Hormonal status and clinical relevance of hirsutism in elderly women

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Hirsutism is a common condition of elderly women, but its aethiopathogene and its clinical implications remain unclear. We therefore studied circulating androgen concentrations in elderly women. In addition, this study aims to define a possible relationship between hirsutism and anthropometric determinations, bone mass and serum lipids. Androgen levels were determined at basal state, after adrenocorticocortrophin (ACTH) stimulation and after dexamethasone administration in 10 hirsute elderly women and compared to 10 age-matched non-hirsute women. Anthropometric determinations included measurements of skinfold thickness and body mass index. Spinal bone mass density was assessed using dual photon absorptiometry. Hirsute women presented significantly higher levels of testosterone than controls (1.49 ± 0.38 vs 0.59 ± 0.05 nmol/l mean ± SEM; p < 0.05) and dihydrotestosterone (0.54 ± 0.07 vs 0.32 ± 0.03; p < 0.02). 17-hydroxyprogesterone levels after ACTH stimulation tended to be higher in hirsute women than in controls. No differences were observed between the two groups in serum oestrogen concentrations, plasma lipid pattern or bone mineral density. Hirsute women had a lower body mass index and lower calculated percentage body fat than the control group. We conclude that:

(i) hirsutism of elderly women is associated with increased androgen levels, probably from adrenal origin;
(ii) in some cases, enhanced response in 17-hydroxyprogesterone after ACTH stimulation suggests a partial adrenal 21-hydroxylase deficiency;
(iii) hirsute women present anthropometric characteristics compatible with the known anabolic effect of androgens on fat-free mass.

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Hirsutism is a condition frequently encountered in elderly women but its aethiopathogene remains unclear, e.g. it is not known if it is related to an excess of circulating androgens, if it is a consequence of low circulating oestrogens, or both. Moreover, it is unclear as to whether the hirsutism of these elderly women is just a consequence of sexual hormone abnormalities or whether it involves abnormalities in other steroid hormones. It is also not known whether hirsutism is accompanied by other clinical changes. We therefore measured circulating androgen concentrations in hirsute elderly women and related them to anthropometric determinations, bone mass and serum lipids.

Methods

Patients

Twenty women (10 hirsute and 10 age-matched non-hirsute women) aged 65–92 years were studied. Hirsutism was present for at least 2 years. It was moderate to severe, mostly confined to the face, without major signs of virilization and when assessed according to the method of Ferriman and Gallwey (1) it ranged from 9 to 14 (mean 11 ± 1).

There was no personal or familial history of salt-losing syndrome. Results of gynaecological examinations were normal. No enlarged ovaries were found on pelvic examination.

Patients who took medications that could affect adrenal function or bone metabolism were excluded from the study.

Informed consent was obtained from each patient and the study was approved by the ethical committee of the hospital.

Hormonal determinations

These included measurements of basal plasma testosterone, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulphate (DHEAS), 17-hydroxyprogesterone, ACTH, cortisol, prolactin, gonadotrophins and oestrogens.

Free testosterone was determined following the method of Wiest et al. (2).
Table 1. Hormonal plasma levels (mean ± sem) in 10 controls and 10 hirsute women at basal state and after a 5-day low-dose dexamethasone suppression test (2 mg daily by mouth in divided doses for 5 days).

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Hirsute</th>
<th>Dexamethasone suppression</th>
<th>Controls</th>
<th>Hirsute</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Dexamethasone</td>
<td></td>
<td>Basal</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Progesterone (nmol/l)</td>
<td>0.54 ± 0.03</td>
<td>0.45 ± 0.06</td>
<td>0.66 ± 0.48</td>
<td>0.48 ± 0.12</td>
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<tr>
<td>17OHP (nmol/l)</td>
<td>1.02 ± 0.12</td>
<td>1.05 ± 0.15</td>
<td>0.50 ± 0.08</td>
<td>0.34 ± 0.09</td>
<td></td>
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<tr>
<td>A4 (nmol/l)</td>
<td>5.56 ± 0.84</td>
<td>6.11 ± 0.80</td>
<td>1.88 ± 0.49</td>
<td>1.57 ± 0.59</td>
<td></td>
</tr>
<tr>
<td>DHEAS (nmol/l)</td>
<td>1.23 ± 0.21</td>
<td>2.33 ± 0.60</td>
<td>0.37 ± 0.08</td>
<td>0.63 ± 0.21</td>
<td></td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>0.59 ± 0.05</td>
<td>1.49 ± 0.38*</td>
<td>0.48 ± 0.02</td>
<td>0.55 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>DHT (nmol/l)</td>
<td>0.32 ± 0.03</td>
<td>0.54 ± 0.07*</td>
<td>0.27 ± 0.02</td>
<td>0.27 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>SHBG (pmol/l)</td>
<td>23 ± 3</td>
<td>24 ± 0.02</td>
<td>Traces</td>
<td>Traces</td>
<td></td>
</tr>
<tr>
<td>ACTH (pmol/l)</td>
<td>4.86 ± 0.18</td>
<td>5.04 ± 0.26</td>
<td>143 ± 41</td>
<td>66 ± 30</td>
<td></td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>510 ± 39</td>
<td>483 ± 36</td>
<td>2.8 ± 0.4</td>
<td>2.3 ± 0.5</td>
<td></td>
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<tr>
<td>LH (μg/l)</td>
<td>2.5 ± 0.3</td>
<td>2.1 ± 0.4</td>
<td>18.7 ± 1.7</td>
<td>13.4 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>FSH (μg/l)</td>
<td>16.0 ± 1.5</td>
<td>13.7 ± 1.1</td>
<td>Traces</td>
<td>Traces</td>
<td></td>
</tr>
<tr>
<td>PRL (μg/l)</td>
<td>12.6 ± 2.1</td>
<td>13.7 ± 1.1</td>
<td>117 ± 48</td>
<td>98 ± 36</td>
<td></td>
</tr>
<tr>
<td>Oestrone (pmol/l)</td>
<td>188 ± 23</td>
<td>210 ± 29</td>
<td>34.1 ± 13.6</td>
<td>16.5 ± 3.3</td>
<td></td>
</tr>
<tr>
<td>Oestradiol (pmol/l)</td>
<td>27.9 ± 8.1</td>
<td>17.3 ± 3.7</td>
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</tbody>
</table>

* 17OHP: 17-hydroxyprogesterone; A4: androstenedione; DHEAS: dehydroepiandrosterone sulphate; DHT: dihydrotestosterone; SHBG: sex hormone-binding globulin.

* Significantly different from controls; p < 0.05.

**Adrenocorticotropic stimulation test.** No prior dexamethasone suppression was administered in order to assess resting basal steroid levels. A heparin lock was placed in the forearm and the patient was allowed to rest for 15 min. A baseline blood sample was then obtained (0 min) and immediately afterwards 0.25 mg of synthetic 1-24 ACTH (Synachten, Ciba) was administered iv over 60 s. A second blood sample was obtained 60 min after ACTH was given. Serum was then separated and stored at −20°C until measurements.

**Dexamethasone suppression test.** A 5-day low-dose dexamethasone (DXM, 0.5 mg q.d.s.) suppression test was performed in all patients, as described by Ehrmann et al. (3).

**Serum lipid measurements**

These included fasting serum total cholesterol (Tc), HDL cholesterol (HDLc) and triglyceride (TG) using commercial kits. Serum LDL cholesterol (LDLc) was calculated according to Friedewald’s formula (LDLc = Tc – TG/5 – HDLc).

**Anthropometric determinations**

Skinfold thicknesses at four sites—biceps, triceps, subscapular and suprailiac—were measured on the right side of the body with the Lange caliper (Cambridge Scientific Industries, Inc., Cambridge, MD, USA) as described by Durnin et al. (4). The body density and the percentage body fat were calculated as described by Blanchard et al. (5). The body mass index (BMI) was calculated as the ratio of the body weight (kg) to the square of the height (m²).

**Bone density**

Vertebral bone densitometry was assessed by dual photon absorptiometry of the spine.

**Statistics**

Results are expressed as means ± sem. Two-sided t-tests were used to assess the significance of the differences. Pearson’s correlation coefficient was used to evaluate a possible linear association between each of the hormonal parameters and the anthropometric measurements.

**Results**

**Hormonal determinations**

**Basal state.** Hirsute women had significantly higher circulating serum testosterone and dihydrotestosterone levels when compared to the control group (p < 0.05 and p < 0.02, respectively). The calculated free testosterone level was also higher in the hirsute women than in the controls (15.0 ± 5.9 vs 5.9 ± 0.6 nmol/l; p < 0.05). No significant differences were found in the other circulating hormone determinations (Table 1). No correlations were found between androgen levels and anthropometric determinations or bone mineral density.

**Dexamethasone inhibition.** Inhibition by DXM of serum cortisol and circulating androgens was not significantly different between the two groups, although DHEAS
Fig. 1. Plasma progesterone, 17-hydroxyprogesterone, androstenedione, testosterone, dihydrotestosterone and cortisol (mean±SEM) in 10 controls and 10 hirsute women, before (open bars) and 60 min after iv injection of 0.25 mg of synthetic 1–24 ACTH (hatched bars).

Table 2. Serum levels (mmol/l) of total, HDL and LDL cholesterol (mean±SEM) in 10 controls and 10 hirsute elderly women.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Hirsute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>5.55±0.41</td>
<td>4.89±0.23</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.01±0.08</td>
<td>1.01±0.05</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>3.65±0.28</td>
<td>3.29±0.26</td>
</tr>
</tbody>
</table>

levels before and after DXM tended to be higher in hirsute women (Table 1).

Adrenocorticotrophin stimulation. Both groups showed the same degree of response in terms of serum cortisol after ACTH administration (Fig. 1). However, in hirsute women, the response of androgens was higher than in controls, although the difference was not significant (Fig. 1). Two hirsute patients had a 17-hydroxyprogesterone level after ACTH stimulation that was over the mean ± 1 SD of the control group.

Lipid determinations
No significant difference in serum cholesterol levels was observed (Table 2).

Anthropometric determinations
Subscapular and suprailliac skinfold thicknesses were lower in hirsute than in non-hirsute women (9.7±0.7 vs 13.5±1.2 and 9.8±1.2 vs 14.1±1.1 mm, respectively; p<0.02). Calculated percentage body fat was significantly lower in the hirsute group compared to the control group (38±2 vs 48±2%, respectively;
p < 0.01). The weights and the heights of the subjects were not significantly different (51 ± 2 kg and 1.56 ± 0.02 m for hirsute women and 54 ± 2 kg and 1.51 ± 0.02 m for controls). The BMI was significantly lower in the hirsute group compared to the control group (21.0 ± 0.8 vs. 23.6 ± 0.7 kg/m², respectively; p < 0.05).

**Bone densitometry**

No significant difference between the groups was observed in vertebral bone densitometry (0.757 ± 0.037 for hirsute vs. 0.735 ± 0.065 g/cm² for non-hirsute women).

**Discussion**

The present study shows that the only significant difference between the hirsute and non-hirsute elderly women concerns the circulating concentrations of testosterone and dihydrotestosterone, which are significantly higher in the hirsute group. No difference was observed in circulating oestrogens, suggesting that hirsutism in these patients was not secondary to the lack of oestrogens.

Dexamethasone administration led to normal inhibition of androgens and this ruled out any tumoral androgen secretion (3).

The tendency of an enhanced androgen response after ACTH administration may represent a consequence of an adrenal enzymatic defect. Indeed, in two of the hirsute women, we observed an increased 17-hydroxyprogesterone response to ACTH, which fulfilled the biochemical criteria of Eldar-Geva defining a heterozygote 21-hydroxylase deficiency (6). It had been speculated that the identification of patients with adrenal enzymatic deficiency is not only of academic interest but also has practical therapeutic implications because it is known that these patients are theoretically at risk of cortisol deficiency, at least during moments of stress (7). Nevertheless, our patients did not present overt cortisol deficiency because they presented normal cortisol response after ACTH administration. We were not able to pinpoint whether this enzymatic abnormality observed in some of our patients represented a classical “late-onset adrenal hyperplasia” or whether it was an age-related functional defect.

Another theoretical clinical relevance of increased androgen impregnation found in hirsute women concerns the known anabolic effects of androgens. Androgens have an important role in the regulation of bone cell metabolism (8) and it has been reported that bone density is positively correlated to serum androgen levels in women (9). However, this was not the case in the present study because no correlation was found between androgen levels and bone density, owing perhaps to the small number of subjects and the multiple determinants of bone density.

The higher calculated percentage of body fat with the increased BMI observed in the non-hirsute group suggests that hirsute women have an increased fat-free mass that may represent an anabolic effect of their increased plasma androgen concentrations.

The lower fat tissue and the lower DHEAS inhibition by DXM observed in the hirsute women indicate that adrenal factors rather than ovarian or peripheral factors are possibly of importance.

We did not find any differences in the plasma lipid pattern between the groups, although androgens are known to influence lipid metabolism (10).

In conclusion, hirsutism in elderly women is associated with increased levels of androgens, probably from adrenal origin. In some cases, androgen excess may be secondary to adrenal steroidogenic block. In addition, hirsutism is associated with anthropometric characteristics that may reflect the anabolic effects of androgens.

**References**


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