 DOI 10.1111/j.1365-2133.2005.06953.x

Female pattern hair loss, sebum excretion and the end-organ response to androgens

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Accepted for publication
26 May 2005

Key words:
alopecia, androgens, sebum excretion

Conflicts of interest:
None declared.

Summary

Background Although female pattern hair loss can be a feature of hyperandrogenism, many women with hair loss show no clinical or biochemical features of androgen excess. It is possible that hair loss in nonhyperandrogenic women is due to a high level of response to androgens by scalp hair follicles. In this study we explored this idea using sebum excretion as a marker of the cutaneous end-organ response to androgens.

Objectives To test the hypothesis that hair loss in nonhyperandrogenic women is due to an increased cutaneous end-organ response to androgens.

Methods We studied 100 women, 41 with female pattern hair loss (without hirsutism), 29 with hirsutism (with and without scalp hair loss) and 30 subjects without hair problems. We measured hair density on the frontal scalp, forehead sebum excretion, serum free androgen index (FAI), and body mass index (BMI).

Results The mean FAI was significantly raised in hirsute women compared with nonhirsute women ($P < 0{\cdot}001$), but there was no difference in FAI levels between nonhirsute women with and without hair loss. The mean BMI was also significantly elevated in hirsute women ($P < 0{\cdot}01$) but there was no difference in BMI between nonhirsute women with and without hair loss. The mean sebum excretion was higher in hirsute women than nonhirsute women but the difference was not statistically significant. There was no difference in sebum excretion between nonhirsute women with and without hair loss. There was no correlation between hair density and sebum excretion.

Conclusions Our results show that sebum excretion is not elevated in women with female pattern hair loss. This may indicate that different androgen-response pathways operate in controlling hair growth and sebum excretion. The alternative explanation is that nonandrogenic mechanisms are involved in mediating hair loss in some women.

Female pattern hair loss (FPHL) is a common condition that affects about 5% of women by the age of 50 increasing to over 30% by age 70.[1] It typically presents as a diffuse reduction in hair density, mainly over the crown and frontal scalp, with retention of the frontal hairline. In some cases the entire scalp is involved, including the occipital region. The onset may be at any age from puberty onwards, and exceptionally it may start in childhood.

FPHL is generally thought to be the female equivalent of male balding and, like male balding, is often termed androgenetic alopecia in the belief that its expression requires both a genetic predisposition and androgens.[2] Scalp hair loss is undoubtedly a feature of hyperandrogenism in women, and several investigators have reported that women with hair loss are more likely to have elevated androgen levels or show an increased frequency of other features of androgen excess than women without hair loss. Futterweit *et al.* studied 109 women with hair loss and reported that 38·5% showed clinical or biochemical evidence of androgen excess.[3] In a series of 187 women with hair loss, Vexiau *et al.* reported abnormal hormonal profiles, mostly of minor degree, in 67% of women with hair loss alone and in 84% of women who were also hirsute.[4] In a recent series of 89 women presenting to a trichology clinic with hair loss, 67% showed ultrasound evidence of polycystic ovaries compared with 27% in a control group of 73 women, and 21% were significantly hirsute compared with 4% of controls.[5] However, other investigators have failed to find evidence of raised androgen levels in women with FPHL[6] and in all studies there is a variable proportion of women with hair loss who do not show clinical or biochemical signs of androgen excess.

The aim of this study was to test the hypothesis that female pattern hair loss in nonhyperandrogenic women is the result of increased end-organ sensitivity to androgens. To do this we compared scalp hair status, measured both subjectively and objectively, to sebum excretion, in a group of women with and without hair loss. The sebaceous gland is a hair follicle appendage and its activity is regulated by androgens.[7,8] However, sebum excretion rates correlate poorly with serum androgen levels and although sebum excretion tends to be higher in men than women there is wide interindividual variation and a considerable degree of overlap between the sexes.[9] These observations have led to the idea that end-organ factors play an important role in determining the response of the sebaceous gland to androgens, a concept for which there is some experimental support.[10,11] We hypothesized that, if female pattern hair loss is due to increased end-organ sensitivity to androgens, such women would have a higher level of sebum excretion than women without hair loss.

Methods

The study was approved by the South Sheffield Research Ethics Committee. Full informed consent was obtained from each subject.

Subjects

Subjects were recruited from premenopausal women, aged 18–50, referred to dermatology or gynaecology clinics with female pattern hair loss or hirsutism. Subjects without hair loss or hirsutism were recruited from women attending a dermatology clinic with benign noninflammatory nonhair-related conditions such as melanocytic naevi. Exclusion criteria included women using hormonal medications, such as oral contraceptives or antiandrogens, or other treatments that may affect hair growth (e.g. minoxidil lotion), pregnancy, thyroid disease and other hair disorders (e.g. alopecia areata). All subjects were caucasian.

Clinical assessment of hair status

Scalp hair status was assessed using the Ludwig classification.[2] All women classed as having hair loss were in the Ludwig I category or greater. Facial hirsutism was assessed using the modified Ferriman and Galwey method.[12,13] Women with a facial score of 4 or greater were classed as hirsute. Women without terminal hair growth on the face and who denied excessive hair growth elsewhere on the body were classed as nonhirsute.

Measurement of scalp hair density

Scalp hair density was measured in all subjects using a macrophotographic method. A 1-cm^2 site on the frontal scalp, midway between the frontal hairline and the vertex, was shaved and photographed, as previously described.[1] The number of hairs per unit area was counted from the photographic prints.

Sebum excretion

Sebum excretion was measured using two methods. First, a Sebumeter (Courage+Khazaka electronic GmbH, Cologne, Germany) was applied to the centre of the forehead for 30 s to measure the casual sebum level (i.e. the amount of sebum on the skin surface). Subjects had not washed their foreheads for at least 4 h prior to the measurement. The forehead was then cleansed with an alcohol wipe and Sebutape (CuDerm Corporation, Dallas, TX, U.S.A) was applied for 30 min. Sites of sebum excretion appear as clear dots in the white Sebutape, which is then photographed under a light microscope. The area of the dots was measured using Scion image analysis software (http://www.scioncorp.com, accessed 9 July 2005) and expressed as a percentage of the total area of the measured field. Four random nonoverlapping fields were studied at a final magnification of $\times 180$ and the results averaged for each subject. The Sebutape method probably measures the follicular sebum reservoir rather than the true sebum excretion rate but these two variables are closely related.[14]

Serum androgens

Blood was taken from each subject for measurement of total serum testosterone, sex hormone binding globulin and the free androgen index (FAI).

Body mass index

The body mass index (BMI) was calculated for each subject from height and weight measurements.

Statistical analysis

Differences between the subject groups were analysed by ANOVA with *post-hoc* testing and, where appropriate, by a t-test. Relationships between variables were studied by linear regression analysis.

Results

One hundred women were recruited into the study. Thirty subjects had no hair problems, 41 had typical female pattern hair loss alone and 29 had facial hirsutism. Thirteen of the hirsute women also had scalp hair loss. Of the 21 women in whom hirsutism was the presenting complaint seven (30%) also had scalp hair loss.

Hair densities were significantly lower in the hair loss groups, in both hirsute and nonhirsute women, than in the nonhair loss groups (Fig. 1, Table 1).

Hirsute women had significantly higher androgen levels (given as FAI) than nonhirsute women (Fig. 2). In nonhirsute women there was no difference in androgen levels between those with and without scalp hair loss. Hirsute women with scalp hair loss had androgen levels similar to hirsute women without hair loss.

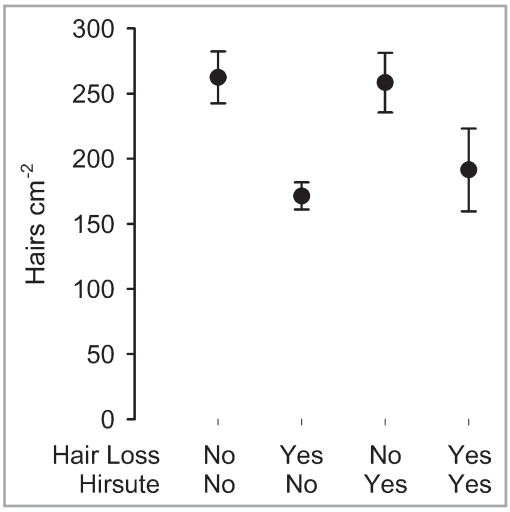

Fig 1. Hair density in control subjects without hair problems, in nonhirsute women with female pattern hair loss, and in hirsute women with and without hair loss. Results show means and 95% confidence intervals of the means.

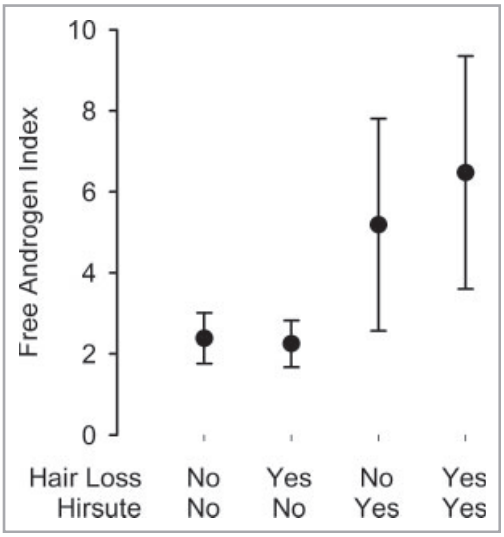

Fig 2. Free androgen index in control subjects without hair problems, in nonhirsute women with female pattern hair loss, and in hirsute women with and without hair loss. Results show means and 95% confidence intervals of the means.

The BMI was elevated in hirsute women compared with nonhirsute women (t-test $P < 0{\cdot}01$). Within these two groups there was no difference in BMI between those women with and without scalp hair loss (Fig. 3).

There was no significant difference in Sebutape readings between the four groups of subjects (Fig. 4). The average Sebutape reading was higher in hirsute (mean 5·34%, SD 2·19) than in nonhirsute women (mean 4·77%, SD 3·75) but the interindividual levels varied widely and the difference was not statistically significant. There was no difference in Sebutape readings between women without hirsutism (mean 4·71%, SD 3·75) and hirsute women (mean 4·74%, SD 3·32) with normal androgen levels (FAI < 5). Sebutape readings were higher in hirsute women with FAI > 5 (mean 6·16%, SD 2·66) but the difference when compared with nonhirsute women was not statistically significant. Similar results were obtained when sebaceous activity was measured using a Sebumeter (results not shown).

There was no correlation between hair density and Sebutape measurements (Fig. 5) or Sebumeter readings. There was also no correlation between the FAI and hair density or sebum excretion.

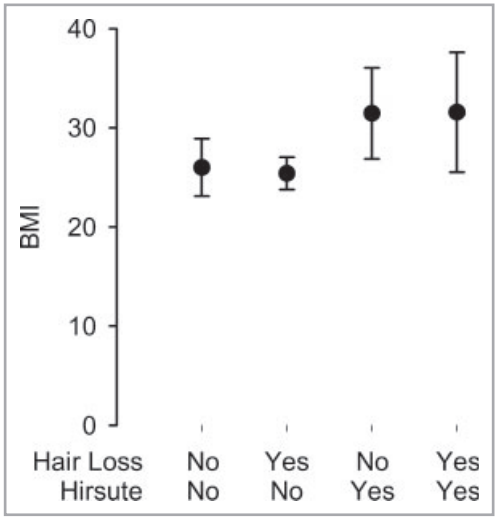

Fig 3. Body mass index (BMI) in control subjects without hair problems, in nonhirsute women with female pattern hair loss, and in hirsute women with and without hair loss. Results show means and 95% confidence intervals of the means.

Table 1 Probability that differences between groups occur by chance. Analysis between individual groups was by a Tukey's *post-hoc* test

	All groups (ANOVA)	Control vs. hair loss	Control vs. hirsute	Control vs. hirsute + hair loss	FPHL vs. hirsute	FPHL vs. hirsute + hair loss	Hirsute vs. hirsute + hair loss
Hairs cm^{-2}	< 0·001	< 0·001	0·992	< 0·001	< 0·001	0·497	< 0·001
FAI	< 0·001	0·997	0·013	< 0·001	0·005	< 0·001	0·626
BMI	< 0·01	0·981	0·087	0·115	0·035	0·054	1·000
Sebutape	0·896	0·974	0·949	0·901	0·995	0·977	0·999

FPHL, female pattern hair loss; FAI, free androgen index; BMI, body mass index.

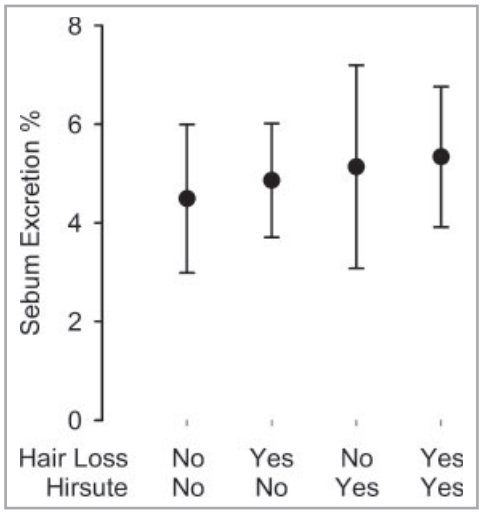

Fig 4. Sebutape readings, given as the percentage of the Sebutape field showing uptake of sebum, in control subjects without hair problems, in nonhirsute women with female pattern hair loss, and in hirsute women with and without hair loss. Results show means and 95% confidence intervals of the means.

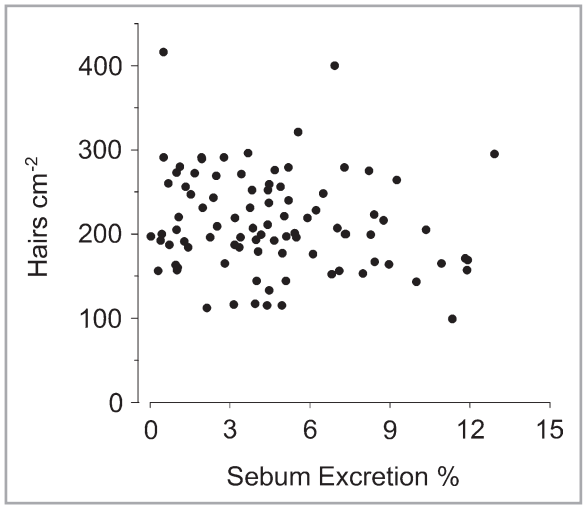

Fig 5. Scatter plot showing relationship between Sebutape readings and hair density in all subjects. Each datum point represents the result for an individual subject.

Discussion

The role of androgens in stimulating hair growth in most body sites is well established. Female hirsutism is known to be associated with raised androgen levels and other clinical features of androgen excess[15,16] and this is apparent from the results of our study. We also found that 30% of women presenting with hirsutism had scalp hair loss compared with an expected frequency of about 5% in this age group,[1] supporting the view that androgens play an important part in driving hair loss in some women. However, in a previous study of 873 hyperandrogenic women only 4% had scalp hair loss,[17] whereas hirsutism was present in 75·5%. Thus hair loss is a less common feature of hyperandrogenism than hirsutism. Our results also show that there is a group of women with hair loss who are not hirsute, have normal androgen levels and who show no other clinical features of androgen excess. It is possible that more detailed endocrine evaluation would have revealed evidence of increased androgen activity in some of these women. We did not measure serum levels of androgen metabolites which have been reported to be elevated in nonhirsute women with hair loss.[4,18] This finding has been interpreted as indicating increased hair follicle 5α-reductase activity but, as a group, women in these studies also showed evidence of hyperandrogenaemia, making it difficult to conclude that increased levels of androgen metabolites were solely due to increased peripheral metabolism. Furthermore, some women in these studies showed no endocrine abnormalities (37% in the study by Vexiau *et al.*[4]). In our study we adopted a different approach, using sebum excretion as a marker of the cutaneous end-organ response to androgens. We hypothesized that, if the hair loss is the result of a high level of follicular sensitivity to androgens, women with hair loss in the absence of other evidence of androgen excess would have higher levels of sebum excretion than women without hair loss. However, we found no difference in sebum excretion between women with and without scalp hair loss.

Strauss and Pochi reported that in women with normal androgen levels the mean sebum excretion was greater in hirsute women than in nonhirsute women, in keeping with the idea that sebum excretion can be used as a marker of the hair follicle end-organ response to androgens.[19] In our study the average sebum excretion was higher in the hirsute subjects than nonhirsute subjects but the interindividual variation was very wide and the difference was not statistically significant. At best, then, the association between sebum excretion and facial hair growth, both clearly androgen-dependent processes, is weak. It is possible that different androgen response pathways are involved in the regulation of hair growth and sebum production. It is also possible that other factors which are thought to modulate sebum excretion, such as oestrogens, prolactin, glucocorticoids and proopiomelanocortin derivatives,[20] are not involved in regulating hair growth. Burton *et al.* found no difference in sebum excretion between bald and nonbald men,[21] perhaps providing some support for these ideas. However, results obtained in men may not be relevant to women because of the much higher androgen levels in the former. The alternative explanation for the lack of correlation between sebum excretion and scalp hair loss in women is that hair loss is not necessarily due to androgen action.

Conclusive evidence for the role of androgens in female pattern hair loss is difficult, if not impossible to obtain. We therefore have to rely on the accumulation of items of evidence, none of which, on its own, gives a definitive answer. Thus, the lack of correlation between sebum excretion and scalp hair loss in this study does not prove that female pattern hair loss is not androgen-dependent. However, it adds to the growing body of evidence that nonandrogen-dependent

mechanisms are involved in driving hair loss in some women. FPHL has been reported to occur in the absence of androgens[22] and families have also been reported in which female pattern hair loss appears to inherit through the female line independently of male balding.[23] The 5α-reductase inhibitor finasteride, which is effective in the treatment of male balding, has been reported to stimulate hair growth in a small case series of hyperandrogenic women with FPHL.[24] However, in a large controlled trial in postmenopausal women with normal androgen levels finasteride failed to halt the progression of hair loss.[25] In a particularly instructive trial comparing the androgen receptor blocker cyproterone acetate with topical minoxidil in premenopausal women with hair loss,[26] as a group, the subjects taking cyproterone acetate continued to lose hair over the course of the trial (whereas the minoxidil group improved). However, subset analysis showed a small improvement with cyproterone acetate treatment in those women with menstrual disturbance or raised BMI values, suggesting that both androgenic and nonandrogenic mechanisms are involved in causing female hair loss.

In summary, the results of this study provide some support for the idea that nonandrogenic mechanisms are involved in the aetiology of female pattern hair loss in some women. Even if female pattern hair loss is exclusively androgen-dependent the results indicate it is much less likely to be associated with clinical and biochemical features of androgen excess than hirsutism, suggesting a more potent contribution of other factors, presumably genetic in nature. This may be analogous to the male condition where balding affects only a proportion of men whereas virtually all show beard growth. Understanding the role of androgens in female pattern hair loss is important because, if factors other than androgens are involved in the aetiology, treatments aimed at interfering with androgen pathways are unlikely to be uniformly successful and we should turn our attention elsewhere in the search for more effective therapy for this common and distressing condition.

Acknowledgments

This study was supported by a grant from the Sheffield Hospitals Charitable Trust.

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