Acta Obstetricia et Gynecologica. 2010; 89: 199–204

informa
healthcare

MAIN RESEARCH ARTICLE

Specific dermatologic features of the polycystic ovary syndrome and its association with biochemical markers of the metabolic syndrome and hyperandrogenism

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Abstract

Objective. To investigate biochemical and metabolic abnormalities in relation with cutaneous features of polycystic ovary syndrome (PCOS). *Design.* Prospective descriptive analysis. *Setting.* University-based tertiary care. *Sample.* One-hundred and fifteen untreated consecutive women diagnosed as having PCOS. *Methods.* Each woman underwent an evaluation of body habitus, acne, hirsutism, seborrhea, androgenic alopecia and acanthosis nigricans. Associations between cutaneous features and hormonal and metabolic parameters were analyzed by means of multivariate logistic regression models. *Main outcome measures.* Prevalence of cutaneous features in PCOS and associations among the features and biochemical and metabolic parameters. *Results.* The prevalence of acne, hirsutism, seborrhea, androgenetic alopecia and acanthosis nigricans was 53%, 73.9%, 34.8%, 34.8% and 5.2%, respectively. Acne was not associated with the hormonal, metabolic and anthropometric variables. Hirsutism had positive associations with total testosterone, fasting glucose and total cholesterol, and a negative association with age. Seborrhea was found to be related with free testosterone, fasting glucose and insulin. A negative association was determined among androgenic alopecia and free testosterone, low-density lipoprotein and insulin. *Conclusions.* Acne and androgenic alopecia are not good markers for the hyperandrogenism in PCOS. Hirsutism appears to be strongly related with hyperandrogenism and metabolic abnormalities in PCOS women.

Key words: *Polycystic ovary syndrome, cutaneous features, hyperandrogenism, metabolic abnormality*

Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent female endocrine disorder and is characterized by androgen excess and oligomenorrhea or amenorrhea (1,2). Genetic and environmental factors influence the prevalence and phenotype of PCOS. The development of obesity has negative effects on the clinical manifestations and endocrinologic profile of the disorder. Insulin also plays a role in pathogenesis of PCOS, acting to increase unbound and active androgen level by enhancing androgen production by theca cells and inhibiting hepatic synthesis of sex hormone–binding globulin (SHBG) (3). Dyslipidemia has been found to increase the risk of cardiovascular disease associated with PCOS (4). Cutaneous signs of hyperandrogenism in PCOS include hirsutism, acne, seborrhea, androgenic alopecia and acanthosis nigricans (AN). However, there is considerable heterogeneity in the clinical features and endocrinologic profiles among women with PCOS.

The development of the cutaneous features in PCOS is quite complex. Androgens play an important role in the development of the cutaneous features. Although positive or negative associations between androgens and the cutaneous features have been reported in the literature, the clinical manifestations

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(Received 13 April 2009; accepted 18 September 2009)

ISSN 0001-6349 print/ISSN 1600-0412 online
DOI: 10.3109/00016340903353284

of hyperandrogenism can be observed in the absence of biochemical hyperandrogenism (5,6). Hormonal and metabolic factors in PCOS influence each other. Therefore, the metabolic abnormalities may also contribute to occurrence or worsening of the cutaneous features in PCOS. The previous studies have usually investigated the association between androgens and the cutaneous features of the syndrome. However, there are limited data on the association between metabolic parameters and the cutaneous features.

In this prospective study, we aimed to investigate the associations between the cutaneous features and biochemical and metabolic changes in women with PCOS.

Material and methods

This prospective study was conducted between November 2006 and July 2008 at the gynecology outpatient clinic of Meram Medical Faculty. A total of 115 consecutive PCOS women aged between 15 and 41 years were included. The diagnosis of PCOS was made according to the consensus criteria adopted in May 2003 in Rotterdam (7). PCOS was diagnosed in the presence of two of the three following criteria: 10 or more follicles measuring 2–8 mm in diameter in each ovary and/or an echodense stroma defined polycystic ovaries on ultrasound (8) and/or oligomenorrhea (defined as fewer than six menstrual periods per year or a cycle duration of at least 45 days), and *clinical and/or biochemical signs of hyperandrogenism*. Levels of prolactin, thyroid stimulating hormone and 17-α-hydroxyprogesterone (17-α-OHP) were measured in all patients to rule out other causes of chronic anovulation. We excluded from our study patients with 17-α-OHP levels greater than 2 ng/mL and those taking hormonal medications or drugs such as atorvastatin calcium, simvastatin calcium, metformine hydrochloride or glipizide, which are known to affect lipid metabolism, during the two months preceding the study. The study was approved by the ethics committee of Meram Medical Faculty. Each patient gave written informed consent to participate.

The waist and hip circumferences were measured in centimeters at the level of the umbilicus (waist) and at the level of the greater trochanters (hip) by the same examiner (S.Ö.). Waist-to-hip ratios and body mass index (BMI; kg/m^2) were calculated, and blood samples were obtained on the second day of spontaneous menstruation for assessment of baseline levels of the following: follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), total testosterone (TT), free testosterone (FT), dehydroepiandrosterone sulfate (DHEAS), prolactin (PRL) and SHGB; total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides; and fasting plasma glucose and insulin (I). The free androgen index was calculated as TT level (in nmol/L) divided by SHBG level (in nmol/L) and multiplied by 100; insulin sensitivity was calculated as the glucose/insulin (G/I) index; and the homeostasis model assessment (HOMA) value was calculated as fasting glucose level (in mmol/L) multiplied by fasting insulin level (in μU/mL) and divided by 22.5.

To unify the measurement units, the values for testosterone were converted from ng/dL to nmol/L (1 ng/dL = 0.0347 nmol/L) and those for fasting glucose were converted from mg/dL to mmol/L (1 mg/dL = 0.0555 mmol/L).

The subjects were examined with regard to presence of acne, hirsutism, seborrhea, AN and hair loss due to androgenic alopecia by the same dermatologist (M.Ö). The presence of comedones on the face, neck, upper chest, upper back and upper arms were classified as acne (9); pigmented raised warty skin patches on the intramammary folds, nape of neck and antecubital fossae were classified as AN. Androgenic alopecia was evaluated according to Ludwig's classification. Hirsutism was assessed using the modified Ferriman-Gallwey (F-G) score, in which a score > 8 indicates hirsutism (10). The presence of greasy or oily and shiny skin on the nasolabial folds, the forehead or behind the ear and the hair were defined as seborrhea or oily skin (11). A questionnaire was given to each of the women for documenting their subjective skin type. Women were asked 'do you feel greasy or oily and shiny on your nasolabial folds, forehead or behind ear and hair?' and they chose an answer from two choices (yes or no).

Serum analysis

After overnight fasting, venous blood samples were drawn into serum separator, clot activator tubes (Vacuette line, Greiner Bio-One, Germany) for all assessments. The samples were allowed to stand 15 minutes at room temperature for clot formation and sera were then separated by centrifugation. Glucose and lipid concentrations were determined using Synchron LX20 analyzers (Beckman Coulter, Fullerton, California, USA) with original Beckman reagents by means of the following methods: the glucose oxidase and oxygen electrode method for glucose; the timed-endpoint method for triglycerides and TC, with three coupled enzymatic steps using glycerol kinase, glycerophosphate oxidase and horse radish peroxidase for triglycerides and two coupled enzymatic steps using

cholesterol esterase and cholesterol oxidase for TC; and the direct enzymatic method without precipitation (using kits from Randox Laboratories, Crumlin, UK) for HDL cholesterol, with LDL cholesterol concentrations calculated by the Friedewald formula. FSH, LH, E2, PRL, DHEAS, TT and SHBG concentrations were determined by chemiluminescent immunoassay using an Immulite 2000 immunoanalyzer (DPC–Siemens Healthcare Diagnostics, Deerfield, IL, USA) with original DPC reagents and analysis for FT was performed using a radioimmunoassay kit (BioSource Laboratories, Nivelles, Belgium).

Sample size and statistical analysis

The sample size was estimated on the basis of the expected TT level. The reported mean TT level is 72.5 ± 16.5 ng/dL for women with PCOS (12). We estimated that a sample size of 115 patients would have 90% power at the 5% level to detect a difference of 5 ng/dL in the mean TT level.

Data are presented as medians, confidence intervals, odds ratios and percentages.

Non-normally distributed variables were compared between women with and without the cutaneous features using the Mann–Whitney's U test with the median values of each variable. Comparison of categorical (nominal) data such as acne, hirsutism and seborrhea was performed using the $\chi 2$-test. A stepwise multivariate logistic regression with backward selection was used to analyze hormonal and metabolic risk factors. The backward selection model started with all candidate variables in the model. At each step, a variable that is not significant ($p > 0.05$ by a likelihood ratio test) was removed. This process continued until no non-significant variables remained. A p value <0.05 was considered significant.

Results

The baseline characteristics of the study population are shown in Table 1. The prevalence of the cutaneous features are listed in Table 2. The most common presenting feature was hirsutism in 85 (73.9%) women and AN was only noted in six (5.2%).

The acneic women had higher median values of DHEAS ($p = 0.001$) and FT ($p = 0.001$) than the women without acne. W/H ratio ($p = 0.009$) and frequency of hirsutism ($p = 0.006$) were significantly higher in acneic women, but there were no significant differences between women with and without acne for metabolic parameters. However, any association among acne and the hormonal, metabolic and anthropometric variables was not detected by multivariate analysis.

The women with hirsutism had significantly higher median values of DHEAS ($p = 0.001$), TT

Table 1. Anthropometric, hormonal and metabolic characteristics of the study women.

Characteristics	Women with PCOS (n = 115)
Age (years)	23 (16–40)
BMI (kg/m^2)	22.8 (17.6–35.1)
Waist-to-hip ratio	0.85 (0.72–0.93)
FSH (IU/mL)	6.08 (2.56–8.77)
LH (IU/mL)	9.70 (5.43–18.40)
Estradiol (pg/mL)	41.0 (11.0–95.0)
Total testosterone (ng/dL)	73 (51–91)
Free testosterone (pg/mL)	2.84 (1.7–3.8)
SHBG (nmol/L)	36 (17–113)
Free androgen index	6.55 (1.8–14.8)
DHEAS (μg/dL)	187 (69–536)
Prolactine (ng/mL)	12 (3.8–30)
Total cholesterol (mg/dL)	182 (120–220)
HDL (mg/dL)	52 (32–98)
LDL (mg/dL)	92 (57–167)
Triglycerides (mg/dL)	86 (27–183)
TC/HDL index	3.5 (1.8–5.9)
Fasting glucose (mg/dL)	86 (76–106)
Fasting insulin (μUI/mL)	8.2 (3.77–36)
Glucose/insulin ratio	11.3 (1–27)
HOMA value	1.72 (0.79–7.72)

Note: BMI, body mass index; FSH, follicle stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone–binding globulin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; HOMA, homeostasis model assessment; PCOS, polycystic ovary syndrome; DHEAS, dehydroepiandrosterone sulfate. *, Values are given as median and range.

Table 2. Prevalence of the cutaneous features in women with PCOS.

Skin features	Women with PCOS (n = 115) N (%)
Acne	61 (53)
Hirsutism	85 (73.9)
Seborrhea	40 (34.7)
Female pattern hair loss	40 (34.7)
Acanthosis nigricans	6 (5.2)

Note: PCOS, polycystic ovary syndrome.

Table 3. Results of logistic regression analysis for the cutaneous features as dependent variables.

Skin findings	Regression Coefficient	Standard Error	Significance	OR (95% CI)
Hirsutism				
Age	−0.409	0.115	0.001	0.66 (0.53–0.83)
Total testosterone*	0.137	0.036	0.001	1.14 (1.06–1.23)
Fasting glucose	0.144	0.057	0.011	1.15 (1.03–1.29)
Total cholesterol*	0.092	0.024	0.001	1.09 (1.04–1.14)
Seborrhea				
Free testosterone*	0.008	0.003	0.007	1.00 (1.00–1.01)
Fasting glucose*	0.137	0.038	0.001	1.14 (1.06–1.23)
Insulin*	0.128	0.047	0.006	1.13 (1.03–1.24)
Androgenic alopecia				
Free testosterone*	−1.434	0.530	0.007	0.23 (0.08–0.67)
Insulin*	−0.116	0.050	0.019	0.89 (0.80–0.98)
LDL*	−0.022	0.010	0.026	0.97 (0.95–0.99)

Note: *Significant in univariate analysis only. OR, odds ratios; CI, confidence interval; LDL, low-density lipoprotein.

($p = 0.006$), FT ($p = 0.026$) and free androgen index ($p = 0.006$), TC ($p = 0.001$), HDL ($p = 0.012$), LDL ($p = 0.015$) and lower TC/HDL index ($p = 0.029$) when compared with non-hirsute women. In addition, hirsute women had a higher percent of acne ($p = 0.006$) and lower percent of androgenic alopecia ($p = 0.001$). While a positive association among hirsutism and TT, FG and TC was found by multivariate analysis, there was a negative association between hirsutism and age (Table 3).

The seborrheic women had higher values of LH ($p = 0.007$) and FT ($p = 0.001$), and lower SHBG ($p = 0.003$). LDL ($p = 0.044$), TG ($p = 0.001$), TC/HDL ($p = 0.004$), FG ($p = 0.001$), insulin ($p = 0.004$) and HOMA levels ($p = 0.001$) were significantly higher in women with seborrhea compared with non-seborrheic women. In addition, HDL levels ($p = 0.030$) were significantly lower in women with seborrhea. These women had lower median age ($p = 0.001$) and higher W/H ratio ($p = 0.001$). In multivariate analysis, seborrhea had a positive association with FT, FG and insulin (Table 3).

In univariate analysis, the women with androgenic alopecia had lower median values of FT ($p = 0.029$) and E2 ($p = 0.004$) when compared with women having no alopecia. The median values of TC ($p = 0.01$), LDL ($p = 0.03$), TG ($p = 0.006$), insulin ($p = 0.002$) and HOMA levels ($p = 0.003$) were significantly lower in the women with androgenetic alopecia than those without alopecia. These women had higher median age ($p = 0.028$) and BMI ($p = 0.013$) and lower percentage of hirsutism ($p = 0.001$). However, a negative association among androgenic alopecia and FT, LDL and insulin was detected by logistic regression analysis (Table 3).

The prevalence of AN in this population was small (5.2%) and not considered for all statistical analysis. However, positive association of AN with LH (0.013), PRL (0.038), TT (0.024), FT (0.04), FG/Insulin index (0.03), HOMA (0.013), seborrhea (0.003), and negative association with HDL (0.001) and acne (0.024) were found by univariate analysis.

Discussion

The cutaneous features including acne, hirsutism, androgenic alopecia and seborrhea are important for early diagnosis of PCOS. Although androgen excess and insulin resistance play a major role in the development of the cutaneous features, the exact etiology of the features is not known (6,13). Insulin is directly related to AN. Because insulin leads to increase in androgen levels by direct and indirect mechanisms, it may also be related to other cutaneous features (14,15). Abnormal changes in carbonhydrate metabolism have also been reported in some cutaneous features (6,16). It was shown that many patients with PCOS have some degree of dyslipidemia at baseline (17). In the present study, we found some degree of abnormal glucose, lipid and hormone profiles in the cuteneous features of PCOS. While acne was not associated with any hormonal and metabolic parameters, abnormal lipid and glucose profiles were determined in women with hirsutism, seborrhea and androgenic alopecia in multivariate analysis.

The prevalence of acne in PCOS women has been reported in the range of 9.8–34% (18–20). It was found higher in the present study (53%) compared with previous reports. The reason might be partly due to the diagnostic criteria used for acne definition. Hormonal abnormalities related to acne were only detected in some reports. Usually, a positive correlation between acne and elevated levels of testosterone, and a negative correlation of acne with SHBG levels has been reported (21,22). Similarly, FT and DHEAS was found to be associated with acne in women with PCOS in the present study. However, multivariate analysis could not determine any clinical and laboratory parameter as a risk factor for acne. Although androgens play an important role in the pathophysiology of acne, other factors such as changes in lipid composition and *propionibacterium acnes* are also important in the development of acne. This suggests that androgen-dependent or independent acne may occur together in women with PCOS.

Hirsutism is the second most common manifestation of PCOS after oligomenorrhea. The prevalence of hirsutism in PCOS varies according to the racial and geographic characteristics, and it has been reported in the range of 40–92% in Europe and America (13,16). We detected a prevalence of 73.9% and a negative association with age for hirsutism. Hirsutism in PCOS has usually been found to be associated with a high level of androgens and insulin resistance, and a low level of SHBG in the literature (16,23). Similarly, a positive association was found with TT, FG and TC for hirsutism in our study. These results suggest that PCOS women with hirsutism may have some biochemical and metabolic abnormalities. Falsetti et al. also reported abnormalities in glucose metabolism associated with hirsutism in PCOS (16). Differently, we did not determine a relation between hirsutism and abnormal glucose metabolism.

Seborrhea has also been described as a cutaneous feature in PCOS. However, its prevalence in PCOS is not exactly known (6,13). The prevalence of seborrhea was found to be 34.7% in the present study. The women with seborrhea had a variety of changes in some hormone, lipid and carbohydrate parameters in univariate analysis compared with non-seborrheic women. In multivariate analysis, seborrhea was only associated with higher levels of FT, FG and insulin.

In addition to androgen hormones, the patient's genetic predisposition, climate and emotional factors are other important factors affecting seborrhea occurrence. Seborrhea may also be associated with seborrheic dermatitis, androgenetic alopecia and acne vulgaris, which are not related to PCOS (11). For these reasons, clinical, serological and radiological examinations are important for the diagnosis of seborrhea related to PCOS. We evaluated seborrhea in a parametric way. It may be suggested that hormonal and metabolic factors related with seborrhea in PCOS should be assessed using a Sebumeter for a metric measurement.

Only a few reports have specifically examined androgenic alopecia in women with PCOS. Although the prevalence of PCOS was studied in women with pattern or diffuse hair loss, there were not enough data on the prevalence of androgenic alopecia in PCOS women. In a number of reports, the prevalence of PCOS in women with alopecia has been reported in the range of 67–77.8% (20,24). The prevalence of androgenic alopecia in PCOS women was 34.7% in the present study. Some studies have found higher levels of serum androgens in women with androgenic alopecia, while other studies have not (24,25). Interestingly, androgenic alopecia was negatively associated with FT, LDL and insulin in the present study. In a previous study, similar negative correlations with androgens and acne have also been reported in women with PCOS (26). These findings suggest that local androgens levels in the scalp may be important mediators in the development of androgenic alopecia rather than the level of circulating androgens.

In conclusion, hirsutism is closely related to the metabolic abnormalities, while acne is not a good marker for hyperandrogenism. Androgenic alopecia is also not a strong marker for hyperandrogenism and not strongly related to hirsutism. As a result, hyperandrogenism and an abnormal carbohydrate and lipid metabolism may initiate or contribute to the development of the cutaneous manifestations in PCOS.

Disclosure of interest: All authors declare no conflict of interest.

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