

EXPERIMENTAL METHODS FOR CLINICAL PRACTICE

Sex Hormone-Binding Globulin, Serum Testosterone, and Androgen Receptors in the Skin in Papulopustular and Conglobata Forms of Acne Vulgaris

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It is shown that in 14-20- and 21-28-year-old men two clinical forms of acne vulgaris, papulopustular acne and acne conglobata are related to the disturbances in androgenic status.

Key Words: *acne vulgaris; men; sex hormone-binding globulin; skin androgen receptors; hyperandrogenemia*

Acne vulgaris is the most common dermatosis occurring in young people, especially during puberty [1,13]. It was demonstrated that the skin is a typical target tissue for androgens [6,13] and testosterone (TS), a major androgen in human blood that stimulates many metabolic processes in the endothelium of sebaceous glands [12]. Therefore, sex steroid hormones are thought to play an important role in the pathogenesis of some skin diseases. The same is true for acne vulgaris, especially during puberty, which is characterized by activation of gonads and considerable changes in the synthesis of gonadotropic hormones [11].

The incidence of different clinical forms of acne vulgaris varies considerably [9]. There are also grounds to suppose that clinical forms of this disease are related to some disturbances in the endocrine status, in particular, to hyperandrogeny of a varying severity [11,14]

The aim of the present study was to evaluate the degree of hyperandrogeny in male patients in their

teens and 20s with two most common forms of acne vulgaris: papulopustular acne and acne conglobata.

MATERIALS AND METHODS

Male patients aged 14-20 and 21-28 years with two clinical forms of acne vulgaris: papulopustular acne (30 patients) and acne conglobata (17 patients) were examined. Control groups comprised age-matched healthy subjects. Fasting blood samples were obtained from the cubital vein at 08:00-09:00 before treatment. The serum was routinely prepared and stored at -20°C for no more than 3 weeks. The serum concentration of total TS and sex hormone-binding globulin (SHBG) was measured by radioimmunoassay using Farnos Diagnostica kits. Fractions of free TS and TS bound to serum proteins (albumin and SHBG) were determined as described elsewhere [4]. Androgen receptors were assessed in 25 biopsy specimens of affected skin, 16 specimens of visually healthy skin from patients with acne vulgaris, and 16 skin biopsy specimens from the back of healthy individuals without endocrine pathology and acne vulgaris. Androgen receptors (AR) were assessed in the cytosol

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fraction by protamine sulfate precipitation of the hormone-receptor complex [10] after binding to 5α - ^3H -dihydrotestosterone (^3H)DHT, Amersham). The data were processed using medical statistic software. The significance of differences was determined using the Student's *t* test.

RESULTS

The total serum TS was found to be a noninformative parameter, since no differences in it were observed between the patients and controls (Table 1). SHBG plays a very important role because the proportion between free (biologically active) and bound (inactive) fractions of sex steroid hormones and, in particular, TS depends on the concentration of SHBG [16]. The concentration of SHBG in patients with acne vulgaris of both age groups was lower than in the control (Table 1). Moreover, this parameter varied in patients with different clinical forms of the disease independently of the age.

In male patients in their teens and 20s with two most common forms of acne vulgaris, the fraction of SHBG-bound TS was found to be decreased in comparison with the age-matching controls of both age groups (Table 1). The concentration of free biologically active TS is undoubtedly a more specific parameter, since the dynamic balance between free and SHBG-bound TS determines the action of TS, the major androgen in men, on the target tissues. The fraction of free TS was higher in all patients compared with the controls. In acne conglobata, the level of free TS in 14-20-year-old patients surpassed that in 21-28-year-old patients. It should be noted that free TS also differed in the control groups, being higher in 14-20-year-old subjects. These data are consistent with other investigations demonstrating considerable age-dependent variations in the activity of the endocrine glands regulating reproductive organs in males over 14 [3].

Recently, the role of androgens in acne vulgaris has been extensively studied. Changes in the androgen status have been demonstrated in many cases [5]. The intergroup differences in the serum fraction of free TS in patients observed by us suggest that endocrine imbalance, specifically, changes in the level of biologically active serum TS, probably promotes the development of this dermatosis and various clinical manifestations in different forms of acne vulgaris in men in their teens and twenties. This assumption has been recently confirmed by experimental results [11]. From the data presented in Table 1 it can be concluded that not only the level of free TS but also the blood concentration of SHBG vary in the two forms of acne vulgaris. These data attest to hyperandrogenemia in these patients.

The sensitivity of target tissue to androgens was judged from the binding of ^3H)DHT in cytosol fraction prepared from skin biopsy samples. To this end, 25 skin biopsy specimens from affected areas of the back and 16 specimens of visually healthy skin remote from affected areas were obtained from patients before treatment, and 16 skin samples were obtained from healthy male subjects aged 15-28. The occurrence and the mean level of AR in the skin of patients with acne vulgaris and healthy individuals are presented in Table 2.

In both papulopustular and conglobata forms of dermatosis, skin androgen receptors were detected with the same frequency, the mean level of AR in involved areas being significantly higher in papulopustular acne ($p < 0.05$). In patients with acne vulgaris, the level of AR in healthy skin was significantly higher than in involved areas. The lower level of AR in involved areas may be due to the fact that the majority of DHT-specific binding sites is occupied by endogenous androgen probably elevated in this disease. This assumption was to a certain extent confirmed by the increased serum content of free TS in patients with acne conglobata (Table 1). It cannot

TABLE 1. Some Endocrinological Parameters of the Serum in Patients with Two Forms of Acne Vulgaris and Healthy Men in Two Age Groups

Parameter	Clinical forms of acne vulgaris					
	14-20-years-old			21-28-years-old		
	control (n=12)	papulopustular (n=16)	conglobata (n=14)	control (n=10)	papulopustular (n=8)	conglobata (n=9)
Total TS, nmol/liter	13.4±3.5	13.3±1.8	13.8±1.0	16.2±2.4	16.9±3.1	12.5±1.1
SHBG, nmol/liter	29.0±2.0	21.0±1.4 ¹	20.3±1.9 ^{1,2,3}	36.1±3.4	26.5±5.6 ¹	29.1±1.7 ^{1,3}
SHBG-bound TS, %	41.0±3.1	31.0±1.4 ^{1,2,3}	34.8±2.5 ^{1,2,3}	45.9±2.2	38.7±4.9 ³	44.5±1.8 ³
Free TS, %	2.72±0.13	3.04±0.08 ^{1,2}	3.12±0.11 ^{1,3}	2.37±0.09	2.94±0.23 ¹	2.61±0.08 ^{1,3}

Note. Significance of differences ($p < 0.05$): ¹compared with the control; ²between patients; ³between patients of different age groups.

TABLE 2. Androgen Receptors (AR) in the Cytosol Fraction of Skin Specimens in Patients with Acne Vulgaris and Healthy Individuals

Skin specimens (from the back)	n	AR range, fmol/mg protein	Incidence of AR, %	Mean level of AR, fmol/mg protein
From involved regions:				
papulopustular acne	14	10—56	85	48.7±10.0
acne conglobata	11	12—32	80	18.5±8.2
Healthy skin	16	15—60	40	31.2±8.4
Skin samples from healthy subjects	16	60—210	44	115.0±25.0

be ruled out that active DHT metabolism in the skin of these patients [1] results in a down-regulation of the synthesis of the receptor protein in androgen-sensitive target tissues.

AR were detected in 7 out of 16 samples of healthy skin (44%) from patients with acne vulgaris, the level of AR varied from 15 to 60 fmol/mg protein. The mean level of AR in the skin from healthy male subjects aged 15-28 surpassed that in age-matching patients with acne vulgaris. This may be related to hyperandrogenemia (reduced level of SHBG and elevated content of free TS in the blood) in patients with acne vulgaris. Since only free androgens enter steroid-sensitive target cells, the elevated blood content of free TS in acne vulgaris may lead to its enhanced transport across the plasma membrane and stimulate the formation of DHT [8], which binds to free AR. The level of AR is thereby considerably lower in patients with acne vulgaris than in healthy individuals.

These data are not only of theoretical importance. Treatment of patients with acne vulgaris is a complex problem, and in light of this our findings suggest the necessity of endocrine component in the therapy of different forms of acne vulgaris, and first of all, antiandrogen therapy. The results obtained indicate that acne vulgaris is an endocrine-dependent disease. Three important conclusions can be made from our findings. First, acne vulgaris in young men is related to endocrine disturbances. Different clinical forms of acne vulgaris are presumably due to varying severity of endocrine disturbances in these patients and, first of all, imbalance in the SHBG-bound/free

TS system in the blood. Second, hormone profile and primarily androgen status or at least the blood content of SHBG should be determined in all forms of acne vulgaris. Third, this disease requires rigorous differential methods of therapy, including the endocrine component, in case when specific endocrine disturbances are revealed.

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