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Serum Total and Unbound Testosterone and Sex Hormone Binding Globulin (SHBG) in Female Acne Patients Treated with Two Different Oral Contraceptives

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Serum total an unbound testosterone (T) and sex hormone binding globulin (SHBG) levels were studied in fifty-four female acne patients before treatment and during the treatment by two different oral contraceptives, the other containing 0.150 mg desogestrel plus 0.03 mg EE and the other 0.150 mg levonorgestrel plus 0.03 mg EE. Pretreatment values were abnormal in 57% of the patients. A borderline significant correlation between the severity of acne and SHBG was found. Ater six months' treatment a 250% increase in SHBG was seen in desogestrel/EE group and no significant change in SHBG in levonorgestrel/EE group. However, at the same time serum free testosterone fell 60% in both treatment groups. SHBG cannot be the only regulator of serum free testosterone. Acne improved significantly in both treatment groups. It is likely that the improvement was in connection with the free testosterone decrease and the improvement was better in the desogestrel/EE group where also SHBG elevation was seen. *Key words:Acne; Oral contraceptives; Total testosterone; Free testosterone; SHBG; Desogestrel; Levonorgestrel* (Received December 6, 1983.)

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Acne vulgaris is generally accepted to be a multifactorial disease. Although the skin is an androgen end-organ (1) and androgen action is necessary for the development of acne (2, 3), any direct correlation between the severity of acne and a specific abnormality in androgen metabolism has not yet been demonstrated.

The rate of conversion of testosterone to 5α-dihydrotestosterone is 2–20 fold higher in the acne areas (4) and the levels of circulating androgens are frequently elevated in female acne patients.

Increased serum testosterone and decreased sex hormone binding globulin (SHBG) levels are the most common pathological findings in female acne (5, 6, 7, 8).

Oestrogens in doses higher than 0.05 mg (9) and combined oral contraceptives are useful in treating female acne (10). The effect of oral contraceptives is also dependent on the amount and endocrinological properties of the progestagen component.

Progestagens shown to be effective in the treatment of the female virilizing symptoms are chlormadinoneacetate, megestrolacetate and cyproteroneacetate, all three having antiandrogenic properties (11). Oestrogens act by suppressing androgen production and thus decreasing the available circulating androgens (12), however, they are also known to elevate SHBG levels. SHBG is a carrier protein of testosterone and oestradiol (13). Only

about 2% of testosterone is free in serum (13). There is considerable evidence to suggest that the free androgen fraction in the serum is the biologically effective compound (14, 15, 16) and that the percentage of free androgen is sensitive to changes in SHBG capacity, since SHBG is the major carrier protein for testosterone and 5α-dihydrotestosterone (17, 18, 14). Smaller amounts of testosterone are also bound to albumin and transcortin. Oestrogens increase SHBG synthesis in the liver and androgens and progestagens counteract this effect (13). It is thought that the SHBG level is an indicator of oestrogen-androgen balance in the serum.

The aim of the present study was twofold. First we investigated the possible correlation between the severity grades of acne and serum total and free testosterone and SHBG levels in patients suffering from acne. Secondly our aim was to answer the questions whether an elevation in SHBG induced by combined oral contraceptives (0.150 mg desogestrel + 0.030 mg ethinyloestriol and 0.150 mg levonorgestrel + 0.030 mg ethinyloestradiol) would produce a fall in serum total or free testosterone levels in female acne patients, and further whether this expected decrease in circulating androgens is accompanied by an improvement in acne.

PATIENTS AND METHODS

Fifty-four women between the ages 18 and 35 years (mean 24) suffering from persistent acne were selected for the study. The patients were randomly divided into two groups and they were treated for six months with one of two different oral contraceptives. Group A (26 patients) were given the combination 0.150 mg desogestrel + 0.030 mg ethinyloestradiol and group B (28 patients) the combination 0.150 mg levonorgestrel + 0.030 mg ethinyloestradiol. The patients did not use any hormonal medication for three months preceding the study and they had no diagnosed thyreoidea, liver or cardiovascular disease or other contraindications for oral contraceptive use. Blood pressure, liver function and gynecological status were checked before starting treatment. No systemic treatment for acne was allowed.

Severity of acne, sex hormone binding globulin, total and free testosterone were estimated before the treatment and at the end of the sixth treatment cycle, generally on cycle-days 16–22. Plasma was immediately separated and stored at −20°C until required for analysis at Organon Laboratories, Holland.

The severity of acne. The patients were photographed at each visit. The following severity grades were estimated using almost the same scale as Allen & Smith 1982 (19). The following grading was used:

Grade 0: the facial area is perfectly clear or contains only few small lesions.

Grade 1: mild acne. Few pustules and about ten papules are present.

Grade 2: moderate acne. About half of the face is affected and numerous lesions are present.

Grade 3: severe acne. Numerous active lesions and general inflammation of the facial skin is present.

Laboratory methods. The binding capacities of SHBG for 5α-dihydrotestosterone were estimated using modifications of DEAE-cellulose filter assay (20) described by Mickelson & Petra (21). The results were expressed as nMol 5α-DHT bound per L serum.

The percentage free testosterone was estimated using a modification of the precipitation assay

Table 1. *SHBG, total testosterone and percentage free testosterone*

Means and standard deviations before treatment in 54 female acne patients and 46 normal female controls in fertile ages

	SHBG (nmol/l)	Total T (nmol/l)	% fT
Acne patients (n=54)	54±17	2.9±0.5	1.9±0.54
Control group (n=46)	78±23	2.5±0.5	1.6±0.41

described by Tremblay & Dubé 1974 (20). Total testosterone was determined by radioimmunoassay using a commercial available kit from the Radiochemical centre of Amsterdam (cat. no. JRK 600).

Statistical analysis. The paired *t*-test was used to analyse intragroup differences and the Student *t*-test was used for analysing inter-group differences. The pretreatment correlations of the parameters were analysed by the two-variable linear regression estimation. The significance was as follows: $p<0.05$ borderline significance, $p<0.01$ was significant and $p<0.001$ was highly significant.

RESULTS

Pretreatment

Thirty-one out of fifty-four female acne patients displayed abnormalities in SHBG, total and free testosterone (T) levels alone or in combination. The mean values of laboratory parameters before treatment are given in Table I. SHBG was lower and total T and free T levels higher than in the control group of 46 healthy Finnish women in fertile ages (ages between 20–36, mean 24: blood samples were drawn during the last 5 days of the cycle).

SHBG was below 50 nmol/l in 24/54 patients and below 40 nmol/l in 12/54 patients. Four of twenty-four patients with low SHBG had elevated total T and eight elevated free T.

Serum total T values were elevated (more than 3.1 nmol/l) in 14/54 patients, nine of whom had elevated free T and five decreased SHBG.

High serum free T levels greater than 60 pmol/l were recorded in 14/54 patients, nine of whom had elevated free T and five decreased SHBG.

Linear regression analyses of the laboratory parameters and the severity grades of acne before treatment revealed the following:

Acne/SHBG: $r = 0.308$ (borderline significance).
Acne/total testosterone: $r = 0.061$ (not significant).
Acne/free testosterone: $r = 0.101$ (not significant).
Acne/% fT: $r = 0.238$ (not significant).

Table II and III. *Improvement of acne, SHBG, total and free testosterone*

Mean values and significance sof the changes during 6-month treatment (paired *t*-test)

Parameter	Before treatment	Treatment cycle 6	Significance
II. *Desogestrel/EE*			
Acne 0–3	1.72	0.78	$p<0.001$
SHBG, nmol/l	51	176	$p<0.001$
Total T, nmol/l	2.82	2.58	NS
Free T, pmol/l	64	36′	$p<0.01$
% fT	2.07	1.43	
$n=18$			
III. *Levonorgestrel/EE*			
Acne 0–3	1.66	1.26	$p<0.01$
SHBG, nmol/l	55	70	NS
Total T, nmol/l	3.23	2.07	$p<0.001$
Free T, pmol/l	62	41	$p<0.001$
% fT	1.82	1.93	
$n=15$			

NS=not significant.

Comparative study between Marvelon (EE + desogestrel) and Microgynon (EE + levonorgestrel)

After six months treatment all laboratory values and photographs were available from 18 patients in desogestrel/EE group and 15 patients in the levonorgestrel/EE group.

Statistical analyses of the pre- and post-treatment changes are given in Tables II and III. The differences between the two treatment groups are shown in Table IV.

Improvement of acne

The severity of acne was well comparable before treatment in both groups, the mean severity was 1.7 and 1.66. There was improvement of acne in both groups ($p<0.001$ in the desogestrel/EE group and <0.01 in the levonorgestrel/EE group). The mean degree of improvement was from moderate to mild acne ($2\rightarrow 1$). Out of ten severe or moderate graded acnes nine turned to mild in the desogestrel/EE group and five from nine in levonorgestrel/EE group made the same change. Acne seemed to react better to the desogestrel/EE combination ($p<0.05$).

SHBG capacity

The desogestrel/EE combination induced substantial increase (250%) and levonorgestrel/EE combination no statistically significant increase in the SHBG capacity after six months of treatment. The difference between the effects of the two combination preparations was highly significant ($p<0.001$).

Total testosterone level

The desogestrel/EE combination induced a small decrease in serum total T, which was not statistically significant. Levonorgestrel/EE combination reduced serum total T 36% ($p<0.001$). The difference between the groups was significant ($p<0.01$).

Free testosterone level

The values obtained for total testosterone and per cent free testosterone were used to calculate the free testosterone level. Both combinations induced similar 60% decreases in

Table IV. *Desogestrel/EE contra levonorgestrel/EE*

SHBG, toal and free testosterone and the improvement of acne. Mean values, standard deviations and significance (Stundent's *t*-test)

Parameter	Desogestrel/EE ($n=18$)	Treatment cycle 6 Levonorgestrel/EE ($n=15$)	Significance
Acne 0–3			
Mean	0.78	1.26	$p<0.05$
SD	0.548	0.561	
SHBG nmol/l			
Mean	179	63.5	$p<0.001$
SD	47.4	17.16	
Total T nmol/l			
Mean	2.451	2.072	$p<0.05$
SD	0.59	0.446	
Free T pmol/l			
Mean	35.6	40.66	NS
SD	11.85	11.305	

the mean value of free T and there was no statistically significant difference between the two groups. Pre- and post-treatment values were comparable in both groups.

Side effects and drops out

From desogestrel/EE group (26 patients) two patients dropped out because of worsening of acne, one improvement of acne, two had drug related side-effects (irregular bleedings) and from three patients the blood sample of the sixth month was not available.

Out of levonorgestrel/EE group (28 patients) four patients were lost because of worsening of acne, three had irregular bleedings, blood samples were lost in three cases and three patients did not come to the last control.

DISCUSSION

Out of 54 women, older than 18 years and suffering from acne, 57% had abnormalities in serum total and/or free testosterone and/or carrier protein SHBG alone or in combination: 44% of the patients had low SHBG (50 nmol/l), 26% elevated total T (3.1 nmol/l) and 26% elevated free T (60 nmol/l) levels. There appeared to be a borderline correlation between the severity of acne and SHBG-levels (linear regression analysis of 54 patients). Darley et al. (7) could not find any correlation between serum total T or SHBG and the severity of acne. Förström et al. (5) reported elevated total T values in 14/31 female acne patients and Lim & James (22) decreased SHBG in 3/18 patients. Also other androgens such as dehydroepiandrosterone sulphate have been found to be elevated in acne patients (23). Our results and those found by others suggest that imbalance in androgen metabolism is frequent in female acne patients.

Early studies using oral combined contraceptives with a high dose of oestrogen showed an improvement of acne and also a reduction in the sebum excretion rate (9, 12). The influence was also dependent on the progestagen component used (10). In 1982, Pocchi (12) suggested the beneficial effects of oestrogens in acne to be a result of suppression of androgen production. Oestrogens have limited, if any, potential to decrease sebum synthesis in man. Saihan & Burton (24) used simultaneous OC and prednisolone treatment and they found a 50% fall in sebum excretion rate and also improvement in acne.

There is considerable evidence to suggest the free androgen fraction in the serum to be the biologically active component (14, 15, 16) and the percentage of free androgen to be sensitive to changes in SHBG capacity, since SHBG is the major carrier protein for T and 5α-DHT (18). Darley et al. (25) suggested that patients with low SHBG could be treated by oral contraceptives elevating SHBG and those with high total T with prednisolone. We also expected that improvement in acne should be associated with higher SHBG and lower androgen levels. In our study there was a 250% increase in SHBG levels in the desogestrel/EE group and no significant SHBG elevation in the levonorgestrel/EE group. However, serum free testosterone fell 60% in both treatment groups. In this study there was an inversed correlation between SHBG and percentage free T levels. These findings suggest that there is no direct correlation between serum SHBG and free testosterone levels. Other factors, such as testosterone production rates and metabolic clearance, seem to be of importance in the regulation of serum-free T levels.

Acne improved significantly in both treatment groups ($p<0.001$ in the desogestrel/EE group and $p<0.01$ in the levonorgestrel/EE group). This was associated with the decrease of free T in both treatment groups and the great increase in SHBG in the desogestrel/EE group. As the same oestrogen dose was used in both preparations, we consider desogestrel to be less androgenic than levonorgestrel.

If we consider which parameter under investigation in this study is of greatest value in

choosing the treatment of acne, low SHBG may be the best indicator of hormonal inbalance in females suffering from acne.

Acne is common in both sexes and there does not appear to be any simple and direct correlation between the level of circulating sex steroids and the severity of acne. However, oral contraceptives decreasing free testosterone and also elevating SHBG are of value in treating severe and moderate cases of female acne, because the ideal medicine has not yet been found.

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