystic ovaries on ultrasonography (excluding other etiologies). PCOS can be suspected if only one of the following two criteria is met: (I) clinical signs of hyperandrogenism or biochemical hyperandrogenism; (Π) polycystic ovaries on ultrasonography. Even with these clinical requirements, PCOS cannot be confirmed until other factors that give rise to hyperandrogenism and ovulation failure

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have been excluded. Hyperandrogenism is a complex and variable syndrome that has not been clearly defined in PCOS. Hirsutism is a common manifestation of hyperandrogenism; other clinical signs of androgen excess include acne, seborrhea, androgenic alopecia and virilization[3]. Virilization, including clitoromegaly, deepened voice, increased muscle mass and decreased breast size, is less uncommon. These clinical signs are usually associated with markedly elevated levels of circulating androgen from ovarian or adrenal tumors, but controversies remain, including racial differences.

There is considerable heterogeneity in clinical studies among women with hyperandrogenism and there could be multiple clinical phenotypes, even in a single patient at different age. Andy *et al.*[4], in a study of 716 patients diagnosed with PCOS, found that the prevalence of hyperandrogenemia, acne and hirsutism [modified Ferriman–Gallwey (mF-G) score >6] in PCOS was 75.3%, 14.5% and 72.2%, respectively. Reilly *et al.*[5] found a significantly higher prevalence of acne and signs of hyperandrogenism in women with polycystic ovaries compared with those with normal ovarian morphology. The prevalence of acne in women with PCOS has been estimated to be 10%-34%, which is significantly higher than that in normal women[6]. Conversely, Demir *et al.* found no correlation between serum total testosterone levels and the prevalence of hirsutism in patients with PCOS[7]. Moreover, about 50% of normal women with acne do not have clinical or biochemical evidence of hyperandrogenism. Ozdemir *et al.* inferred that acne is not associated with hormonal variables, but that hirsutism has a positive association with total testosterone in PCOS[8]. These issues have led to confusion and reflect lack of understanding about hyperandrogenism in PCOS, and asynchronicity between clinical metabolic signs and hyperandrogenism needs to be explained. This study was designed to investigate the complex symptoms of hyperandrogenic disorders and correlations between metabolism and hyperandrogenism in patients with PCOS from an outpatient reproductive medicine clinic in China.

Materials and methods

Subjects

We studied 125 Chinese adult women with PCOS diagnosed according to Rotterdam Criteria and 130 women with regular menses as controls. They were aged 21-36 years. Subjects with other reproductive endocrinology diseases and metabolism disorders were excluded. The subjects were prospectively recruited among outpatients at Center for Reproductive Medicine of Jiangsu Province Hospital from October, 2013 to December, 2014. The study protocol was approved by the institutional review board of the Research Institute for Endocrine Sciences. All subjects provided signed informed consent.

Study protocol

The diagnosis of PCOS was based on the revised criteria of the 2003 European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine[2]: (1) oligomenorrhea and/or anovulation (eight or fewer menstrual cycles in 1 year or menstrual cycles >35 days in length); (2) clinical and/or biochemical signs of hyperandrogenism; (3) polycystic ovaries (presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume >10 mL) and exclusion of other etiologies (e.g. congenital adrenal hyperplasia, androgen secreting tumors, Cushing's syndrome). Patients who had received hormone therapy in 3 months before initiation of our study were excluded to avoid sex hormone interference. The clinical data of 130 reproductive-aged women with normal menses period were collected as control. None of the subjects used any lipid-lowering or antihypertensive drugs. All of the women were in good health. We used questionnaires to obtain information of their medical history, family history, lifestyle, hormone levels and clinical signs of hyperandrogenism (e.g. hirsutism, acne). Body mass index (BMI) was calculated as weight (kg)/height (m^2). According to the Asia–Pacific criteria of BMI for obesity, BMI $\geqslant$25 kg/m^2 was defined as overweight[9]. Waist:hip ratio (WHR) was calculated as waist circumference (cm)/hip circumference (cm) and used to measure abdominal obesity[10]. We divided the PCOS patients into 2 subgroups: hyperandrogenism (HA)/non-hyperandrogenism (NHA) and the groups with hyperandrogenism signs (HS) /non-hyperandrogenism signs (NHS) according to their serum total testosterone and clinical signs of androgen excess. Hyperandrogenism was defined as total testosterone (nmol/L) higher than the 95% confidence interval (CI) of the control group (2.67 nmol/L), patients with higher total testosterone belonged to the HA Group. Clinical signs of hyperandrogenism were acne, hirsutism, seborrhea, androgenic alopecia and virilization. Patients with one of clinical hyperandrogenic signs were assigned to the HS group, and others were in the NHS group. The amount of excess terminal hair growth was assessed using the mF-G method, scoring the presence of terminal hairs over nine body areas (upper lip, chin, chest, upper and lower abdomen, thighs, upper and lower back, and upper arms) from 0 to 4, hirsutism was defined as mF-G score $\geqslant$6[11]. The presence of acne and seborrhea was also recorded, though there is no specific scoring system for this factor.

Clinical and biochemical measurements

Clinical variables including waist circumference, hip circumference, body weight and height were assessed in all subjects. Whole blood was sampled on day 2–3 of the menstrual cycle or during amenorrhea in PCOS patients. Basal sex hormone levels were measured in all PCOS and control subjects, including serum luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, prolactin and total testosterone. Total testosterone and sex hormone binding globulin (SHBG) were measured by radioimmunoassay (North Institute of Biological Technology, Beijing, China) and analyzed using an automatic clinical chemistry analyzer (Olympus AU5400). Free androgen index (FAI = total testosterone/SHBG × 100%) was used to evaluate free testosterone levels[12]. To evaluate glucose metabolism in PCOS, we calculated the homeostasis model assessment-estimated insulin resistance (HOMA-IR) value[13].

Statistical analysis

Data analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). All parameters were given as mean ± standard deviation. Independent *t*-test was used to compare difference between two groups. Correlations between age and PCOS related parameters were evaluated using Pearson's correlation coefficients with two-tailed significance tests. Chi-square analyses were used to compare the prevalence of acne, hirsutism and obesity between PCOS subgroups. We calculated prevalence and 95% CIs for the various groups, and odds ratio (OR) was determined for symptoms. Categorical variables were compared by the chi-square or Fisher's exact test as appropriate. $P < 0.05$ was considered statistically significant.

Results

Of the 125 PCOS patients, 5.6% were obese (BMI ⩾ 30 kg/m^2), 9.6% overweight (BMI 25-30 kg/m^2) and 66.4% underweight (BMI < 25 kg/m^2). Fifty-six patients had a family history of metabolic disease. Among them, 14.4% (13/125) had type 2 diabetes, 4.8% (6/125) had cardiac or cerebrovascular disease, 25.6% (32/125) had hypertension, 2.4% (3/125) had malignant tumor and 1.6% (2/125) had PCOS.

Table 1 shows the clinical characteristics of PCOS patients and controls. BMI, total testosterone, LH/FSH, SHBG and FAI of PCOS patients were significantly higher than those of the control group.

As shown in ***Table 2***, there was no significant difference in mF-G score or WHR between the HA and the NHA groups. Compared with the NHA group, the HA group showed no significant elevation of HOMA-IR and WHR.

***Table 1*. Comparison of clinical characteristics of PCOS group and controls (mean±SD)**

Parameter	PCOS, n = 125	Control, n = 130	P value
Age	27.92 (2.13)	28.37 (2.78)	0.14
BMI (kg/m^2)	24.04 (3.4)	21.57 (2.96)	<0.0001***
TT (nmol/L)	2.29 (0.99)	1.25 (0.77)	<0.0001***
LH/FSH	1.59 (0.83)	0.62 (0.53)	<0.0001***
SHBG (nmol/L)	44.42 (42.12)	59.53 (30.07)	<0.0001***
FAI (TT/ SHBG)	0.099 (0.10)	0.036 (0.029)	<0.0001***

BMI: body mass index; TT: total testosterone; LH: luteinizing hormone; FSH: follicle stimulating hormone; SHBG: sex hormone binding globulin; FAI: free androgen index.
***$P < 0.0001$.

Our data indicated that PCOS patients with general clinical signs of hyperandrogenism tended to have a higher BMI than patients without clinical signs (P = 0.002), whereas total testosterone, SHBG and WHR showed no significant differences between these two groups (***Table 3***). HOMA-IR was similar in PCOS patients with signs of hyperandrogenism (HS group) to that in patients without signs (t = −0.026, P = 0.967).

As shown in ***Table 4***, the ORs for hirsutism was 1.866, but there was no significant correlation between these clinical signs of androgen excess and PCOS. The OR of acne was significantly lower in PCOS patients with hyperandrogenism (P = 0.01). The OR was 2.27 (95%CIs: 1.22-4.2, P = 0.009) for overweight, which suggested that women with a high BMI had a significantly higher risk of PCOS.

As shown in ***Table 5***, PCOS patients with hyperandrogenism showed no significant increase in acne or hirsutism (P = 0.72, OR = 3.36, 95%CI: 0.54–20.9; P = 0.25, OR = 0.61, 95%CI: 0.26–1.41, respectively).

***Table 2*. Comparison of clinical characteristics of PCOS HA and NHA groups(mean±SD)**

Parameter	PCOS HA, n = 40	PCOS NHA, n = 85	P value
Age	26.15 (3.11)	26.87 (3.00)	0.53
BMI (kg/m^2)	25.38 (4.23)	23.65 (3.2)	0.017*
mF-G score	2.57 (3.8)	2.44 (3.22)	0.846
TT (nmol/L)	3.34 (0.73)	1.75 (0.59)	<0.0001***
SHBG (nmol/L)	34.10 (31.48)	57.25 (58.12)	0.018*
FAI (TT/SHBG)	0.19 (0.12)	0.054 (0.05)	0.000**
WHR	0.83 (0.07)	0.82 (0.07)	0.379
HOMA-IR	2.83 (1.38)	2.39 (1.29)	0.08

HA: hyperandrogenism; NHA: non-hyperandrogenism; Hyperandrogenism is defined as TT (nmol/L) higher than the 95% confidence interval of the control group (2.67 nmol/L); BMI: body mass index; TT: total testosterone; SHBG: sex hormone binding globulin; FAI: free androgen index. WHR: waist-hip circumference rate; HOMA_IR:homeostasis model assessment-estimated insulin resistance. *$P < 0.05$, **$P < 0.001$, ***$P < 0.0001$.

***Table 3*. Comparison of clinical characteristics of PCOS HS and NHS groups (mean±SD)**

Parameter	PCOS with HS, $n = 50$	PCOS without HS, $n = 75$	P value
Age	28.35 (2.94)	28.59 (2.97)	0.26
BMI (kg/m^2)	25.26 (4.01)	23.15 (3.51)	0.002*
SHBG (nmol/L)	49.73 (49.51)	44.28 (28.20)	0.43
TT (nmol/L)	2.08 (1.07)	2.26 (1.00)	0.33
FAI	0.082 (0.087)	0.10 (0.12)	0.36
WHR	0.80 (0.14)	0.81 (0.11)	0.65
HOMA-IR	2.67 (0.95)	2.66 (1.51)	0.976

HS, hyperandrogenism signs; NHS: no hyperandrogenism signs. BMI: body mass index; TT: total testosterone; SHBG: sex hormone binding globulin; FAI: free androgen index. WHR: waist-hip circumference rate; HOMA_IR: homeostasis model assessment-estimated insulin resistance.
*$P < 0.05$.

***Table 4*. Prevalence and OR value of hyperandrogenism signs compared between PCOS and control groups**

	Hirsutism	Acne	Overweight*
Prevalence (%)			
Control $n = 130$	5.4	21.5	14.6
PCOS $n = 125$	9.6	8	28
OR	1.866	0.382	2.27
X^2	1.64	6.4	6.84
P value	0.2	0.01*	0.009*

*$P < 0.05$.
Hirsutism was defined as mF-G score ⩾6.
Overweight was defined as BMI ⩾25 kg/m^2.

The HA group had higher BMI and lower SHBG than the NHA group ($P = 0.017$, $P = 0.018$, ***Table 2***) and a higher risk of overweight (OR = 4.41, 95%CI: 1.78–9.67, $P = 0.001$). However, hirsutism, acne and abdominal obesity were not significantly more common in the HA group than in the NHA group. The standard deviation of the mean value of SHBG in both PCOS patients and controls was high (31.48, 52.18), representing a large range of variation.

Discussion

About 30% of women with PCOS have hyperandrogenism – a clinical and/or biochemical excess of androgens. Acne and hirsutism are generally considered the primary clinical indicators of androgen excess. Testosterone is the major circulating form of androgen. More than 90% of plasma testosterone is bound to SHBG, so FAI level in plasma is a more sensitive indicator of hyperandrogenism than total testosterone[14]. Obesity significantly affects the circulating concentrations of total testosterone and SHBG. In adult women with hirsutism and PCOS, obesity is associated with increased total testosterone and decreased SHBG, which results in significantly elevated free and bioavailable testosterone[15]. In this study, we found that PCOS patients with clinical signs of hyperandrogenism tended to have a higher BMI than PCOS patients without signs. However, the differences in serum total testosterone and SHBG were insignificant between PCOS patients with and without the symptom of hyperandrogenism. PCOS patients and normal women seemed to have equal risks of suffering from hyperandrogenism.

Clinical symptoms of hyperandrogenism include acne, hirsutism, seborrhea, androgenic alopecia and virilization. In PCOS patients, acne, seborrhea and hirsutism are the most common signs, because the areas where these occur express the androgen receptor (AR)[16]. AR localization in women could be similar in different areas of skin[17]. Choudhry *et al.*[18] reported the expression of ARs in keratinocytes within pilosebaceous ducts and concluded that androgen directly influences keratinization in the acne process. Acne is a chronic inflammatory disorder of the pilosebaceous unit resulting from increased sebum production induced by androgen, altered keratinization, inflammation and bacterial colonization of hair follicles on the face, neck, chest and back[19]. Hirsutism is the presence of excess hair growth in women and may indicate an underlying disorder of androgen production; in most cases, hirsutism results from a combination of mildly increased androgen production compared with non-hirsute women and increased skin sensitivity to androgens. The sensitivity of hair follicles to androgen is governed largely by 5α-reductase activity in the skin[20]. Androgen-independent hirsutism can be a familial trait (familial hypertrichosis) and is caused by several drugs[19]. Following a prospective controlled study, Slayden[21] reported that hyperandrogenemia was evident in most non-hirsute, acneic patients, regardless of age. Several studies have shown that there is no correlation between serum total testosterone and the prevalence of hirsutism in patients with PCOS[7,22], which is similar to our results. Although we did not find any significant results in our HOMA-IR analysis, another study has demonstrated that hyperandrogenism carried a significant risk of hyperinsulinemia because of stimulation of ovarian androgen secretion and inhibition of hepatic SHBG production[23]. Limitations of our study such as sample size and the sensitivity of our evaluation method may explain the lack of significant findings.

Our data show that BMI is potentially related to the endocrine environment of patients with PCOS. PCOS patients with higher BMI seemed more likely to suffer

***Table 5*. Prevalence and OR value of hyperandrogenism signs compared between PCOS HA and NHA groups**

	HA $n = 40$	NHA $n = 85$	HA $n = 40$	NHA $n = 85$	OR	X^2	*P* value
Hirsutism	7.5	2.4	0.554–18.3	0.86–1.04	3.36	1.87	0.72
Acne	25	35.3	0.38–1.30	0.91–1.47	0.61	1.325	0.25
Overweight	45	16.5	1.51–4.92	0.49–0.885	4.41	11.62	0.001*
Abdominal obesity	60	59	0.75–1.39	0.62–1.53	1.05	0.016	0.90

Hirsutism was defined as mF-G score ⩾6. Overweight was defined as BMI ⩾25 kg/m^2. Abdominal obesity was defined as WHR ⩾0.8. HA: hyperandrogenism; NHA: non-hyperandrogenism.
*$P < 0.05$.

hyperandrogenism or to exhibit the clinical signs of androgen excess. Especially, it is necessary to explore the pathogenesis of acne and hirsutism in women with high BMI. Increased adipose mass is associated with the production of numerous factors including aromatase, leptin, plasminogen activator inhibitor 1, insulin resistance and dyslipidemia, all of which can lead to tissue damage. Obese patients with PCOS have been shown to exhibit significantly more severe insulin resistance than obese women[24]. Insulin increases 17α-hydroxylase and 17-20 lyase (both are components of the P450c17 enzyme system) activity[25] and stimulates the expression of 3β-hydroxysteroid dehydrogenase in human luteinized granulosa cells[26]. However, insulin decreases SHBG, which results in concomitant elevation of free androgen tissue availability[27]. In a study of 265 cases, obese women with PCOS had a significantly higher prevalence of hirsutism than non-obese subjects[28], and our results are similar to this finding. However, following a study including 627 women in Taiwan, China, Yang *et al.* reported that obese women, regardless of serum testosterone level, had a lower incidence of acne than non-obese women[29]. We observed that some PCOS patients with normal BMI also presented clinical/biomedical hyperandrogenism. Lin *et al*.[30-31] have concluded that AR gene polymorphism influences androgen metabolism, which might explain this phenomenon.

In summary, serum testosterone and SHBG levels did not differ between PCOS patients with and without androgen excess. It is necessary to define clearly hyperandrogenism in PCOS. Moreover, we prove that BMI is a more sensitive, at least an important supplementary, diagnostic criterion of clinical/biomedical hyperandrogenism in PCOS than total testosterone. It is therefore critical for PCOS patients with clinical signs of androgen excess to maintain a normal body weight.

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