European Review for Medical and Pharmacological Sciences 2018; 22: 4411-4418

Hormonal and metabolic aspects of acne vulgaris in women with polycystic ovary syndrome

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Abstract. – OBJECTIVE: Acne vulgaris in women can indicate a systemic disease, such as polycystic ovary syndrome (PCOS), which is associated with hormonal and metabolic disorders. The aim of this study was to investigate the influence of hormonal and metabolic disorders on acne vulgaris in women with PCOS.

PATIENTS AND METHODS: The study included 110 women with PCOS. Women were divided according to their androstenedione concentration: within reference range (n=66) or higher (n=44). All patients were between 17-36 years old.

Acne was graded according to the US FDA scale for a five-category global system (acne global severity scale). Hirsutism was defined using a modified Ferriman-Gallwey method. Fasting plasma glucose, insulin, luteinizing hormone, follicle-stimulating hormone, 17α-hydroxyprogesterone, 17-beta-estradiol, sex hormone-binding globulin and androgen (androstenedione, total testosterone, free testosterone, dehydroepiandrosterone sulfate) were assessed, as were prolactin and cortisol concentrations. Thyrotropin and free thyroxine concentrations were also measured. The free androgen index (FAI) and homeostatic model assessment-insulin resistance (HOMA-IR) index were calculated.

RESULTS: The average age and rating on the hirsutism scale were similar in both analyzed groups. A higher percentage of severe acne was observed in the group of women with an androstenedione concentration within reference range than in the group with the higher concentration. Meanwhile, the severity of acne in the group of PCOS women with the higher androstenedione concentration was correlated with higher concentrations of total testosterone, free testosterone, dehydroepiandrosterone sulfate, and cortisol. Increased glucose concentration was also proportional to the severity of acne. We did not observe a statistically significant correlation between the severity of acne and the androstenedione concentration. In the group of PCOS women as a whole, the severity of acne was correlated only with higher dehydroepiandrosterone sulfate concentration; other androgens did not affect the severity.

CONCLUSIONS: The acne global severity scale in PCOS women is associated with higher concentrations of total testosterone, free testosterone, dehydroepiandrosterone sulfate, and FAI value. Higher concentrations of androstenedione did not affect acne severity.

Key Words
Acne, Polycystic ovary syndrome, Androgens, Hormonal disorders.

Introduction

Acne vulgaris is one of the most frequently encountered, externally visible skin diseases in dermatology for individuals between 15 and 40 years of age[1]. Prevalence estimates are difficult to compare because definitions of acne and acne severity have differed so much between particular studies[2]. Acne is often mistakenly thought to affect the teen-aged group exclusively[3]. Although it does affect more than 85% of adolescents, it often continues into adulthood[4], persisting into the 20s for 64% of people and to the 30s for 43% of people[5]. It has been shown that women are more affected by acne than men in all groups over 20 years of age[6]. Hormonal disorders play a crucial role in acne development. The hormones implicated in acne pathogenesis include mainly androgens, estrogens, progesterone, insulin and insulin-like growth factor-1 disorders[7-9].

Baseline androgen synthesis is regulated via the alteration of gene transcription by luteinizing hormones (LH)[10]. Androgens enlarge the sebaceous glands and increase sebum production[7]. Moreover, they cause abnormal desquamation of follicular epithelial cells. Formation of comedo-

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nes and colonization by *Propionibacterium acne* leads to inflammation and the creation of papules, pustules, nodules, cysts and scars[11]. Sebum production is also regulated by other hormones, including estrogens, growth hormone, insulin, insulin-like growth factor-1, glucocorticoids, adrenocorticotropic hormone and melanocortins[8]. Women have three major sources of androgens: the ovaries, the adrenal gland and the skin, which contains the enzymes responsible for producing and converting weak androgens into strong androgens[12].

Ovarian-derived androgens include androstenedione and testosterone, whereas the adrenal glands produce dehydroepiandrosterone (DHEA), *dehydroepiandrosterone sulfate* (DHEA-S), androstenedione, and testosterone. Peripheral conversion of androstenedione and DHEA also generates testosterone in women[13].

Besides the androgens, many different factors play a role in this process, from follicular plugging and genetics, to diet and medications[13]. It is important to remember that persistent acne in a woman can also indicate a systemic disease, such as polycystic ovary syndrome (PCOS)[12], which is associated with hormonal and metabolic disorders[14-16]. The role of androgens in adult women with acne has been well supported in the literature[17-19]. The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group suggested that acne is not commonly associated with hyperandrogenemia and therefore should not be regarded as evidence of hyperandrogenemia[17]. Therefore, the aim of this study was to investigate the association between acne vulgaris expressed using the acne global severity scale (AGSS) and parameters associated with hyperandrogenemia in PCOS women.

Patients and Methods

Patients

This study was conducted in the Gynecological Endocrinology Clinic of the Silesian Medical University in Katowice, Poland, between January and June 2017, and was approved by the Bioethical Committee of the Medical University of Silesia. Informed consent was obtained from all participants. The study included 110 women with PCOS. Women were divided according to their androstenedione concentration: within reference range (group I) or higher (group II). Group I consisted of 66 women with androstenedione concentrations between 0.5-3.3 ng/mL and group II consisted of 44 women with androstenedione concentrations above 3.3 ng/mL. All patients were between 17-36 years old (Table I). The diagnosis of PCOS was based on the Rotterdam criteria[20] with at least two of the following three criteria present: the existence of oligomenorrhea, clinical or biochemical hyperandrogenism, and polycystic appearance of the ovaries on ultrasonography. Other causes of hyperandrogenism, such as Cushing's syndrome, congenital adrenal hyperplasia, or virilization, were excluded. Subjects taking any drugs or supplements in the last 6 months were excluded from the study. Smoking and alcohol abuse were also among the exclusion criteria.

Table I. Anthropometric parameters of study population.

Studied parameters	Group I	Group II
Number of case	n=66	n=44
PCOS phenotype (1-4)	2.4±1.0	1.6±0.8*
Age (years)	24.4±4.3	25.3±4.6
BMI (kg/m2)	22.1±4.1	24.6±5.3*
WHR	0.8±0.1	0.9±0.1*
Hirsutism score	7.4±3.4	7.8±4.7
AGSS (five-category scale)	2.6±1.1	2.2±1.1

*$p<0.05$ statistically significant difference when compared between studied groups.
Legend: PCOS – polycystic ovary syndrome; BMI – body mass index, WHR – waist/hip ratio; AGSS- acne global severity scale.

Acne was graded according to the US FDA AGSS scale for a five-category global system. In this scale, the five categories ranged from:

1. Clear, indicating no inflammatory or non-inflammatory lesions;
2. Almost clear, rare non-inflammatory lesions with no more than one papule/pustule;
3. Mild, some non-inflammatory lesions, no more than a few papules/pustules but no nodules;
4. Moderate, up to many non-inflammatory lesions, may have some inflammatory lesions, but no more than one small nodule;
5. Severe, up to many non-inflammatory and inflammatory lesions, but no more than a few nodules.

Hirsutism was defined using a modified Ferriman-Gallwey method (mFG). An mFG score of ≥ 8 was considered hirsutism[21,22]. Patients were tested for follicle-stimulating hormone (FSH), luteinizing hormone (LH), sex hormone-binding globulin (SHBG), 17-beta-estradiol (17-β-E2), 17α-hydroxyprogesterone (17-OH-P), andro-

Table II. Percentage of different phenotypes of polycystic ovary syndrome in studied groups.

PCOS phenotype	Group I	Group II
	[%]	
1	21	52*
2	38	32
3	23	16*
4	18	0*

*$p<0.05$ statistically significant difference when compared to group I.

stenedione, total testosterone, free testosterone, DHEA-S, cortisol, and prolactin (PRL) during the follicular phase (within 3 and 5 days of the menstrual cycle). On the same day, fasting glucose, insulin, thyroid stimulating hormone (TSH), and free thyroxine (FT4) concentrations were also determined.

The characteristics of the studied groups are presented in Tables I, II and III. Serum was collected according to the routine procedure: after an overnight fast during the follicular phase. The samples were stored at −70°C until the assays were done.

Hormone Assay

FSH, LH, PRL, 17-β-E2, total testosterone, free testosterone, androstendione, DHEA-S and SHBG were determined by ELISA (DRG Instruments GmbH, Marburg, Germany) with a lower limit of sensitivity 0.86 IU/L, 1.27 IU/L, 0.35 µg/L, 9.7 ng/L, 0.083 µg/L, 0.002 ng/L, 0.019 µg/L, 0.044 mg/L and 0.2 nmol/L respectively; the respective intra and interassay coefficients of variations were 5.5% and 6.1% for FSH, 5.6% and 6.2% for LH, 4.5% and 5.9% for PRL, 4.7% and 7.8% for E2, 3.6% and 7.1% for testosterone, 6.4% and 8.0% for free testosterone, 6.5% and 10.2% for androstendione, 4.8% and 7.5% for DHEA-S and 5.3% and 9.0% for SHBG[23]. 17-OH-P and cortisol were assayed by RIA (Diagnostic Products) with lower detectable concentrations of 0.2 nmol/L and 5.5 nmol/L, respectively. The respective inter- and intraassay coefficients of variation were 5.6% and 8.0% for 17-OH-P and 4.3% and 5.2% for cortisol. TSH and FT4 levels were determined by two Roche Cobas Elecsys 600.

Table III. Percentage of Acne Global Severity Scale (AGSS) in patients with PCOS.

AGSS	Group I	Group II
	[%]	
1	15	28*
2	28	39*
3	35	19*
4	20	12*
5	2	2

*$p<0.05$ statistically significant difference when compared to group I.

Laboratory Analysis

Plasma glucose was estimated by colorimetric methods using commercially available test kits (Roche).

Serum insulin concentration was determined by ELISA (DRG Instruments GmbH, Marburg, Germany) with a lower limit of sensitivity of 1.76 mIU/mL and intra- and interassay coefficient of variation (CV) values of 2.2% and 4.4% respectively.

Calculations

The homeostatic model assessment of insulin resistance (HOMA-IR) index was calculated using the standard formula: HOMA-IR = fasting concentration of insulin (µIU/mL) x fasting concentration of glucose (mmol/L)/22.5. The free androgen index (FAI) was calculated according to the standard formula.

Statistical Analysis

The data was expressed as a mean with standard deviation (X±SD). The normality of the variables was tested using the Shapiro-Wilk W-test. Differences between groups were tested using the Student *t*-test. When a lack of normal distribution and variance uniformity occurred, the differences between groups were analyzed by means of a non-parametric U Mann-Whitney test. The correlation was expressed by Spearman's rank correlation coefficients (r). In all instances, $p<0.05$ was considered statistically significant. Statistical calculations were done using the Statistical Software Package, version 12.0 (Polish version: StatSoft, Krakow, Poland).

Results

110 patients with PCOS were involved in the study. The average age and rating on the acne global severity scale were similar in both analyzed groups. In group II, we observed higher values of BMI and waist-to-hip ratio (WHR) than in group I. We did not observe any statistically

Table IV. Hormonal parameters in studied groups.

Hormonal parameters	Group I	Group II
LH (mIU/ml)	5.5±4.0	6.1±4.6
FSH (mIU/ml)	5.2±1.8	4.5±1.3*
SHBG (nmol/l)	71.2±32.4	56.9±31.0*
17-β-E2 (pg/ml)	47.9±60.1	47.5±21.6
17-OH-P (nmol/l)	1.5±0.4	2.0±0.6*
Androstenedione (ng/ml)	2.3±0.6	4.8±1.6*
FAI	2.0±1.3	4.6±4.2*
Total testosterone (nmol/l)	0.4±0.1	0.6±0.5*
Free testosterone (pmol/l)	1.5±1.6	2.4±1.3*
DHEA-S (µg/ml)	355.5±142.7	456.9±167.3*
Cortisol (µg/dl)	15.4±5.1	18.4±5.5*
PRL (ng/ml)	10.5±9.7	9.4±4.4
TSH (µIU/ml)	2.1±0.9	1.7±0.9*
fT4 (ng/dl)	1.1±0.2	1.1±0.3

*$p<0.05$ statistically significant difference when compared between studied groups
Legend: LH – luteinizing hormone; FSH – follicular stimulating hormone; SHBG – sex hormone binding globulin; 17 β E2 – 17-beta-estradiol; 17-OH-P - 17α-hydroxyprogesterone; FAI - free androgen index; DHEA-S dehydroepiandrosterone sulfate; PRL – prolactin; TSH- thyrotropin, fT4-free thyroxine.

significant differences in hirsutism score between the analyzed groups (Table I).

A higher percentage of PCOS phenotype 1 was found in group II when compared to group I (Table II), whereas a higher percentage of severe acne was observed in group I than in group II. More cases with clear (28%) and almost clear skin (39%) were found in group II than in group I (15 and 28%, respectively) (Table III).

The androstenedione concentration, as well as other hyperandrogenemia parameters such as total testosterone, free testosterone, DHEA-S concentration and, FAI value (Table IV), were significantly higher in group II than group I.

We did not observe any statistically significant difference in LH concentration between the analyzed groups, although a lower concentration of FSH was found in group II than group I. We also found higher 17-OH-P and cortisol in group II than in group I. The concentration of PRL was similar in both groups. A lower TSH concentration in the serum was observed in group II, but no statistically significant difference in FT4 concentration between the analyzed groups was detected (Table IV).

Fasting glucose concentration and G/I ratio were similar between the patients from group I and group II. Insulin resistance, evaluated by HOMA-IR, was also similar in both analyzed groups. Only fasting insulin concentration was statistically significantly higher in group II when compared to group I (Table V).

Table V. Biochemical and metabolic characteristics of the studied population.

Studied parameters	Group I	Group II
Fasting glucose (mmol/L)	89.8±4.9	91.5±7.2
Fasting insulin (µIU/ml)	8.6±3.8	9.3±4.7*
Fasting G/I ratio	13.3±6.1	12.2±6.5
HOMA-IR	2.0±1.9	2.1±1.1

*$p<0.05$ statistically significant difference when compared to female with WHR<0.8
Legend: HOMA-IR - homeostatic model assessment of insulin resistance

Correlations

In the group of PCOS women with an androstenedione concentration within normal range (group I), we observed positive correlations among total testosterone, free testosterone, DHEA-S concentrations and the AGSS value. Increased BMI was proportional to the AGSS value. There were no associations among androstenedione, LH, FSH, PRL, or cortisol concentrations and the AGSS value. No statistically significant correlations were found between age or glucose and the AGSS value, either (Table VI).

In the group of PCOS women with a higher androstenedione concentration (group II), we found positive correlations among total testosterone, free testosterone, DHEA-S and cortisol concentrations and the AGSS value. There were no associations between androstenedione or PRL and the AGSS value. A negative correlation was found for LH and FSH concentrations and the AGSS value. The increased glucose concentration was proportional to the AGSS value. There were no correlations between age or value of BMI and AGSS (Table VI). For all analyzed subjects, we only observed statistically significant correlations between the AGSS value and the concentration of DHEA-S (Figure 1).

Discussion

Acne is the most common skin disorder and may be a sign of an underlying disease[17]. A study conducted by Uysal et al[17] revealed that acne is an important sign of androgen excess disorders and that three quarters of patients with acne may have

Table VI. Correlation between value of Acne Global Severity Scale (AGSS) and selected parameters in studied groups.

Correlation coefficients		Group I	Group II
AGSS	Age	NS	NS
	BMI	r=0.23*	NS
	Glucose (mmol/l)	NS	r=0.28*
	Total testosterone (nmol/l)	r=0.32*	r=0.30*
	Free testosterone (pmol/l)	r=0.25*	r=0.30*
	Androstendione	NS	NS
	DHEA-S (µg/ml)	r=0.42*	r=0.42*
	LH (mIU/ml)	NS	r= -0.39*
	FSH (mIU/ml)	NS	r= -0.34*
	PRL (mU/l)	NS	NS
	Cortisol (µg/dl)	NS	r=0.34*

*$p<0.05$
Legend: AGSS - acne global severity scale; BMI – body mass index; DHEA-S - dehydroepiandrosterone sulfate; LH – luteinizing hormone; FSH – follicular stimulating hormone; PRL – prolactine.

some disorder. Some 64% of patients with acne were found to have hyperandrogenemia, while 36% of the patients had normal serum androgen levels[17].

The most common cause of androgen excess in women is PCOS. In this disorder, gonadotropin-dependent functional ovarian androgen excess is the major source of the hyperandrogenemia[10,24]. A study conducted by Eden reported that 74% of women with acne were found to have PCOS[25]. Recently, however, the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group suggested that acne is not commonly associated with hyperandrogenemia[26]. A study conducted by Ozdemir et al[27] has shown that acne is not associated with hormonal variables, and therefore is not a good marker for hyperandrogenism in a group of PCOS women.

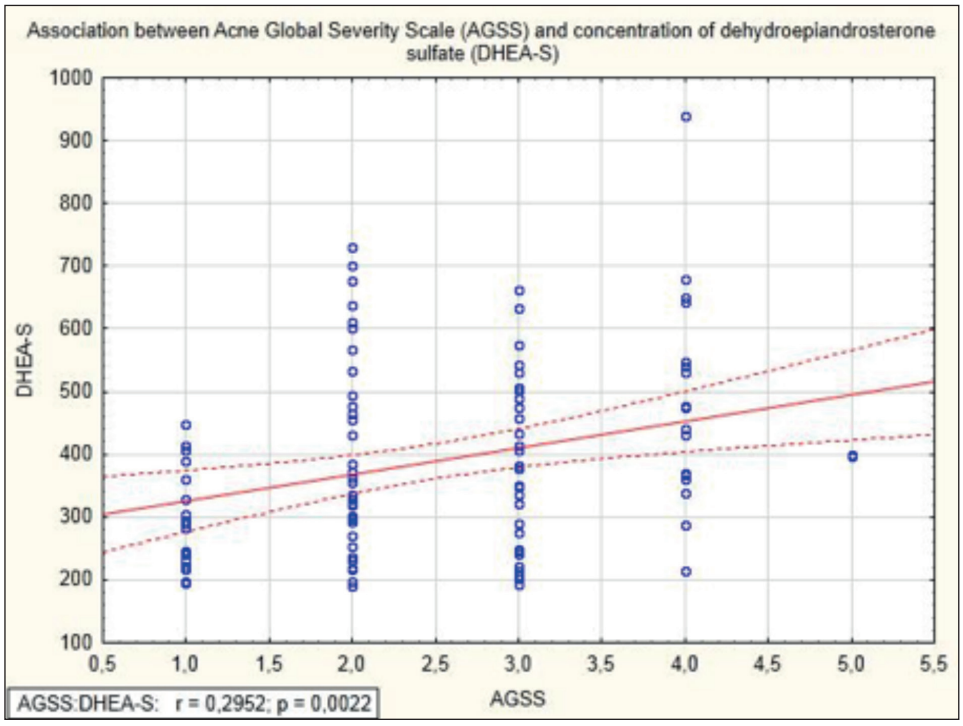

Figure 1. The association between acne global severity scale and dehydroepiandrosterone sulfate concentration in whole analyzed subjects.

In present work, the percentage of PCOS women with moderate to severe acne was about 18.2% (20 cases/110 cases). Interestingly, a higher patients of patients with moderate and severe acne was found in the group of PCOS women whose androstenedione concentration was within normal range (22%) than in the group of PCOS women with a higher concentration of androstenedione (14%). On the other hand, in group II, there were more PCOS women with phenotype 1 (52%) than in group I (21%). Overall, however, in whole group of PCOS women, we did not find any correlation between the phenotype of PCOS and severity of acne as measured on the acne global severity scale (Table II and III).

Several scholars[11] have attempted to correlate the clinical presentation of acne with markers of hyperandrogenism, such as androstenedione, free and total testosterone, and DHEA-S. Although some authors have shown a correlation between acne and high levels of androgens, others did not corroborate this finding.

In present report, we have also investigated the relationship among values on the acne global severity scale and parameters of hyperandrogenism: androstenedione, total and free testosterone concentrations, DHEA-S concentration, and FAI values in women with PCOS. The women with PCOS were divided into two groups: those with serum androstenedione within normal range (group I) and those with androstenedione concentration above 3.3 ng/mL (group II). In group II, we found statistically significantly higher concentrations of total and free testosterone, DHEA-S and FAI when compared to group I. We did not observe any statistically significant correlations between the value on the acne global severity scale and androstenedione concentration in either analyzed group (Table VI). However, we identified a positive correlation among DHEA-S, total and free testosterone concentration, and the value on the acne global severity scale in both analyzed groups. Our results are also corroborated by the investigation conducted by Uysal et al[17], who found that the development of acne, especially in the prepubertal period, has been associated with elevated serum levels of DHEA-S, the precursor for testosterone[17]. Another study has also shown a correlation between acne and high levels of DHEA-S[28]. Notably, in our research, we found the same value for the correlation coefficient (r=0.42) between the acne global severity scale and DHEA-S concentration in the groups with androstenedione concentration within reference range and those with higher concentrations (Table VI). When we analyzed the relationship between the acne global severity scale and androgens in the whole group of PCOS women, we found a positive correlation only between the acne global severity scale value and DHEA-S concentration (r=0.30; $p<0.002$) (Figure 1). When we divided the PCOS women into two groups according to their androstenedione concentration (≤3.3 and >3.3. ng/mL), we additionally observed a positive correlation among the rating on the acne global severity scale and free testosterone or total testosterone concentrations. Azziz et al[29] have shown that the prevalence of PCOS among women with acne is not high; only PCOS women with hirsutism are characterized by acne. But in our study, the value of mFG was similar in both analyzed groups, and we did not observe any statistically significant correlation between the AGSS value and mFG scale of hirsutism in either analyzed group. It is also possible that a higher concentration of androgen (androstenedione, total and free testosterone, DHEA-S concentrations) in group II was due to a higher percentage of PCOS women with phenotype 1 (52%) and an absence of phenotype 4 cases (in which normal androgen levels are found) than in group I (21% of phenotype 1 and 18% of phenotype 4). Additionally, in group II, we found a negative correlation for the phenotype of PCOS and the concentration of total testosterone, free testosterone, and DHEA-S concentrations. This also confirmed that the type of phenotype in PCOS affects hyperandrogenism[30] and can cause higher metabolic disorders than in group I.

In group II, a higher concentration of cortisol may influence the severity of acne, as suggested by a positive correlation between the cortisol concentration and the average value of the acne global severity scale in this group (r=0.34).

We also found a higher fasting insulin concentration in group II, whereas the HOMA-IR value was similar in both analyzed groups. It was shown that hyperinsulinemia resulting from insulin resistance leads to an increase in the production of androgens and also in their biological activity[11,31]. However, we did not observe any statistically significant correlations among fasting insulin or HOMA-IR value and the average value of AGSS in either analyzed group. Our study indicates that acne severity in

PCOS women is mainly associated with a higher concentration of total and free testosterone as well as DHEA-S.

Conclusions

We showed that:

1. The value on the acne global severity scale in PCOS women is associated with higher concentrations of DHEA-S, total testosterone and free testosterone.
2. Higher concentration of androstenedione did not affect acne severity.

Consent for publication

All researchers give their permission for the publication of this study.

Conflict of Interests

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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