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CLINICAL REPORT

Correlation between Endocrinological Parameters and Acne Severity in Adult Women

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Many studies demonstrate increased androgen levels and high prevalence of polycystic ovaries in women affected by acne. We evaluated the relationship between clinical features, ultrasonographic data on polycystic ovaries and hormonal parameters in 129 women >17 years of age with acne. Serum levels of androgens of ovarian and adrenal origin were measured. Menstrual cycle regularity, hirsutism, body mass index and ultrasonographic evaluation of ovaries were recorded. Raised levels of at least one androgen were evident in a majority of our patients. Only 19% of them had polycystic ovary syndrome. Hirsutism and acne severity correlated negatively with serum sex hormone-binding globulin (SHBG) levels ($p < 0.05$). No correlation between acne severity and hirsutism was found. In post-pubertal women, severity of acne seems to depend on peripheral hyperandrogenism, with a negative relationship between the acne severity and serum SHBG levels. We strongly recommend the evaluation of serum SHBG levels in women with acne in order to select patients who can have a better response to appropriate hormonal regimes. ***Key words: acne; polycystic ovary; ultrasound examination; sex hormone-binding globulin; sebocyte.***

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Acne vulgaris, depending on definition, affects 20–90% of all adolescents, with spontaneous resolution, in most cases, in the late teens or early twenties (1). However, in a steadily increasing group of patients – especially women – community-based studies (2, 3) have shown that acne may persist into middle-age, so called *acne tarda*. Many hypotheses have been proposed to explain this trend, for example, oral contraceptives containing progestogens with strong anti-oestrogenic properties and inappropriate application of cosmetics, but the exact mechanism is still unknown. A recent study showed the importance of familial factors for the development of persistent facial acne, suggesting that genetic factors may influence the failure of acne-prone follicles to evolve into acne-resistant follicles in early adult life (4).

It is well known that the function of the sebaceous glands is strongly influenced by biologically active androgens of ovarian and adrenal origin (5). The peripheral effects of androgens are mediated by their binding to nuclear androgen receptors. In the skin, the sebocyte plays a key role in the androgen homeostasis by synthesis or inactivation of testosterone and its biologically active metabolite, 5α-dihydrotestosterone (6).

Acne is a common feature in the course of endocrine diseases, characterized by raised levels of androgens, and often responds positively to oral contraceptives, suggesting a striking pathogenetic role of hyperandrogenism. Further evidence is provided by the positive correlation between increased rate of sebum excretion, regulated by androgens, and degree of acne severity (7). However, although the involvement of androgens in the pathogenesis of acne is well established, it is still not exactly clear how the hormonal stimulation is related to the clinical expression and the course of the disease.

We carried out an open study to evaluate the relationship between clinical features, hormonal parameters of pituitary, adrenal and ovary function, and ultrasonographic data in a large group of women with acne.

SUBJECTS AND METHODS

We enrolled 129 women (mean age 24.0±4.5 years; mean duration of the disease 5.9±4.6 years) referred to our unit for acne in 1999–2000. None of the patients had used oral contraceptive treatment, anti-androgen therapy, systemic antibiotics or isotretinoin therapy during the previous 6 months.

Informed consent was obtained after the modalities and aims of the study had been fully explained.

The history of each patient was taken with particular regard to the presence of oligomenorrhoea. In accordance with literature, oligomenorrhoea was defined as a menstrual cycle longer than 35 days (8, 9).

Weight and height were recorded to calculate body mass index (BMI). BMI scores between 19 and 25 were considered normal. The presence of hirsutism was scored in every woman by a single investigator, using the Ferriman-Gallwey index (Fi) (10, 11). Hirsutism was defined as a Fi score >8.

All subjects were clinically evaluated by the same

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dermatologist and the Acne Severity index (ASi) was determined using the Burke and Cunliffe technique (12). 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 our study because of their low numbers, which were insufficient to perform valid statistical analyses.

Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin (PRL) were measured by EIA (enzyme immunoassay). RIA (radio-immunoassay) was used to measure 17-OH progesterone (17OH-PG), free testosterone (FT), androstenedione (ASD), dehydroepiandrosterone sulphate (DHEAS) and sex hormone-binding globulin (SHBG). Blood was withdrawn in the early morning from all women during the follicular phase, between the second and the fourth day of the menstrual cycle.

Serum levels of all hormones were then evaluated in comparison with normal values, calculated by our laboratory on a database of 237 age- and sex-matched healthy subjects. For hormones varying during menstrual cycle, normal values for early follicular phase (within fourth day of the cycle) were considered.

The normal ranges of values were: FSH 3.3–11.3 mIU/ml, LH 1.6–7.9 mIU/ml, PRL 93–467 μg/ml, 17OH-PG 0.40–1.02 ng/ml, FT 0–3.6 pg/ml, ASD 0.21–3.08 ng/ml, DHEAS 1.2–3.6 μg/ml and SHBG 39–77 nmol/l.

Ultrasonographic evaluation of ovaries was performed in the early follicular phase by the same radiologist, using a 3.5 MHz convex probe. Polycystic ovaries were defined according to the criteria of Adams: 10 or more cysts of diameter 2–8 mm, localized peripherally, with increased ovarian volume and stroma (13).

Polycystic ovary (PCO) syndrome was defined according to NIH/NICHHD 1990 endocrine criteria by the presence of clinical findings of menstrual disturbances and hyperandrogenism, pelvic ultrasound imaging of PCO and elevated LH to FSH ratio (14).

Statistical analysis

Results were expressed as mean ± SD. Correlation analysis (Spearman's rank correlation test) was performed for each possible pair of considered parameters. Differences between groups were evaluated with Student's *t*-test for continuous variables, while the χ^2 test was performed to assess the differences in the frequencies of discrete variables. To perform the χ^2 test, we considered all the data as discrete variables, defining three possible values for hormone levels (below normal, normal and above normal) and hirsutism (absent, Fi ≤ 8, Fi > 8), and two possible values for PCO (present/absent), oligomenorrhoea (present/absent), LH/FSH ratio (≤1 or >1), BMI (≤25 or >25). A $p < 0.05$ was considered significant.

RESULTS

Anthropometric and clinical data of our population, overall and in each group, are summarized in Table I. Clinical evaluation showed minor, mild or moderate acne in 55, 50 and 24 patients, respectively. Hirsutism was observed in 25 of 129 patients (19.38%), oligomenorrhoea in 20 (15.5%) and BMI >25 in 11 (8.53%) cases. Acne duration in group C was significantly longer than in group A (7.2 ± 4.2 vs 4.9 ± 4.6 years, $p < 0.05$). Acne severity (ASi) correlated positively with disease duration ($\rho = 0.2$, $p < 0.05$), but not with hirsutism (Fi) ($\rho = 0.1$, NS) or with BMI ($\rho = 0.09$, NS). As for the occurrence of hirsutism, overweight and oligomenorrhoea, no statistically significant differences were observed among the three groups.

Table I. *Anthropometric and clinical data for three groups of patients with different severity of acne*

	Group	Mean ± SD	Median	CI 95%
Age (years)	A	24.8 ± 5.2	24	23.4–26.1
	B	23.5 ± 3.9	23	22.4–24.6
	C	23.5 ± 3.6	23	22.0–25.0
Weight (kg)	A	56.3 ± 7.8	54	54.2–58.3
	B	55.9 ± 8.7	54	53.5–58.3
	C	58.2 ± 9.9	57	54.2–62.2
Height (m)	A	1.6 ± 0.1	1.6	1.6–1.7
	B	1.6 ± 0.1	1.6	1.6–1.7
	C	1.6 ± 0.1	1.6	1.6–1.7
Body mass index (BMI)	A	21.0 ± 2.8	20.2	20.2–21.7
	B	20.9 ± 3.4	20.5	20.0–21.9
	C	21.9 ± 3.6	21.0	20.5–23.3
Ferriman-Gallwey (hirsutism) index	A	2.1 ± 3.3	0.0*	1.2–2.9
	B	2.6 ± 3.3	0.0*	1.7–3.5
	C	3.0 ± 4.0	0.0*	1.4–4.6
Disease duration† (years)	A	4.9 ± 4.6	3.0	3.7–6.2
	B	6.5 ± 4.6	5.5	5.2–7.8
	C	7.2 ± 4.2	7.0	5.5–8.9

A = minor ($n = 55$); B = mild ($n = 50$) and C = moderate ($n = 24$) acne.
*The reason the median is 0 is that this is the result for >50% of the group.
†The difference in disease duration between group A and group C is statistically significant ($p < 0.05$). No other significant differences between groups were found.

Endocrinological evaluation, overall and in each group, is shown in Table II. Mean serum PRL, LH, FSH, LH/FSH ratio, 17OH-PG, DHEAS, ASD and FT levels were not significantly different among the three groups, whereas the mean serum SHBG value was significantly lower in group C (43.6 ± 14.9 nmol/l) than in group B (55.8 ± 27.5 nmol/l, $p < 0.05$) and group A (60.3 ± 28.1 nmol/l, $p < 0.001$). The prevalence of low SHBG levels was also significantly increased in group C versus the other groups when evaluated by χ^2 test ($p < 0.05$). Serum PRL and 17-OHPG values were increased in 25 (19.38%) and 70 (54.26%) of 129 patients, respectively. LH/FSH ratio was increased (>1) in 38 of 129 patients (29.46%). Other endocrine parameters resulted in above normal limits in only a few cases: ASD in 12 subjects (9.30%), FT in 7 (5.43%) and DHEAS in a single patient (0.78%). Ultrasonographic evidence of PCO was demonstrated in 60 of 129 (46.51%) patients, but LH/FSH ratio was increased in only 19 of them. The ultrasonographic evidence of PCO was not significantly associated with increased LH/FSH ratio.

Serum SHBG values correlated negatively both with ASi ($\rho = -0.22$, $p < 0.02$) and with Fi ($\rho = -0.18$,

Table II. *Hormonal serum values in the three groups of patients with acne*

	Group	Mean ± SD	Median	CI 95%
LH (mIU/ml)	A	5.1 ± 3.1	4.7	4.3 – 5.9
	B	4.8 ± 2.3	4.5	4.2 – 5.5
	C	4.9 ± 2.6	4.5	3.9 – 6.0
FSH (mIU/ml)	A	6.5 ± 2.9	6.1	5.7 – 7.2
	B	5.8 ± 1.7	5.8	5.3 – 6.2
	C	5.7 ± 1.9	5.9	4.9 – 6.4
LH/FSH	A	0.8 ± 0.5	0.8	0.7 – 1.0
	B	0.9 ± 0.4	0.7	0.7 – 1.0
	C	0.9 ± 0.5	0.8	0.8 – 1.1
17OH-PG (ng/ml)	A	1.2 ± 0.7	1.0	1.0 – 1.4
	B	1.4 ± 0.9	1.1	1.1 – 1.6
	C	1.6 ± 0.8	1.5	1.3 – 2.0
PRL (μg/ml)	A	314 ± 181	271	266 – 362
	B	374 ± 236	286	309 – 439
	C	412 ± 303	287	291 – 534
DHEAS (μg/ml)	A	1.4 ± 0.6	1.3	1.2 – 1.5
	B	1.4 ± 0.6	1.3	1.2 – 1.6
	C	1.6 ± 1.2	1.3	1.2 – 2.1
ASD (ng/ml)	A	1.9 ± 0.9	1.7	1.6 – 2.1
	B	1.8 ± 0.8	1.8	1.6 – 2.1
	C	2.1 ± 0.8	2.0	1.7 – 2.4
FT (pg/ml)	A	1.4 ± 1.0	1.1	1.1 – 1.6
	B	1.6 ± 1.0	1.3	1.3 – 1.8
	C	1.8 ± 1.1	1.7	1.4 – 2.2
SHBG* (nmol/L)	A	60.3 ± 28.1	54.4	52.9 – 67.7
	B	55.8 ± 27.5	51.2	48.1 – 63.4
	C	43.6 ± 14.9	42.0	37.6 – 49.6

A = minor, $n = 55$; B = mild, $n = 50$; C = moderate, $n = 24$; SHBG, sex hormone-binding globulin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; PRL, prolactin; 17OH-PG, 17-hydroxy-progesterone; FT, free testosterone; ASD, androstenedione; DHEAS, dehydroepiandrosterone sulphate.

*Statistically significant differences were found in SHBG serum levels, between group A and group C ($p < 0.001$) and between group B and group C ($p < 0.05$).

$p < 0.05$), while FT ($\rho = 0.20$, $p < 0.05$) and ASD ($\rho = 0.28$, $p < 0.002$) correlated positively only with Fi. Positive but not significant correlations were found between serum PRL, LH/FSH ratio, 17OH-PG, DHEAS, ASD and FT values versus ASi. Moreover, LH/FSH ratio correlated positively with 17OH-PG ($\rho = 0.23$, $p < 0.01$) and with ASD ($\rho = 0.22$, $p < 0.02$).

DISCUSSION

Several studies report high prevalence of PCO and raised levels of circulating androgens in women with acne, but many of them correlate, often with different conclusions, acne severity with a single parameter, either clinical, instrumental or hormonal (15 – 22). Only a few investigations provide an integrated evaluation of all parameters. Walton et al. (8) reported, on a sample of 36 women, a significant positive correlation between levels of ASD and DHEAS and acne severity and a negative correlation between SHBG and acne severity, with a low prevalence (two cases) of PCO. Cibula et al. (9), with a sample of 90 women, did not demonstrate a positive correlation between the degree of acne severity and any of the clinical and laboratory markers of androgenism. On the contrary, they found that acne severity was negatively correlated with FT and hirsutism and positively correlated with SHBG. Ultrasound findings of polycystic ovaries were reported in 50% and LH/FSH ratio >1 in 38% of their patients.

Polycystic ovaries, however, are a common finding in women of reproductive age. Both instrumental and laboratory investigations should be performed to select patients requiring adequate treatment with oral contraceptives, as confirmed by our results (60 patients had polycystic ovaries on ultrasound examination, but only 19 had a real PCO syndrome).

Hyperandrogenism (at least one hormone level above normal range) was evident in a majority of our patients. The positive although weak correlation between LH/FSH ratio and 17OH-PG levels could suggest that hyperandrogenism is due to ovary hyperfunction in most cases. Hyperprolactinaemia, found in a significant number of patients, can be a feature of PCO or can induce ovary hyperandrogenism.

SHBG values were significantly lower in subjects with moderate acne than in those with minor or mild acne. Moreover, the degree of acne severity, expressed as ASi score, showed a weak negative correlation with serum SHBG levels. ASi also correlated positively, although not significantly, with FT values. A possible explanation of these data is that the decrease in serum SHBG levels, main carrier of testosterone, increases levels of peripheral FT, potentially able to produce peripheral hyperandrogenism and to favour acne development (5). Genetic factors could play a role in the synthesis and/or metabolism of SHBG, determining a relatively insufficient synthesis, an excessive catabolism and/or the synthesis of forms of this carrier having a lower affinity for hormones. Our results also provide an explanation for the therapeutic effects of oral contraceptives on acne: these drugs reduce the availability of biologically active testosterone by enhancing hepatic production of SHBG. Moreover, they decrease the ovarian production of testosterone, through direct gonadotropin suppression.

However, a closer look at individual cases shows that endocrinological parameters are often extremely variable, also within a group of patients with a similar clinical degree of acne. This suggests that current classifications, almost completely based on visual clinical features, could be significantly improved through an integrated evaluation of the patient, including consideration of the endocrinological and genetic background. This could lead to the definition of several subgroups, with different patterns of response to the different therapeutic schemes available, and thus

to the definition of the most appropriate therapy for each patient. Although the cost of this new approach could be expensive, the cost/benefit ratio could be significantly improved because of the avoidance of inappropriate treatments and, more importantly, the patient's satisfaction with better and probably more rapid clinical results.

The lack of correlation between ASi and Fi, both signs of hyperandrogenism, could be explained, at least in part, by the different metabolism of androgens in sebocytes, keratinocytes and dermal papilla cells. All these cells are stimulated by androgens, and are able to convert testosterone to the more potent 5α-dehydrotestosterone through 5α-reductase type 1. In sebocytes and keratinocytes, a second metabolic pathway is present and testosterone is converted progressively in less active metabolites: 17β-hydroxysteroid dehydrogenase (17βHSD) type 2 transforms testosterone in ASD and, thereafter, this becomes androsterone, through the sequential activity of 5α-reductase type 1 and 3α-hydroxysteroid dehydrogenase. In addition, sebocytes synthesize isoform 3 of 17βHSD, able to reduce ASD to testosterone (6). Inter-individual variations in the activity of one or more of these enzymes could influence the intracellular levels of highly active androgens in sebocytes and keratinocytes, and could be responsible for the poor correlation between acne severity, hirsutism and serum FT levels.

In conclusion, acne can be considered the result of the action of several different factors. Although it cannot be simply defined as an endocrine disorder, androgens certainly play an important role in its pathogenesis. Our study shows that, in post-pubertal women with acne, hyperandrogenism of ovarian and/or adrenal origin is present in a majority of cases. In these patients, the severity of acne seems to depend on peripheral hyperandrogenism, with a negative relationship between the acne severity and serum SHBG levels. We strongly recommend the evaluation of serum SHBG levels in women with acne so as to select patients who can have a better response to appropriate hormonal regimes.

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