Acta Derm Venereol (Stockh) 1986; 66: 225–230

Pituitary Function and DHEA-S in Male Acne and DHEA-S, Prolactin and Cortisol before and after Oral Contraceptive Treatment in Female Acne

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Palatsi R, Reinilä M, Kivinen S. Pituitary function and DHEA-S in male acne and DHEA-S, prolactin and cortisol before and after oral contraceptive treatment in female acne. Acta Derm Venereol (Stockh) 1986; 66: 225–230.

Pituitary function (TRH-LHRH stimulation test) was investigted in male acne patients and serum levels of dehydroepiandrosterone sulphate (DHEA-S), sex hormone binding globulin (SHBG) and other biochemical parameters were investigated in male acne patients and in female acne patients before and after treatment with an oral contraceptive. The TRH-LHRH stimulation test was performed with 15 male patients suffering from severe cystic acne and 7 healthy volunteers. Basal and stimulated prolactin, LH and FSH levels were statistically similar in the patients and control groups. However, the stimulated LH levels of the patients were 60% higher than those in controls. SHBG levels were significantly) higher in the patient group compared to those in the control group. Thirty-three female acne patients were randomly divided into two groups and treated for six months with an oral contraceptive containing 0.030 mg ethinylestradiol (EE) plus 0.150 mg levonorgestrel or 0.150 mg levonorgestrel. After six months' treatment a 30% decrease in DHEA-S levels were observed in the desogestrel/EE group and a 15% decrease in the levonorgestrel/EE group; the difference was not statistically significant. At the same time serum total cortisol increased by 75–100% and free testosterone fell by 30-40% in both groups, whereas SHBG elevated 250% in the desogestrel/EE group and 30% in the levonorgestel/EE group. Acne improved significantly in both groups, desogestrel/EE showing greater improvement. A decrease in SHBG and increase in DHEA-S levels appear to be the most common hormonal changes in acne. Oral contraceptive treatment induces an increase in SHBG and decrease in DHEA-S and also improves acne. *Key words: Acne; DHEA-S; SHBG; Oral contraceptives; Desogestrel; Levonorgestrel.* (Received November 7, 1985.)

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Androgen excess has been described to be frequent in women with acne (1–5). In particular the importance of dehydroepiandrosterone sulphate (DHEA-S) in acne has been the subject of several investigations over the past few years. Marynick et al. (2) found DHEA-S levels to be elevated in 80% of both their male and female acne patients; improvement of acne by oral contraceptives and/or dexamethasone was associated in females with a decrease in DHEA-S. However Van der Meeren & Thijssen (5) could not find any striking difference between DHEA-S levels in 35 male patients with severe acne and those in controls. Darley et al. (6) used oral contraceptives or prednisolone to suppress androgen excess in 39 female acne patients; DHEA-S levels were significantly lower after 4 months' therapy in all patients and this was associated with an improvement in acne (6). Hyperprolactinemia is known to stimulate adrenal androgen production (7) and disturbances in the FSH/LH ratio can induce the polycystic ovarian syndrome (2). The role of pituitary function in acne is still obscure. In animal experiments there is evidence that prolactin and growth hormone sensitize the response of sebaceous cells to testosterone (8, 9).

In order to get better information regarding the importance of DHEA-S as well as the

role of pituitary function, especially prolactin, in acne, we firstly studied pituitary function (TRH-LHRH stimulation test), DHEA-S, testosterone and SHBG levels of male patients with severe active cystic acne and compared the parameters to those in healthy male volunteers. In men pituitary function is easier to compare with controls because of the absence of menstrual cycle. Secondly we measured serum prolactin, DHEA-S and cortisol before treatment and after six months' treatment with two different oral contraceptives (OC's) containing 0.030 mg ethinyloestradiol (EE) plus 0.150 mg desogestrel or levonorgestrel in female acne patients with papulopustulotic acne; serum SHBG, total and free testosterone were also assayed (10).

PATIENTS AND METHODS

Male acne patients

Fifteen males aged 24 years (mean 19.7±7.5) suffering from serious cystic acne and 7 healthy control males aged 15–36 years (mean 24.1±7.9) were selected for the study. All patients had active acne with wide purulent and cystic lesions, leucocytosis and elevated E.S.R.

Pituitary function of the male patients and healthy volunteers were investigated using the TRH-LHRH stimulation test. The combination 200 μg thyrotropin releasing hormone (Roche Diagnostics, Basel) plus 100 μg gonadotropin releasing hormone (Fering AB, Malmö) was injected intravenously and venous blood samples were collected mid-mornings at 8–10 o'clock 0, 20 and 60 min after the injection. Plasma was prepared immediately and stored at −30°C until required for analysis. Prolactin, FSH and LH were analysed. In addition SHBG, testosterone and DHEA-S were analysed from the samples taken before stimulation.

Female acne patients

The patients, aged 18–35 (mean 24 years) and suffering from persistent papulopustulotic acne, were randomly divided into two groups; eighteen patients were treated for six months with an oral contraceptive (OC) preparation containing 0.030 mg EE plus 0.150 mg desogestrel and fifteen patients with an OC preparation containing 0.030 mg EE plus 0.150 mg levonorestrel. The patients had no other internal medication before treatment and no contraindicationfor OC use.

Severity of acne, serum DHEA-S, prolactin and cortisol were assayed before treatment and at the end of the sixth treatment cycle, generally on cycle-days 16–22. Previously the samples collected from these patients had been analyzed for serum total and free testosterone and SHBG (10).

Pre-treatment DHEA-S values were compared to those in a control group of 37 healthy women aged 22–24 years (mean 22 years). Blood specimens of the control women were taken at 0800—0900 h on days 7–8, 12–13, 14–15, 20–21, and 22–23 of the menstrual cycle. This schedul allowed the determination of hormone concentrations during the mid- and late follicular and luteal phases of the cycle.

The severity of acne was estimated using nearly the same cale as Allen & Smith (11). The following severity grades were used: Grade 0: facial area is perfectly clear or contains only a few small lesions. Grade 1: mild acne, few pustules and about ten papules present. Grade 2: moderate acne, about the half of the face is affected and numerous lesions present. Grade 3: severe acne, numerous active lesions and general inflammation in the facial skin present.

Laboratory methods

Most determination were made using commercial (125) RIA or IRMA-kits. Cortisol, Lutotropin (LH) and Follitropin (FSH) were from Farmos Diagnostica, Farmos Group Ltd., Turku, Finland. For male patients sex-hormone binding globulin (SHBG) (IRMA) and total testosterone were from Farmos Group Ltd., SF-90460, Oulunsalo, Finland. For female patients SHBG, total testosterone and free testosterone were determined as described previously (10). Prolactin was from Diagnostic Products Corporation, Los Angeles, California, USA. Dehydroepiandrosterone sulphate (DHEA-S) was from Radio Isotopen Service/Isotopen production Eldg. Institut für Reaktorforschung, 5303, Würenlingen, Switzerland.

Statistical analysis

The paired *t*-test was used to analyse intragroup differences and Student's *t*-test was used for analysing intergroup differences. The pretreatment correlations between parameters were analysed by a two-variable linear estimation. The significance was as follows: $p<0.05$ significant, $p<0.001$ highly significant.

Table I. *TRH-LHRH stimulation test*

Prolactin, LH and FSH 0, 20 and 60 min after the intravenous injection of 200 μg thyrotropin relesing hormone plus 100 μg gonadotropin releasing hormone. Mean values (and standard deviations) for patients with severe cystic acne and control men

	Prolactin (μg/l)	LH (U/l)	FSH (U/l)
Patients, n=15			
0 min	5.8±3.5	9.3±3.0	5.0±2.6
20 min	28.9±9.6	30.1±24.5	7.5±6.2
60 min	13.8±4.3	25.5±18.0	8.2±7.0
Control group, n=7			
0 min	4.7±2.0	7.3±2.3	4.3±0.6
20 min	27.3±11.5	11.6±7.4	4.8±1.0
60 min	12.4±4.6	16.3±14.6	5.0±0.5

The differences between patient and control groups were not statistically significant (paired *t*-test).

RESULTS

Male patients with severe active cystic acne

All fifteen male acne patients and seven healthy male volunteers responded to the stimulation of TRH-LHRH with clear increases in prolactin, LH and FSH. Mean values (and standard deviations) are given in Table I. Basal and stimulated prolactin, LH and FSH were similar in the patient and control groups.

Mean values (with standard deviations) for DHEA-S, total testosterone and SHBG in male acne patients and healthy volunteers are given in Table II. Five out of fifteen patients had DHEA-S levels about the upper normal limit of 9 nmol/l; however, the mean value for DHEA-S in the patient group was not significantly differnt from that in the contol group.

There was no significant difference between the mean level of total testosterone in the patient and control groups. Two patients (aged 13 and 15 years) had testosterone levels below the lower normal limit of 12 nmol/l. The mean level of SHBG was lower in patients than in controls; the difference was statistically significant ($p<0.01$, paired *t*-test).

Female patients with papulopustulotic acne

Pretreatment parameters. DHEA-S levels were above the upper normal limit of 9 μmol/l in 13 out of 33 patients (39%). The mean level of DHEA-S in the patient group (8.8±5.7 μmol/l) was significantly higher ($p<0.01$) than the mean level of the control group of 37 healthy women (5.46±1.15 μmol/l).

Comparison between desogestrel/EE and levonorgestrel/EE. Group mean pretreatment and treatment values for acne, DHEA-S, prolactin, cortisol, total testosterone, free

Table II. *DHEA-S, total testosterone and SHBG*

Mean values (and standard deviations) in male acne patients and healthy volunteers

Group	DHEA-S (μmol/l)	Total T (nmol/l)	SHBG (nmol/l)
Acne patients, *n*=15	7.0±4.9	23.5±9.7	26±7.8
Control group, *n*=7	5.9±1.9	24.6±12.3	37.2±14.4
Significance (paired *t*-test)	NS	NS	$p<0.01$

Table III. *Improvement in acne, serum cortisol, DHEA-S, prolactin, total testosterone, free testosterone and SHBG*

Mean values (with standard deviations) and significance of the difference between values before treatment and after 6 months' treatment

	Before treatment	Treatment cycle 6	Significance (paired *t*-test)
Desogestrel/EE (n= 18)			
Acne (0–3)	1.72±0.77	0.78±0.55	$p<0.001$
DHEA-S (μmol/l)	9.10±4.24	6.20±2.54	$p<0.05$
Prolactin (μg/l)	15.47±9.73	16.17±8.96	NS
Cortisol (μmol/l)	0.52±0.12	1.05±0.30	$p<0.001$
Total T (nmol/l)	2.82±0.20	2.58±0.59	NS
Free T (pmol/l)	64±6.3	36±12	$p<0.01$
SHBG (nmol/l)	51±4.5	176±47	$p<0.001$
Levonorgestrel/EE (n=15)			
Acne (0–3)	1.66±0.61	1.26±0.56	$p<0.01$
DHEA-S (μmol/l)	7.67±1.85	6.60±1.34	NS
Prolactin (μg/l)	12.41±15.71	18.66±11.19	NS
Cortisol (μmol/l)	0.59±0.28	1.03±0.03	$p<0.001$
Total T (nmol/l)	3.23±0.19	2.07±0.45	$p<0.001$
Free T (pmol/l)	62±5.5	41±11	$p<0.001$
SHBG (nmol/l)	55±2.3	70±17	NS

Significant differences between groups regarding changes after 6 months of treatment (Student's *t*-test): acne ($p<0.05$), total testosterone ($p<0.05$), SHBG ($p<0.001$).

testosterone and SHBG are given in Table III. Improvement in acne in both groups was from moderate to mild (2→1), the desogestrel/EE group showing significantly greater improvement than the levonorgestrel group ($p<0.05$). DHEA-S decreased by 32% in the desogestrel/EE group and 14% in the levonorgestrel/EE group; the difference between the groups was not statistically significant. Prolactin was increased by 5% in the desogestrel/EE group and by 50% in the levonorgestrel/EE group. Because of the large standard deviations, the difference between the groups was not statistically significant. Serum total cortisol increased by 102% in the desogestrel/EE group and by 75% in the levonorgestrel/EE group. The difference between the groups as not statistically significant. The desogestrel/EE combination reduced serum total testosterone by 9%, whereas the levonorgestrel/EE combination induced a reduction of 36%. The difference between the treatment groups was statistically significant ($p<0.05$). Both combinations induced similar decreases in serum free testosterone levels (30–40%. The desogestrel/EE combination induced a substantial increase (245%) in SHBG levels, whereas the levonorgestrel/EE combination induced in increase of (27%). The difference between the groups was statistically significant ($p<0.001$).

DISCUSSION

In the present study we have studied pituitary function and DHEA-S and SHBG levels in male acne patients and the effect of two oral contraceptive preparations on the improvement of acne, DHEA-S, SHBG and other biochemical parameters in female acne patients.

Pituitary function was tested using the TRH-LHRH stimulation test for male patients with severe acne. We had expected that we could find elevated prolactin or LH levels in

these patients, because androgen excess is often described in acne, in hyperprolactinemia in women and in polycystic ovarian syndrome with altered FSH/LH ratio. Stimulated LH levels in patients were 60% higher than in controls. However, both the basal and stimulated prolactin. FSH and LH levels were not statistically different from those in the healthy control male volunteers. Large SDs were due to high individual variations of LH levels. Circadian rhythm of LH secretion was not investigated.

Only 2 out of 33 female acne patients had elevated pretreatment prolactin levels and the slight increase in prolactin induced by both oral contraceptive combinations used in this study were not significant when compared with pretreatment values. Darley et al. previously found elevated prolactin levels in 18% of their female patients (1).

Twenty-five percent of our male and 40% of our female acne patients had DHEA-S levels above the upper limit of 9 μmol/l. SHBG levels in male and female acne patients were lower than in the corresponding control groups. Marynick et al. (2) found elevated DHEA-S in 81% of their acne patients and also SHBG levels were lower than in controls. However, the mean level of DHEA-S in our male patients with serious cystic acne was in normal limit (6.7 μmol/l) and we think, that elevated DHEA-S is a common alteration in acne, but serious acne can exist without DHEA-S elevation. Decreased SHBG level is a good indicator of intracellular androgen influence.

In the present study, the oral contraceptive combinations induced a decrease in DHEA-S after 6 months' treatment: 14% in the levonorgestrel/EE group and 30% in the desogestrel/EE group. The difference between the treatment groups was not statistically significant. Both OC combinations induced a similar 75–100% increase in serum total cortisol. This is thought to be a consequence of the increase in transcortin (12) induced by the combinations and, as a result, serum free cortisol should not increase (13). SHBG rose 250% in the desogestrel/EE group and 27% in the levonorgestrel/EE group, whereas serum free testosterone decreased 30–40% in both treatment groups (10). In our study we found DHEA-S elevation to be frequent in patients with acne, but the pretreatment values did not correlate with the severity of acne (two-variable linear estimation). We also found that SHBG levels were lower in both male and female acne patients compred to healthy controls.

It seems to us that low SHBG and elevated DHEA-S are the most often seen hormonal or hormone-dependent alterations which can be assayed in acne. Our study confirms results givenby Odlind et al. 1982 (3) and Marynick et al. 1983 (2). In our study, however, pretreatment DHEA-S levels did not correlate with the severity of acne and SHBG levels had only a borderline significant correlation with the severity of acne (10). It can be concluded that oral contraceptive treatment is beneficial in acne in female acne patients, at the same time increasing SHBG and decreasing DHEA-S serum levels.

ACKNOWLEDGEMENT

We thank Dr Howard Berkeley for his editorial help in the preparation of this manuscript.

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