Endocrine factors in pre- and postmenopausal women with hidradenitis suppurativa

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Summary
The relationship between hidradenitis suppurativa (HS) and hyperandrogenism is largely based on the finding of an increased free androgen index due to a low sex hormone binding globulin (SHBG). As SHBG is now believed to be regulated by factors that influence body weight, and previous studies were not controlled for body weight, we have re-evaluated the androgen status of female patients with HS. We have studied the endocrine status of 66 women with HS. Twenty-three had acne, and 23 were significantly obese (body mass index: BMI >30). There was no relationship between obesity and disease duration. Nineteen of 56 women were hirsute. A premenstrual flare in disease activity was reported by 32 women, but this was not related to menstrual disturbances. No consistent relationship was reported with pregnancy. Eight women with HS were menopausal at presentation, and one developed her disease 6 years after the menopause. Plasma androgens in women with HS were compared with controls matched for BMI and hirsuties. There was no difference between HS and controls. Testosterone and dehydroepiandrosterone sulphate were normal in all subjects with HS. In obese subjects, SHBG was reduced, consistent with BMI-matched controls. We have found no supporting evidence for biochemical hyperandrogenism in women with HS when compared with age-, weight- and hirsuties-matched controls. We report the continuation and primary development of HS in postmenopausal women.

Hidradenitis suppurativa (HS) is a chronic suppurative disease affecting the apocrine gland-bearing skin in humans. It is related to inflammatory disorders of the other components of the apopilosebaceous unit, such as acne vulgaris, acne conglobata and dissecting cellulitis of the scalp. Although HS is localized in the apocrine-bearing skin, and undoubtedly affects the apocrine glands, there is debate whether the glands are primarily or secondarily involved. A further paradox involves the relationship with androgens, as, despite the relationship of the disease to changes in androgen status, the disease appears to be considerably more common in adult women than men.

Increases in circulating androgens have been proposed by two studies. The first demonstrated a high free androgen index predominantly due to a low sex hormone binding globulin (SHBG), but the patients were not controlled for body mass index (BMI). This finding is compromised, as many HS patients are significantly overweight, and SHBG is negatively correlated with BMI. A second study could only demonstrate hyperandrogenism in a subgroup of women who did not experience a premenstrual flare in their disease. We have re-examined the endocrinology of HS, and have found no abnormality in circulating androgens in premenopausal women. We report the persistence of HS in the postmenopausal years.

Patients and methods
Patients with HS were drawn from the routine dermatological service at the Leeds General Infirmary. This clinic is supported by a collaborating surgeon who will, over the years, have treated the most severely affected cases and will, therefore, have reduced the overall prevalence of patients severely affected with HS. Clinical scoring systems, including BMI (kg/m²), obesity, defined as BMI > 30, and hirsuties, scored using the method of Ferriman and Gallwey. Women scoring > 10 were considered to be hirsute by the single observer, JHB. Assays for testosterone and dehydroepiandrosterone sulphate (DHAS) were performed by in-house radio-immunoassay.

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(RIA), for SHBG by in-house binding assay, and for gonadotrophins by chemiluminescence using an ACS-180 analyser (Ciba Corning Diagnostics, Halstead, U.K.). All immunoassays had inter-assay and intra-assay coefficients of variation of <12%. Median values and ranges are quoted, and statistical tests for non-parametric data have been used.

**Results**

Sixty-six women were seen, with a median age of 33 years (range 16–59). The median age of onset was 25 years (9–48), and the median duration of disease was 72 months (6–360). During this period, 10 men with HS were seen. The disease was distributed as follows: axilla 45 of 66, perineum 21 of 66, inguinal 37 of 66, and submammary 24 of 66. Comedones were detected in 26 women, and pilonidal surgery had been performed in five women.

Acne was present at time of presentation in 23 of 66 patients. There were no differences in age, BMI, plasma testosterone, SHBG or DHAS between those women with HS with or without acne vulgaris (Mann–Whitney U test, \(P > 0.05\)). Nineteen of 56 (34%) women were hirsute. Those women who were hirsute had a tendency towards a longer disease duration of 120 months (13–432) vs. 60 (6–360) months (Mann–Whitney U test, \(P = 0.06; n = 54\)). The median BMI was 28.3 (20.9–55.9) for 53 female patients. Twenty-three of the 66 (35%) patients were significantly obese (BMI > 30). There was no relationship between obesity and disease duration (\(R_S = 0.181, P = 0.22; n = 47\)).

Eight of the 57 premenopausal women were taking an oral contraceptive. Eight women were postmenopausal and three had, or were, taking oral hormone replacement therapy.

Pregnancy

The effects of pregnancy were reported by 38 women; 17 had not been pregnant and there were no data on 10 (total 65). Fourteen women reported no effect by pregnancy, but three reported a deterioration in disease activity. An improvement in disease activity, after pregnancy, was reported by five, and a worsening by one. Eleven had only been pregnant before onset of HS. Two had no recall of the effects of pregnancy. In two, the disease began during pregnancy.

**Effect of menses**

A premenstrual flare in disease activity was reported by 32 women, no flare was reported by 19, and no data were available on a further 14. In the 25 with spontaneous menstrual cycles, 16 reported a premenstrual flare, whereas three of seven patients with irregular cycles reported a premenstrual flare (\(\chi^2 = 2.03; P = 0.05\)). Seven of the eight women taking an oral contraceptive reported a premenstrual flare in their disease.

Postmenopausal woman

Eight women with HS were menopausal at presentation (diagnosed on basis of amenorrhoea and an FSH > 20 IU/l). Their median age was 49 years (39–61). Their disease began at puberty in two, in the early 20s in one, at 12, 5, 2 and 0 years prior to their last menstrual period in one patient each and in one, 6 years after the menopause. The disease was localized to the axillary and submammary area in four, the inguinoperineal and submammary area in one, the inguinoperineal area in three, and the axillary in one. Three women had been, or were currently, receiving hormone replacement therapy for at least 6 months, and had noticed no benefit.

**Hormonal studies**

Plasma measurements of androgens in women with HS were compared with controls matched for BMI and hirsuties (values quoted as median (range); Mann–Whitney U test). Hirsuties is defined as a Ferriman and Gallwey score of >10. These data show no difference between groups (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Testosterone (nmol/l)</th>
<th>SHBG (nmol/l)</th>
<th>DHAS (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HS without hirsuties (n = 18)</td>
<td>1.6 (0.7–2.1)</td>
<td>44.5 (17–103)</td>
<td>5.4 (1.7–14.1)</td>
</tr>
<tr>
<td>Weight-matched non-hirsute controls (n = 27)</td>
<td>1.5 (0.8–2.7)</td>
<td>45 (12–78)</td>
<td>4.3 (2.3–13.6)</td>
</tr>
<tr>
<td>HS with hirsuties (n = 16)</td>
<td>1.6 (1.2–2.5)</td>
<td>27 (11–69)</td>
<td>6 (1.6–13.9)</td>
</tr>
<tr>
<td>Weight-matched hirsute controls (n = 23)</td>
<td>2.0 (0.9–4.2)</td>
<td>30 (7–53)</td>
<td>7.1 (0.9–14.9)</td>
</tr>
</tbody>
</table>

Discussion

HS is an inflammatory disease affecting the apocrine-bearing skin of the axillae and perineoglabular regions. The patients in this study, as in many others, were predominantly female. The disease begins after puberty, with a peak onset in the third decade. We report the continuation of active disease in seven postmenopausal women, and the onset, after the menopause, in a further woman. The disease activity showed a menstrual fluctuation in half our patients, but this gave no predictive effect on the overall course. The effect of pregnancy was not consistent. Affected women had a high prevalence of obesity and hirsuties.

The human apocrine gland, like all the other components of the skin, is likely to be dependent upon sex hormones. This is based on their development at puberty, phylogenetic comparisons with equivalent glands in other mammals, and the androgen dependence of all the other human cutaneous adnexae. However, if the glands were androgen-sensitive, they should be larger and more active in males and, while this is true for the rabbit gland volume, studies in humans have shown no sex difference in apocrine sweat production. Moreover, apocrine glands isolated from adult women show no response to androgen in vitro.

The relationship of HS and androgens is conflicting. Some authors, using data of biochemical hyperandrogenism, propose that androgens play a part in apocrine disease in women. They draw an analogy with acne and hirsuties. However, both these conditions are more severe and more prevalent in males. The hypothesis does not explain the overwhelming excess of females, nor the observation that testosterone has been an effective therapy for HS.

There is clearly a relationship between sex hormones and HS. Disease activity is modified by pregnancy and the menstrual cycle, and childhood cases have been caused by precocious puberty. HS is more prevalent in hirsute women than in weight- and age-matched controls. The relationship is further supported by the exacerbation of the disease activity, in the luteal phase of the menstrual cycle, after a surge in ovarian androgen. We have not been able to show any abnormal increase in androgens, or suppression of SHBG, in females with HS, compared with controls matched for hirsuties.

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References