Hyperandrogenemia Association with Acne and Hirsutism Severity in Croatian Women with Polycystic Ovary Syndrome

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SUMMARY Clinical traits associated with androgen, acne and hirsutism, are important diagnostic features of polycystic ovary syndrome (PCOS). As androgens are necessary for the development of cutaneous signs of PCOS, patients with severe forms of clinical hyperandrogenism are expected to present with higher levels of plasma androgens. This relationship has not been well established and studies examining the relationship have produced inconsistent results. The aim of this study was to analyze the correlation between the severity of clinical traits caused by androgen, acne and hirsutism, with plasma levels of androgens in Croatian women diagnosed with PCOS. One hundred and forty-five women of reproductive age with isolated acne (n=61) or isolated hirsutism (n=84), oligo/amenorrhea and polycystic morphology of the ovaries were enrolled in the study. Acne grade, hirsutism grade, body mass index (BMI) and waist to hip ratio (WHR) were recorded. Hormonal profiles were measured and assessment of insulin resistance was performed. There were no significant associations between acne severity and BMI, WHR and examined hormonal and insulin resistance parameters. There was a significant correlation between sex-hormone binding globulin (SHBG) and free testosterone levels and the severity of hirsutism (ρ=-0.611, P<0.001 and ρ=0.337, P=0.002, respectively). No significant association was found between the hirsutism grade and other hormonal and metabolic parameters examined. In conclusion, acne severity in PCOS patients is not linearly associated with serum androgen levels; therefore, their levels should not be used to determine the dose of anti-androgen therapy. The observed negative correlation between serum SHBG levels and the degree of hirsutism suggests that hormonal contraception, which elevates SHBG, should be used as primary therapy in hirsute PCOS patients.

KEY WORDS: acne, hirsutism, polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy, affecting almost one of five women of reproductive age. The 2003 Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group concluded that two out of the three following criteria should be met to fit the definition: chronic

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anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound examination. Diseases mimicking PCOS should be excluded before establishing the diagnosis (1). With the new PCOS classification, nine clinical subtypes of PCOS cases can be identified. The frequency of subtypes varies among different countries and ethnic groups. We have previously reported that PCOS phenotype I presenting with chronic anovulation, clinical hyperandrogenism and ultrasound appearance of polycystic ovaries is the dominant phenotype of PCOS in the Croatian population (2). The most prominent hyperandrogenic clinical signs in PCOS patients are acne and hirsutism (3). Current data suggest that the majority of patients with hirsutism, 75%-85%, and 20%-40% of patients with persistent acne only, have PCOS (3). Androgens are one of the determining elements in acne commencement due to the influence of two major factors in acne pathogenesis: enhanced follicular keratosis and increased sebum production (4,5). The growth of sexual hair is primarily dependent on the presence of androgens. In androgen-responsive areas, testosterone initiates growth, increases the diameter and pigmentation of the keratin column, and probably increases the rate of matrix cell mitoses in all but scalp hair (3). As androgens are necessary for the development of the cutaneous features found in PCOS, it would be expected that women with severe forms of clinical hyperandrogenism would have a more elevated plasma androgen level. Several studies have reported a correlation between hirsutism and/or acne severity and circulating androgen levels, with inconsistent results (6-8). The variances in published results indicate that hyperandrogenism not only reflects circulating androgen levels, but is also influenced by the peripheral metabolism of androgens (9). Although testosterone is the major circulating androgen, dihydrotestosterone (DHT) is the major nuclear androgen in the pilosebaceous unit and hair follicles. DHT is formed in target cells from testosterone *via* 5α-reductase. 3α-androstenediol is a peripheral metabolite of DHT, and its glucuronide, 3α-androstenediol gluconide (3α-diol-G) has been described as a marker of local androgen excess due to the increased activity of testosterone metabolism, simultaneously increasing 5α-reductase activity in the cells of hair follicle (10). Although many studies have reported increased serum 3α-diol-G in women with cutaneous hyperandrogenism, its role as a marker of peripheral androgen action is still controversial. Furthermore, the manifestation of cutaneous hyperandrogenic stigmata can be influenced by the sensitivity of target tissues to androgens. As previously reported (11), there is evidence supporting that tissue response to androgen is determined by polymorphisms of the androgen receptor (AR) (12). Manifestations of acne and hirsutism in PCOS patients can also be influenced by other hormonal variables, including insulin resistance and compensatory hyperinsulinism (13). At high concentrations, insulin binds to insulin-like growth factor (IGF) receptors. IGF-I augments the thecal androgen response to luteinizing hormone (LH) that leads to increased androgen production in ovarian theca cells (14). Obesity, specifically of abdominal distribution, is associated with hyperinsulinemia and increased androgen production rates resulting in decreased levels of sex-hormone binding globulin (SHBG) and increased levels of free testosterone (FT) (15). However, insulin resistance, an intrinsic finding in PCOS, can be found in PCOS patients independently of obesity. There are other explanations for the discordance in clinical presentation of hyperandrogenism and biochemical values, e.g., significant variability among commercial immunoassays used for measuring serum androgen levels, along with the lack of standardization of androgen testing results (16). It seems that degrees of cutaneous manifestations of hyperandrogenism vary greatly in different ethnic populations. Some reports have even suggested that distinct ethnic groups may significantly differ with respect to the concentrations of specific androgens in serum. Therefore, in this study we tended to analyze the correlation of the severity of cutaneous manifestations of hyperandrogenism, i.e. acne and hirsutism, with plasma levels of androgens in Croatian women with PCOS phenotype I.

PATIENTS AND METHODS

The study group included 145 women diagnosed with PCOS according to the Rotterdam ESHRE/ASRM consensus (1). The study included only patients with PCOS phenotype I, presenting with oligomenorrhea or anovulation, clinical and biochemical manifestations of hyperandrogenism, and a polycystic appearance of the ovaries. Oligomenorrhea or anovulation was determined according to menstrual cycle disturbances as: (a) oligomenorrhea, an intermenstrual interval of 36 days to 6 months; and (b) amenorrhea, an intermenstrual interval of 6 months or longer. Clinical hyperandrogenism was evaluated with the presence of acne and hirsutism. Hyperandrogenemia was defined as a serum level of total testosterone (TT) higher than 2.0 nmol/L, FT level greater than 26 pmol/L, androstenedione (A) level greater than 12 nmol/L or dehydroepiandrosterone sulfate level (DHEAS) level greater than 10 μmol/L. In order to differentiate between the possibility of various pathophysiological mechanisms between acne and

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hirsutism, we included patients with acne (n=61) or isolated hirsutism (n=84) only. All subjects were clinically evaluated by the same dermatologist and the Acne Severity Index (ASI) was determined using the Burke and Cunliffe technique (17). The patients were classified into three groups: group A (ASI 1 – minor acne, total grade <1), group B (ASI 2 – mild acne, total grade 1-2.4) and group C (ASI 3 – moderate acne, total grade 2.5-4). Patients with severe acne were excluded from the study because of the low number, consequently insufficient to perform a valid statistical analysis. For the evaluation of hirsutism, we used the Ferriman-Gallwey (FG) score. A score greater than 8 defines hirsutism. Hirsutism was further divided into three categories: mild (FG 8-9) (group A), moderate (FG 10-14) (group B), and severe (FG >15) (group C) (18). In order to avoid the inter-observer variation in scoring, the subjects were evaluated for hirsutism by the same observer. To fit the diagnosis of biochemical hyperandrogenism, the elevation of one of the androgens, total testosterone (TT), FT, A and DHEAS was an obligatory finding in patients included in the study. Transvaginal ultrasound scanning (TVUS) was performed by a single expert ultrasonographer to avoid subjective influence on interpreting the results. The polycystic appearance of the ovaries was defined as the presence of 12 or more follicles measuring 2-9 mm in diameter in each ovary and/or an ovarian volume >10 mL. Other possible causes of symptoms, such as non-classical congenital adrenal hyperplasia (NCAH), androgen-secreting tumors, hyperprolactinemia, thyroid gland disturbances and Cushing's syndrome were excluded. Prior to entering the study, each participant signed the informed consent form and had her body mass index (BMI) evaluated, along with the waist to hip ratio (WHR) calculation. Patients identified as being overweight were defined according to the World Health Organization (WHO) criteria as a BMI ≥25 kg/m^2. According to the WHO, abdominal obesity is defined as a WHR >0.85 for females.

The patients were included in the study after regular examination at the Division of Human Reproduction and Gynecologic Endocrinology, Department of Obstetrics and Gynecology, University Hospital Center Zagreb, Zagreb, Croatia, during the period from October 2008 to June 2012. Dermatologic examination was performed at the Department of Dermatology and Venereology, University Hospital Center Zagreb, Zagreb, Croatia. Any medications known to affect sex hormones were discontinued for at least six months prior to enrolment. The study protocol was approved by the University of Zagreb School of Medicine Ethics Committee, No. 04-1116-2006.

Biochemical analysis

The patients were recruited during the early follicular phase of spontaneous or progesterone induced menstrual cycle (days 3-5) when blood samples for hormonal and biochemical analysis were drawn and TVUS was performed. Serum luteinizing hormone (LH), follicle stimulating hormone (FSH), thyrotropic hormone (TSH), prolactin (PRL) and total testosterone (TT) concentrations were determined by chemiluminescence immunoassays using LH-Vitros, FSH-Vitros, TSH-Vitros, Prolactin-Vitros and Testosterone-Vitros, respectively (Ortho Clinical Diagnostics, Johnson&Johnson, Rochester, NY, USA). Serum sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS) and androstenediol (A) levels were measured using chemiluminescence immunoassays (SHBG-Immulite, DHEAS-Immulite and Androstenedione-Immulite, respectively) (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA). The concentrations of 3α-diol-G and 17–hydroxyprogesterone (17-OHP) were determined by a solid phase enzyme-linked immunosorbent assay (ELISA) based on the principle of competitive binding (DRG-Diagnostics, Marburg, Germany). The intra-assay and inter-assay coefficients of variation ranged between 1.5% and 7.9%. Free testosterone (FT) was calculated from TT and SHBG as previously described (20) using a web-based calculator (http://www.issam.ch/freetesto.htm). The plasma glucose level (Glc) was determined using the UV-photometric hexokinase method. Serum insulin (Ins) level was determined by chemiluminescence immunoassay using Insulin-Immulite (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA). Insulin sensitivity HOMA-IR was calculated according to the formula: (insulin (mU/L x glucose (mmol/L)) / 22.5). We defined insulin resistance as HOMA-IR ≥2.5 (20). Biochemical analyses were performed at the Department of Clinical Biochemistry, University Hospital Center Zagreb, University of Zagreb, School of Medicine, Zagreb, Croatia.

Statistical analysis

On comparison of the clinical and hormonal parameters, categorical variables were described by percentages and continuous variables as mean ± standard deviation. Comparisons of continuous variables across the acne and hirsutism groups were performed using analysis of variance (ANOVA). Tukey HSD post hoc test was used to determine significant differences between the acne and hirsute groups. Differences in categorical characteristics were assessed by using χ^2-test. Correlation analysis (Spearman's rank correlation test) was performed in order to explore

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the association of acne severity or hirsutism severity with BMI, WHR, HOMA-IR, SHBG and FT. All statistical analyses were completed using the SPSS for Windows (version 15.0, SPSS Inc., Chicago, IL, USA). A *P*-value <0.05 was considered statistically significant.

RESULTS

Clinical, hormonal and biochemical parameters are summarized in Table 1. Patients with acne and hirsute patients are represented distinctly from each other. At least one androgen level was elevated in all subjects enrolled. Serum FT levels were increased in 55.7% of the acne group and 61.9% of hirsute patients, while serum TT levels were increased in 47.5% of the acne group and 51.2% of hirsute patients. Serum A and DHEAS levels were elevated in less than 40% in both groups of patients. The mean serum SHBG levels were low in both groups (Table 1). HOMA-IR as a marker of insulin resistance was elevated in 26.2% in the acne group and 31.0% in the hirsute group of patients (Table 1).

Table 1. Clinical and hormonal characteristics of the polycystic ovary syndrome patients

	Acne group N=61	Hirsutism group N=84
Age (years)	29.7±4.3	27.9±5.7
BMI (kg/m^2)	23.0±4.9	23.9±4.4
BMI >25 (kg/m^2) (%)	29.5	28.6
WHR	0.80±0.07	0.78±0.08
WHR >0.85	23.0	19.0
Acne		
Group A (%)	47.5	0
Group B (%)	32.8	0
Group C (%)	19.7	0
Hirsutism		
Group A (%)	0	31.0
Group B (%)	0	45.2
Group C (%)	0	23.8
FSH (IU/L)	3.1±1.0	3.3±1.1
LH (IU/L)	6.9±3.7	7.4±4.3
TT (nmol/L)	2.1±1.0	2.3±.0.9
TT >2 (nmol/L) (%)	47.5	51.2
FT (nmol/L)	40.3±23.9	41.7±24.0
FT >26.0 (pmol/L) (%)	55.7	61.9
A (nmol/L)	11.2±5.6	12±5.9
A >12 (nmol/L) (%)	42.6	46.4
DHEAS (µmol/L)	6.3±3.2	6.9±2.9
DHEAS >10 (µmol/L) (%)	14.8	16.7
SHBG (nmol/L)	38.5±19.8	36.4±19.2
3α-diol-G (nmol/L)	10.8±2.76	11.4±1.3
HOMA-IR	2.2±1.8	2.5±1.3
HOMA-IR >2.5 (%)	26.2	31.0

BMI = body mass index; WHR = waist to hip ratio; FSH = follicle stimulating hormone; LH = luteinizing hormone; TT = total testosterone; FT = free testosterone; DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone binding globulin; HOMA-IR = homeostatic model assessment of insulin resistance; 3α-diol-G = 3 alpha androstenediol gluconide; values are given as mean ± SD or percentage.

Hormonal serum values in the three groups of patients with acne are presented in Table 2. We found no significant correlation between the severity of acne and BMI (ρ=0.123, *P*=0.347), the severity of acne and WHR (ρ=0.083, *P*=0.526) and the severity of acne and HOMA-IR (ρ=0.029, *P*=0.824).

The mean serum FSH, LH, TT, FT, A, DHEAS, 3α-diol-G and SHBG levels were not significantly different among the three groups (Table 2). The mean serum SHBG levels were lowest in group C and highest in group A, although this finding was not significantly different among the three groups, as presented in Table 2.

There were no significant differences in the mean serum FSH, LH, TT, FT, A, DHEAS and 3α-diol-G levels in the hirsute groups of PCOS patients, while the mean serum SHBG and FT levels were significantly different between the groups (Table 3). The mean serum SHBG levels were lowest in group C (21.2±6.2 nmol/L), moderate in group B (34.7±19.7 nmol/L) and highest in group A (50.7±15.1 nmol/L). The post hoc comparisons using Tukey HSD test indicated significant difference at the p<0.05 level for all three groups (group A *vs*. group B, *P*=0.001; group B *vs*. group C, *P*=0.008; and group A *vs*. group C, *P*=0.001). Consequently, the mean serum FT levels were highest in group C (55.2±28.8), lowest in group A (31.6±17.8) and moderate in group B (41.5±22.0). These differences were significant between groups A and C *P*<0.001), while no significant difference was found between groups B and C (*P*<0.079) and between groups A and B (*P*=0.205) using the post hoc Tukey HSD test. Spearman's rank correlation test confirmed a significant correlation between SHBG and FT levels and the severity of hirsutism (ρ=-0.611, *P*=<0.001 and ρ=0.337, *P*=0.002, respectively). No significant correlation was observed between the severity of hirsutism and BMI (ρ=0.126, *P*=0.253), the severity of hirsutism and WHR (ρ=0.024, *P*=0.827), and the severity of hirsutism and HOMA-IR (ρ=0.172, *P*=0.118).

DISCUSSION

The cutaneous features of acne and hirsutism are important for early diagnosis of PCOS. Androgens are an indispensable factor in the pathogenesis of acne

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Table 2. Hormonal serum values in three groups of patients with isolated acne

	Group A N=29	Group B N=20	Group C N=12	P^a
Age (years)	28.9±4.7	30.4±3.7	30.6±4.3	0.378
BMI (kg/m^2)	23.2±3.8	24.2±5.2	25.1±6.6	0.464
BMI >25 (kg/m^2) (%)	24.1	35.0	33.3	0.678
WHR	0.79±0.06	0.82±0.09	0.80±0.07	0.441
WHR >0.85	13.8	35.0	25.0	0.218
FSH (IU/L)	3.2±1.2	3.0±0.8	3.1±0.8	0.787
LH (IU/L)	7.5±4.8	5.8±2.4	7.6±1.5	0.216
TT (nmol/L)	2.3±1.1	2.1±1.0	1.9±1.0	0.549
TT >2 (nmol/L) (%)	55.2	40.0	41.7	0.522
FT (nmol/L)	41.1±25.1	38.7±20.3	41.1±28.1	0.880
FT >26.0 (pmol/L) (%)	62.1	55.0	41.7	0.487
A (nmol/L)	11.2±5.6	10.7±6.2	12.1±4.7	0.813
A >12 (nmol/L) (%)	48.3	30.0	50.0	0.377
DHEAS (µmol/L)	6.3±3.5	6.2±3.2	6.5±3.1	0.927
DHEAS >10 (µmol/L) (%)	17.2	10.0	16.7	0.765
3α-diol G (nmol/L)	10.9±1.4	11.5±1.7	8.5±4.6	0.428
SHBG (nmol/L)	42.1±20.2	37.1±18.5	32.0±20.5	0.310
HOMA-IR	2.4±2.1	2.2±1.1	2.5±2.0	0.563

BMI = body mass index; WHR = waist to hip ratio; FSH = follicle stimulating hormone; LH = luteinizing hormone; TT = total testosterone; FT = free testosterone; DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone binding globulin; HOMA-IR = homeostatic model assessment of insulin resistance; 3α-diol-G = 3 alpha androstenediol gluconide; values are given as mean ± SD or percentage; [a]ANOVA test for continuous variables; χ^2-test for categorical variables.

due to the potentiating capabilities, which increase sebum production and give rise to follicular retention hyperkeratosis (21). Furthermore, anti-androgen therapy is a highly successful treatment of the disease (22). Studies have shown that the elevation of TT, FT, DHEAS and A in patients with acne vulgaris is frequently associated with other signs of hyperandrogenism, such as hirsutism, alopecia, or menstrual disturbances (23). Hyperandrogenism, defined as at least one hormone level above the normal range, was evident in all of our patients with acne. Therefore, the requirements to fulfill the PCOS phenotype I definition were met. No specific androgen was significantly connected to acne presentation in our study (Table 2).

Although many arguments have been put forth supporting the role of androgens in the etiology of acne, their part in determining the severity of the disease has not been well established. Some studies have shown a positive correlation between the levels of adrenal androgen, DHEAs (24) and a negative correlation with the levels of SHBG (25). In our study, we did not demonstrate any association between the grade of acne severity and laboratory markers of androgenicity or insulin resistance. According to our results, the degree of acne, expressed by the ASI score, showed a weak negative correlation with serum SHBG levels, which is in accordance with the observations of previous studies and in discordance with the findings reported by Cibula *et al*. (8). Some authors have recommended the evaluation of SHBG levels in women with acne in order to select patients who may have better response to appropriate hormone regimens. All combined oral hormonal contraceptives decrease the level of LH and raise the level of SHBG. Only contraceptives with anti-androgenic progestins (cyproterone acetate, chlormadinone acetate, or drosperinone) inhibit androgen receptors and affect 5α-reductase. As in the Croatian population with PCOS, no androgen is specifically connected with acne severity, and the correlation seen with SHBG is not significant. We can speculate that the severity of acne in PCOS mostly depends on peripheral sensitivity to androgens. Therefore, patients with PCOS would benefit more from a treatment with anti-androgenic hormonal contraceptives than the neutral (gestodene or desogestrel) options. One should keep in mind that the pathogenesis of acne includes more than sebum over-production and abnormal sebaceous duct keratinization; changes in lipid composition, bacterial colonization with *Propionibacterium acnes*, and the role of host immune response factors are also associated (21).

Table 3. Hormonal serum values in three groups of patients with isolated hirsutism

	Group A N=26	Group B N=38	Group C N=20	*P*[a]
Age (years)	27.3±5.4	27.4±5.6	28.1±6.0	0.173
BMI (kg/m2)	22.7±1.9	24.2±4.4	25.1±6.3	0.156
BMI >25 (kg/m^2) (%)	11.5	20.4	25.3	0.325
WHR	0.78±0.08	0.80±0.09	0.77±0.07	0.388
WHR >0.85	19.2	23.7	10.0	0.451
FSH (IU/L)	3.4±1.5	3.2±0.8	3.4±0.8	0.639
LH (IU/L)	7.8±5.3	7.0±2.8	8.0±5.1	0.593
TT (nmol/L)	2.1±1.0	2.0±0.8	2.2±0.9	0.776
TT >2 (nmol/L) (%)	53.8	44.7	60.0	0.515
FT (nmol/L)	31.6±17.8	41.5±22.0	55.2±28.8	0.003
FT >26.0 (pmol/L) (%)	57.7	55.3	80.0	0.159
A (nmol/L)	12.5±5.8	12.1±6.4	11.2±4.9	0.761
A >12 (nmol/L) (%)	50.0	42.1	50.0	0.770
DHEAS (µmol/L)	6.9±3.2	6.7±2.7	7.6±3.2	0.507
DHEAS >10 (µmol/L) (%)	15.4	10.5	30.0	0.163
3α-diol G (nmol/L)	11.7±1.3	10.5±1.4	11.5±2.6	0.576
SHBG (nmol/L)	50.7±15.1[b]	34.7±19.7[b]	21.2±6.2[b]	< 0.001
HOMA-IR	2.3±1.0	2.5±1.7	2.8±1.0	0.422

BMI = body mass index; WHR = waist to hip ratio; FSH = follicle stimulating hormone; LH = luteinizing hormone; TT = total testosterone; FT = free testosterone; DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone binding globulin; HOMA-IR = homeostatic model assessment of insulin resistance; 3α-diol-G = 3 alpha androstenediol gluconide; values are given as mean ± SD or percentage; [a]ANOVA test for continuous variables; χ^2-test for categorical variables.

Hirsutism, defined as the presence of terminal hairs with a male distribution pattern in women affects 5%-8% of women of fertile age. As androgens play a definite role in the transformation of vellus into terminal hair during puberty, and in the growth of terminal hair by prolonging its androgen phase in the androgen-dependent areas of the female body, hirsutism is considered as a clinical marker of androgen excess. Previous studies have observed the association between hirsutism and high levels of androgens compared to low levels of SHBG (3,23,26). This is in agreement with the results of our study showing low levels of SHBG and consequently elevated levels of FT as the most prominent signs of biochemical hyperandrogenism. The vast majority of investigations have concluded that the severity of hirsutism correlates poorly with the severity of androgen excess (26-30).

In our study, there was no significant relationship between FG score and LH, FSH, TT, androstenedione, and DHEA. However, the severity of hirsutism positively correlated with FT and negatively with SHBG, indicating that hirsutism severity is mainly dependent on the bioavailabilty of unbound testosterone. As the degree of hirsutism not only reflects circulating androgen levels, it is also influenced by the intraindividual variation of the enzymes (5α-reductase), which affects the intracellular levels of highly active androgen (DHT) in sebocytes and keratinocytes. We expected to find the intensity of symptoms correlate better with a marker of the local androgen excess of 3α-diol-G (31,32). We did not find any correlation between the levels of excess 3α-diol-G and hirsutism severity, which is in accordance with the findings reported by Mecyekalski *et al*. (33). The role of 3α-diol-G as a marker of peripheral 5α-reductase has recently been criticized. It seems that 3α-diol-G largely reflects adrenal androgen secretion and does not reflect primary peripheral 5α-reductase activity (34). Therefore, the measurement of 3α-diol-G may only be useful in monitoring therapy with 5α-reductase inhibitors. The finding suggesting that the levels of SHBG correlate with hirsutism severity may partially explain why pills containing anti-androgenic progestins are superior to their counterpart third-generation pills. Third-generation combined pills containing desogestrel and gestodene block the estrogen-mediated increase in SHBG to a greater extent than anti-androgenic progestins because of their intrinsic androgenicity (35). Therefore, when selecting therapy for patients with gross androgenic symptoms, treatments of choice may include cyproterone acetate (36) and drospirenone (37), which elevate the levels of SHBG.

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It has long been recognized that PCOS is frequently associated with insulin resistance accompanied by compensatory hyperinsulinemia. Insulin resistance with hyperinsulinemia has an important role in initiating hyperandrogenism through the increase in ovarian androgen hormone biosynthesis. In our study, we found no correlation between HOMA-IR and severity of acne and hirsutism, which justifies the recommendation against the use of metformin or other insulin sensitizers as treatment for the hyperandrogenic cutaneous features of PCOS (3).

CONCLUSION

Acne severity in PCOS patients is not linearly associated with serum androgen levels, and therefore their level should not be used to determine the dosage of anti-androgen therapy. The significant negative correlation observed between serum SHBG levels and the degree of hirsutism suggests that hormonal contraception, which elevates SHBG, should be therapy of choice in treating the PCOS patient.

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