Raised Serum Androgens and Increased Responsiveness to Luteinizing Hormone in Men with Acne Vulgaris

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We have investigated the hormone profiles and the relationship between serum testosterone and luteinizing hormone in men with long-standing acne vulgaris. In the controls, age correlated with the free androgen index and with serum dehydroepiandrosterone-sulphate, so for the purposes of comparison 33 men with acne vulgaris were age-matched against 33 controls. Compared with controls, the acne patients had higher medians of serum androstenedione, testosterone and free androgen index. In both groups there was a significant correlation between testosterone and luteinizing hormone levels. For a given level of luteinizing hormone the patients with acne tended to have higher levels of serum testosterone than normal controls. These results indicate that in this group of men with long-standing acne there was either increased responsiveness of the target organ to luteinizing hormone or there was an increased amount of androgen-secreting tissue. *Key words: sebaceous glands; gonadotrophins; testosterone.*

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Although the precise mechanisms of acne vulgaris are unknown, it is accepted that acne is androgen-related on the basis of onset at puberty, exacerbation by androgens (1) and alleviation by anti-androgens (2). Variation in the severity of acne at different sites in the same patient indicates that local factors may have a role. Amongst these are the conversion of testosterone to the more active dihydrotestosterone by 5α-reductase (3–5) and target organ sensitivity perhaps related to the androgen receptor. However, increased androgen synthesis from adrenal or gonadal sites with consequent hyperandrogenaemia may also be important, as indicated by the development of post-adolescent acne in patients with late onset congenital adrenal hyperplasia (6, 7) and by the occurrence of hyperandrogenaemia in a proportion of women with acne (8–11). The sometimes associated hirsutism and menstrual abnormality provide additional clinical evidence of disordered endocrine function in these women. Hyperandrogenaemia has also been described in men with acne in some studies (12, 13) but not in others (14).

When hyperandrogenaemia does occur it may be possible to identify the source and the controlling factors. With adrenal androgen production under ACTH control and ovarian androgen production under luteinizing hormone (LH) control (15), both ACTH and LH influence sizeable proportions of androgen production in women. In contrast, in normal men the adrenal contributes less than 5% of the total daily production of 7 mg testosterone (16), and so LH controls the 95% of androgen production derived from the testis.

The adrenal is the source of the excess androgen in some women with hyperandrogenaemia, but in most hyperandrogenic women the excess androgens are synthesised in the ovary (17) and approximately half of such patients have raised LH levels. In those with normal LH levels and ovarian hyperandrogenism it has been postulated that there is abnormal modulation of ovarian androgen responsiveness to LH (18).

Raised LH levels have not been noted in men with acne vulgaris, but we have looked into the possibility that abnormal testicular responsiveness to LH might occur in men and be responsible for any hyperandrogenaemia.

PATIENTS AND METHODS

Fifty-seven Caucasian men who were referred by their general practitioners for treatment of acne vulgaris, or were incidentally noted to have acne, and 59 normal Caucasian men were included in the study. The controls were fit hospital staff or patients attending the Skin Clinic with minor skin disorders – mostly warts and moles. The face, back and chest were examined in all cases and men were included in the control group only if they were free of acne. Acne was graded as described by Burke & Cunliffe (19) with, however, substitution of mild, moderate and severe for the lowermost, middle and uppermost ranges of their continuous numerical grading scheme. The most severely affected site was used to assess the grade. For the purposes of comparison, each patient was age-matched by year against one control. Blood samples were taken from the patients and controls at the time they attended the clinic. The collection time was recorded as minutes after 0900 h.

Biochemical assays

Serum dehydroepiandrosterone-sulphate (DHEAS) was measured by a competitive radioimmunoassay (Chelsea Kits and Reagents), androstenedione and testosterone by in-house extraction radioimmunoassays and sex hormone binding globulin (SHBG) by immunoradiometric assay (Farmos). LH, follicle stimulating hormone (FSH) and oestradiol were assayed using an automated ELISA system (Boehringer Mannheim ES 700).

Between-batch coefficients of variation were as follows: DHEAS 11.4% (9.1 µmol/l), androstenedione 10.3% (7.5 nmol/l), testosterone 8.1% (16.2 nmol/l), SHBG 9.5% (11.3 nmol/l), LH 6.5% (6.9 U/l), FSH 6.6% (6.0 U/l) and oestradiol 12.5% (200 pmol/l). Assay sensitivities were, respectively, 0.2 µmol/l, 0.8 nmol/l, 1.5 nmol/l, 0.5 nmol/l, 0.5 U/l, 0.5 U/l, 37 pmol/l.

17α-hydroxyprogesterone was measured by an in-house radioimmunoassay, employing iodinated tracer, after ether extraction. Intra-assay imprecision was 7.8, 6.1 and 5.1% at 7.0, 21.1 and 52.5 nmol/l, respectively. Inter-assay imprecision was 12.3, 7.7 and 8.7% at 6.1, 20.3 and 55.0 nmol/l, respectively. The sensitivity was 0.6 nmol/l.

The free androgen index (FAI) was calculated thus: FAI = (testosterone/SHBG) × 100.

Statistics

Using Systat (Mac version 5.2.1) the Wilcoxon signed rank test was used to compare medians, except where there were occasional missing values as in the cases of 17α-hydroxyprogesterone, oestradiol and FSH when the Mann-Whitney U-test was used. Spearman's rank correlation

Table I. *Endocrine values in acne vulgaris patients and controls*

	Normals		Acne vulgaris		P
	median	IQR	median	IQR	
17-OH progesterone nmol/l	4.90	3.35	5.30	2.50	NS
DHEAS μmol/l	9.80	4.10	9.00	6.10	NS
Androstenedione nmol/l	5.80	1.70	7.10	2.60	0.016
Testosterone nmol/l	16.10	6.00	21.20	7.00	0.01
Oestradiol pmol/l	105.00	66.00	115.00	71.00	NS
SHBG nmol/l	25.00	13.00	29.00	11.00	NS
FAI	64.55	17.00	71.56	36.00	<0.001
LH U/l	3.20	1.40	3.00	1.80	NS
FSH U/l	5.10	3.90	5.05	4.55	NS

IQR = interquartile range
NS = not significant

test was used for correlations. Confidence intervals for the difference between the slopes of two regression lines and for the vertical difference between two parallel regression lines were calculated as described by Gardner & Altman (20). $p < 0.05$ was taken to be significant.

RESULTS

After age matching, there were 33 patients aged from 19 to 49 years, mean 29.84 years, SD 6.98. The patients had had acne for from 5 to 32 years, mean 14.40, SD 6.77. The acne was graded as mild in 3 patients, moderate in 14, and severe in 16. In the two groups the times at which blood samples were collected were not significantly different. The mean time for the controls was 180 min after 0900h, SD 120 min: for the acne patients the mean time was 170 min, SD 122 min.

The biochemical results are summarised in Table I. The medians of androstenedione, testosterone and FAI were significantly higher in the acne patients than in the controls (Fig. 1).

In both groups there was a statistically significant correlation between testosterone and LH levels – for acne $r_s = 0.67$, $p < 0.001$, for controls $r_s = 0.47$, $0.01 > p > 0.001$. The scatter-plots for the two groups are shown in Fig. 2. For the normal subjects the regression of testosterone on LH was given by

testosterone = 12.4 + 1.403 LH: that for the acne patients was testosterone = 14.074 + 2.016 LH. The difference between the slopes was 0.613, with a 95% confidence interval of −1.032 to 2.258. This confidence interval includes zero, and the slopes were therefore not significantly different and could be regarded as parallel. The adjusted mean vertical distance between the two slopes was 3.745 nmol/l, SE 1.210, 99% confidence interval 0.5367 to 6.9632.

In the initial group of 59 normal men aged 19 to 49 years, mean 32.46, SD 7.29 age correlated with FAI, ($r_s = -0.33$, $0.02 > p > 0.01$) and with DHEAS ($r_s = -0.39$, $0.01 > p > 0.001$). In the initial group of 57 acne patients the corresponding figures were for FAI $r_s = -0.32$, $0.02 > p > 0.01$, for DHEAS $r_s = -0.32$, $0.02 > p > 0.01$.

DISCUSSION

Our finding and those of others that FAI and DHEAS were negatively correlated with age indicate that precise age-matching of patients with controls is desirable in studies of testosterone in acne (21, 22).

The medians of serum androstenedione and testosterone were higher in the acne patients than in the controls. Also, and
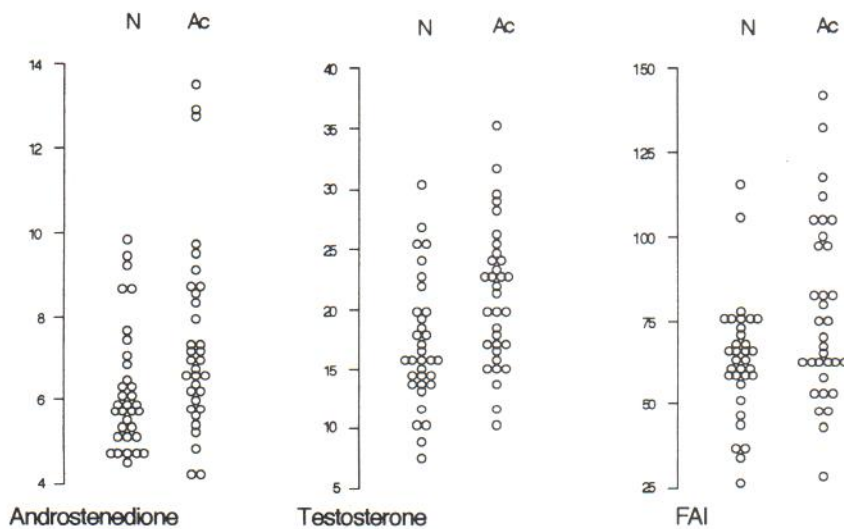

Fig. 1. Serum androstenedione (nmol/l), testosterone (nmol/l) and free androgen index (*FAI*) levels of the normal controls (*N*) and the acne vulgaris patients (*Ac*).
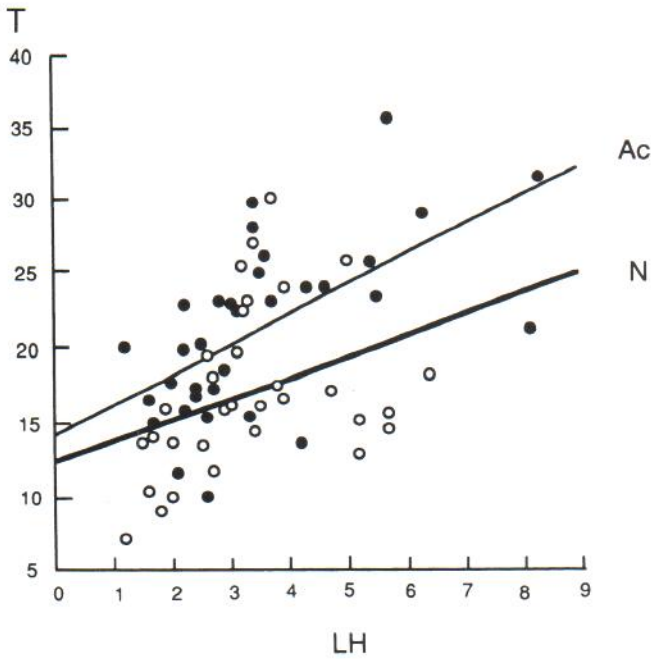
Fig. 2. Serum testosterone (*T*) (nmol/l) and luteinizing hormone (*LH*) (U/l) levels in normal controls (*open circles*) and acne vulgaris patients (*solid circles*). Lower line shows regression of *T* on *LH* for normals (*N*): upper line shows regression of *T* on *LH* for acne patients (*Ac*).

perhaps more significantly because it correlates well with free or biologically active testosterone (23), the median FAI was higher in the acne patients than in the controls.

The dot plots show that few patients had levels above the normal range and in many instances the androstenedione, testosterone and FAI values for the acne patients overlapped those of the controls. This overlap does not, however, preclude the existence of two separate groups of acne patients – one with high serum androgens and the other with normal levels.

The patients in this study had all had acne for a minimum of 5 years, and most were referred by their primary care physicians. They were, therefore, a selected group. Overall, they tended to have higher levels of androgens and, assuming that this was due to increased production rather than diminished loss, the possible sources of excess androgens are the adrenal, the testis and extraglandular peripheral sites. The fact that the adrenally-derived androgen precursor, DHEAS, was not raised in the acne patients is against an adrenal source for the increased androgen output.

The output of testosterone from the Leydig cells of the testis is tightly controlled by LH with close temporal coupling of serum LH and testosterone levels in normal men (24). Consistent with this we found good correlation between testosterone and LH in our controls. The acne patients also showed good correlation between testosterone and LH.

For any given level of LH the patients with acne tended to have higher levels of serum testosterone than controls. One possible explanation might be that the LH of acne patients is more active and produces a greater response. We measured only immunoreactive LH, but bioactive LH may be a more relevant measurement. In women there is evidence that the level of bioactive LH may be more useful for the endocrine diagnosis of

polycystic ovarian disease (25). Also, the bioactivity of the LH molecule is affected by glycosylation, and, in addition, the action of LH on Leydig cells and ovarian thecal interstitial cells may be influenced by the levels of IGF-1 and insulin (26–31).

Other possible explanations for a higher testosterone for a given LH might be that the Leydig cells of acne patients are hyperresponsive to LH or there is an increased volume of androgen-secreting tissue, as has already been suggested for women with post-adolescent acne (11). Autonomous overproduction of testosterone independent of LH seems less likely in view of the correlation between testosterone and LH in the acne patients.

Although acne is undoubtedly a heterogeneous group of disorders, androgens appear to have a fundamental role, and the regulation of androgen synthesis by gonadotrophins and other factors may well be important. The significance of our findings in the pathogenesis of acne remains to be determined, but we have demonstrated that in men with acne vulgaris the relationship between testosterone and LH is different from that found in men without acne.

In summary, we have shown that in a group of males with long-standing acne the serum androstenedione and testosterone and the FAI were on average higher than in controls. Also, the serum testosterone level correlated with LH, and for a given LH the acne patients tended to have higher testosterone levels than acne-free age-matched controls.

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