Androgen Metabolism in Sebaceous Glands From Subjects With and Without Acne

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Objective: To determine if there are differences in the activity of 17β-hydroxysteroid dehydrogenase and 5α-reductase (responsible for the production of testosterone and dihydrotestosterone, respectively) in sebaceous glands obtained from men and women with and without acne.

Design: Single-center examination of androgen levels and sebaceous gland enzyme activity in a cohort of volunteers.

Setting: Academic referral center.

Patients: Thirty-four subjects, consisting of 8 women with acne, 10 women without acne, 8 men with acne, and 8 men without acne.

Interventions: Single visit for blood sampling and 2 biopsies of forehead skin.

Main Outcome Measures: Serum levels of androgens were determined and compared with the activity of 5α-reductase and 17β-hydroxysteroid dehydrogenase in sebaceous glands microdissected from skin samples.

Results: No significant differences in the activity of 5α-reductase or 17β-hydroxysteroid dehydrogenase in sebaceous glands according to the presence of acne were noted in either men or women. The activity of 5α-reductase and 17β-hydroxysteroid dehydrogenase was significantly greater in sebaceous glands from men (n = 16) than women (n = 17). The oxidative activity of 17β-hydroxysteroid dehydrogenase was 2-fold higher in men than women. Serum levels of dehydroepiandrosterone sulfate, androstenedione, testosterone, and dihydrotestosterone were significantly higher in women with acne than in women without acne. No differences in serum androgen levels were noted in men on the basis of the presence of acne.

Conclusions: Higher serum androgen levels are associated with the presence of acne in women. A role for locally produced androgens in this process, however, cannot be excluded.

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EBUM PRODUCTION is stimulated by androgens and is key in the development of acne vulgaris. Several investigators have looked for direct relationships between serum androgen levels, sebum secretion rate, and the presence of acne. The presence of acne in prepubertal girls and sebum production in both sexes correlate with serum dehydroepiandrosterone sulfate (DHEAS) levels. Dehydroepiandrosterone sulfate is an adrenal precursor for synthesis of more potent androgens, such as testosterone and dihydrotestosterone (DHT). Although increased serum androgen levels correlate with the presence of severe nodular acne in men and women, these levels are often within the normal range in mild to moderate acne. This raises the question of whether there is an increased local production of androgens within the sebaceous gland (SG) of patients with acne vulgaris that leads to increased sebum secretion.

The SG possesses each of the steroid metabolizing enzymes needed to convert DHEAS to DHT (Figure 1). 3β-Hydroxy steroid dehydrogenase (3β-HSD) reduces dehydroepiandrosterone to androstenedione. Two isozymes have been identified. 17β-Hydroxysteroid dehydrogenase (17β-HSD) is a reversible enzyme that can use different nucleotide cofactors and act either as an oxidase (to produce androstenedione from testosterone) or as a reductase (to produce testosterone from androstenedione). Recently, 6 isozymes of 17β-HSD have been described. The type 2 isozyme is biochemically active in human SGs. Two isozymes of 5α-reductase (5α-R) (type 1 and type 2) have been identified. The type 1 isozyme of 5α-R is predominant in SGs and is present in higher levels in acne.
SUBJECTS AND METHODS

SUBJECTS

The study was approved by the institutional review board of Pennsylvania State University College of Medicine, Hershey. Men and women aged 18 to 45 years with and without acne were recruited especially for this study. Subjects with acne were defined as having a minimum of 15 comedones and 10 inflammatory papules on the face. Subjects were excluded if they had received oral antibiotics within 1 month before the study; used topical acne medications such as antibiotics, benzoyl peroxide, or tretinoin within 2 weeks before the study; received treatment in the past with oral retinoids; had known underlying endocrine disease, such as congenital adrenal hyperplasia, polycystic ovary syndrome, or adrenal or ovarian tumor; or were currently using oral contraceptives, contraceptive injection, implantable contraceptives, estrogens, prednisone, other corticosteroids, or finasteride.

PROCEDURES

All women were studied in the luteal phase of their menstrual cycle. Blood samples were taken for serum DHEAS, androstenedione, total and free testosterone, DHT, and 3α-androstenediol glucuronide. Skin biopsies of the forehead were performed as follows. A 12-mm elliptical excision (4 mm at its widest point) was made from each side of the forehead, approximately 6 mm from the hairline. Skin was excised in the subcutaneous layer and a layered closure was performed. Skin specimens were transported on ice to the dermatology laboratory, where microdissections were performed according to previously described techniques.22 Samples were incubated at 37°C at pH 5 and 7. Incubations for 5α-R were performed on isolated SG as previously described.22,23 Samples were incubated at 37°C at pH 5 and the presence of acne. Significance of the correlation was tested at a 95% confidence interval with Fisher r to z test.

To date, no studies have been done to determine if there are sex-related differences in the activity of 17β-HSD, but nicotinamide adenine dinucleotide phosphatase as a cofactor. The same isotope was used as the substrate for the oxidative reaction of 17β-HSD, but nicotinamide adenine dinucleotide (1 µmol/L) was used as the cofactor. Tritiated androstenedione (106 disintegrations per minute) in the presence of 10-µmol/L cold androstenedione was used as the substrate for the reductive activity of 17β-HSD, and nicotinamide adenine dinucleotide reduced (1 µmol/L) was used as the cofactor.

Enzyme activity was calculated by means of the net percentage conversion of substrate, the molar concentration of substrate, and the incubation volume. To account for potential differences in the sizes of SG assayed and, hence, differences in enzyme activity, data were normalized to SG protein concentration. Data are expressed as picomoles of product per minute per milligram of protein.

SERUM ANDROGENS

Serum levels of DHEAS, testosterone, DHT, and 3α-androstenediol glucuronide were determined by means of radioimmunoassay methods previously described.11

DATA ANALYSIS

Unpaired t tests on log base 10 transformed data were used to compare enzyme activity between men and women and subjects with and without acne. The same test was used to compare serum androgens between groups. A paired t test using log transformed data was used to compare activity of different enzymes within the same groups. Correlation coefficients between enzyme activities in the SG and serum androgen levels were determined on the basis of sex and the presence of acne. Significance of the correlation was tested at a 95% confidence interval with Fisher r to z test.

RESULTS

A total of 34 subjects were studied: 8 women with acne (mean ± SD age, 31 ± 5 years), 10 women without acne (mean age, 33 ± 7 years), 8 men with acne (mean age, 26 ± 7 years), and 8 men without acne (mean age, 34 ± 7 years). The acne grade was mild in all subjects examined. The mean (±SEM) total lesion counts in men and women with acne were 41 ± 9 and 44 ± 7, respectively.

TISSUE ENZYME ACTIVITIES

Activities of 5α-R and of 17β-HSD in SG from the forehead were compared in men and women with and without acne (Table 1). No significant differences were noted in enzyme activity based on the presence of acne in ei-

SGs from subjects without acne. The goal of this study was to determine if there are differences in the activity of 17β-HSD and 5α-R in SG based on sex or the presence of acne. Serum androgen levels were determined and compared with tissue enzyme activity.
Table 1. Activity of 5α-R and 17β-HSD in Sebaceous Glands

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No.</th>
<th>5α-R</th>
<th>Reductive 17β-HSD</th>
<th>P†</th>
<th>Oxidative 17β-HSD</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>8</td>
<td>33.2 ± 6.0</td>
<td>8.1 ± 2.2</td>
<td>.004</td>
<td>9.6 ± 1.8</td>
<td>.006</td>
</tr>
<tr>
<td>No acne</td>
<td>10</td>
<td>22.0 ± 4.6</td>
<td>4.9 ± 0.9</td>
<td>&lt;.001</td>
<td>7.8 ± 2.7</td>
<td>.02</td>
</tr>
<tr>
<td>P§</td>
<td></td>
<td>.98</td>
<td>.19</td>
<td></td>
<td></td>
<td>.38</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>8</td>
<td>38.7 ± 3.3</td>
<td>16.0 ± 3.1</td>
<td>.004</td>
<td>21.8 ± 4.0</td>
<td>.004</td>
</tr>
<tr>
<td>No acne</td>
<td>8</td>
<td>37.2 ± 7.6</td>
<td>14.0 ± 2.4</td>
<td>.03</td>
<td>15.4 ± 2.8</td>
<td>.02</td>
</tr>
<tr>
<td>P§</td>
<td></td>
<td>.68</td>
<td>.80</td>
<td></td>
<td></td>
<td>.39</td>
</tr>
</tbody>
</table>

*5α-R indicates 5α-reductase; 17β-HSD, 17β-hydroxysteroid dehydrogenase.
†P values for paired t test comparing activity of 5α-R with reductive 17β-HSD.
‡P values for unpaired t test comparing activity of 5α-R with oxidative 17β-HSD.
§P values for unpaired t test comparing activity of enzymes in subjects with vs without acne.

The relationship between serum androgen concentrations and the local production of androgens within sebaceous glands is not clear. Acne is associated with elevated serum androgen levels in women with virilizing tumors and with elevated serum DHEAS levels in both men and women with partial adrenal hydroxylase deficiencies. Whether androgens from the systemic circulation act directly to stimulate the sebaceous glands or whether they act indirectly to stimulate enzymes involved in androgen production within the sebaceous gland itself is not known.

Tissue enzyme activity correlated with serum androgen levels only in women without acne. Reductive activity of 17β-HSD correlated with serum androstenedione level (r = 0.948, P < .001) and total testosterone level (r = 0.673, P = .04). Activity of 5α-R in SG correlated with serum androstenedione level (r = 0.658, P = .04) and DHT level (r = 0.671, P = .03). No correlation was noted between tissue enzyme activity and serum androgens in women with acne or in men with or without acne.

The mean activity (±SEM) of 5α-R in SG was significantly greater than both the reductive and oxidative activity of 17β-HSD in all groups of subjects studied. Corresponding P values are given in Table 1.

**SERUM ANDROGENS**

Mean serum levels (±SEM) of DHEAS, androstenedione, testosterone, free testosterone, and DHT (but not 3α-androstenediol glucuronide) were significantly greater in women with acne than women without acne, by unpaired t test (Table 2). No differences in serum androgen levels were noted in men on the basis of the presence of acne.

**CORRELATION OF TISSUE ENZYME ACTIVITY AND SERUM ANDROGEN LEVELS**

Tissue enzyme activity correlated with serum androgen levels only in women without acne. Reductive activity of 17β-HSD correlated with serum androstenedione level (r = 0.948, P < .001) and total testosterone level (r = 0.673, P = .04). Activity of 5α-R in SG correlated with serum androstenedione level (r = 0.658, P = .04) and DHT level (r = 0.671, P = .03). No correlation was noted between tissue enzyme activity and serum androgens in women with acne or in men with or without acne.
The activity of 5α-R was significantly greater in SGs from men compared with glands from women. In addition, the oxidative activity of 17β-HSD was 2- to 3-fold higher in SGs from men compared with women. As a reversible enzyme, 17β-HSD can either produce the potent androgen testosterone (via reduction) or, in effect, “inactivate” it by converting it back to androstenedione (via oxidation). The type 2 isozyme of 17β-HSD is active in human SGs. This isozyme prefers to oxidize testosterone to its less active precursor. In this regard, it has been suggested that the oxidative activity of the type 2 isozyme may protect target tissues (such as the SG) from the effects of potent androgens. In this study, there was not much difference between the oxidative and reductive activities of 17β-HSD. This is an artifact of the assay system, which uses homogenized glands that were provided with excess amounts of cofactors. In studies of intact SGs without added cofactors, the oxidative activity of 17β-HSD predominates over its reductive activity by a much wider margin than in homogenized SGs.

**COMPARISON OF 5α-R AND 17β-HSD ACTIVITY IN SG**

Few large studies have compared the activities of 17β-HSD and 5α-R in the same SG samples obtained from facial skin of both men and women. Our data demonstrate that 5α-R is 2- to 4-fold more active than 17β-HSD in sebaceous glands from both men and women. Both 5α-R and the oxidative 17β-HSD enzymes compete for testosterone as a substrate. With predominance of 5α-R activity, the net effect within SGs is the conversion of testosterone to the more potent androgen DHT, which in turn is thought to mediate sebum production. Interestingly, the opposite is true in keratinocytes cultured from the infrainfundibulum of vellus follicles of forehead skin. In these cells, the activity of 17β-HSD is 2.5- to 8-fold greater than the activity of 5α-R. Hence, vellus follicles from the face may be better protected from the effects of potent androgens than SGs because of predominance of 17β-HSD oxidative activity over activity of 5α-R.

**THE ROLE OF SERUM ANDROGENS**

Serum androgen levels were significantly higher in women with acne than in those without acne. Interestingly, these values were still within the normal range. No differences in serum androgen levels were noted in men on the basis of the presence of acne. Our data demonstrate that the highest specific activity of 17β-HSD and 5α-R was found in groups with the highest serum androgen levels. For example, enzyme activity was significantly greater in SGs from men than in those from women. Therefore, tissue enzyme activity may be proportional to serum androgen levels. Tissue enzyme activity correlated directly with serum androgen levels only in women without acne.

Possible interpretations of these data include the following: (1) Serum levels of androgens may play a role in the development of acne in women by acting directly on SGs, by stimulating local tissue enzyme activity, or both. (2) Serum androgens are less important than nonhormonal factors in the pathogenesis of acne in men. (3) Tissue enzyme activity in men may be maximally stimulated by their serum levels of androgens.

The effects of androgens on acne are most evident in women. If serum androgens serve as substrates for sebaceous gland enzymes, women with acne may have greater tissue production of androgens than women without acne if the activity of 5α-R is increased within their SGs. Alternatively, serum levels of androgens may be more important than locally produced androgens in modulating sebum production.

**CONCLUSIONS**

It is clear that acne is a multifactorial disease. Sebum is one part of the equation. Many men do not have acne despite their high levels of androgens compared with women. Furthermore, many individuals have high sebum production, yet they do not develop acne. Currently available hormonal therapies for acne act either to reduce the production of androgens by the adrenal gland or ovary or to inhibit the action of androgens at the target site (SG) by blocking the androgen receptor. This in turn leads to decreased sebum production. There

**TISSUE ENZYME ACTIVITIES IN MEN COMPARED WITH WOMEN**

The activity of 5α-R and 17β-HSD was significantly greater in glands from men compared with glands from women. In addition, the oxidative activity of 17β-HSD was 2- to 3-fold higher in SGs from men compared with women. As a reversible enzyme, 17β-HSD can either produce the potent androgen testosterone (via reduction) or, in effect, “inactivate” it by converting it back to androstenedione (via oxidation). The type 2 isozyme of 17β-HSD is active in human SGs. This isozyme prefers to oxidize testosterone to its less active precursor. In this regard, it has been suggested that the oxidative activity of the type 2 isozyme may protect target tissues (such as the SG) from the effects of potent androgens. In this study, there was not much difference between the oxidative and reductive activities of 17β-HSD. This is an artifact of the assay system, which uses homogenized glands that were provided with excess amounts of cofactors. In studies of intact SGs without added cofactors, the oxidative activity of 17β-HSD predominates over its reductive activity by a much wider margin than in homogenized SGs.

**表2. 血浆雄激素水平在有无痤疮者中**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No.</th>
<th>DHEAS, µmol/L</th>
<th>Androstenedione, nmol/L</th>
<th>Total T, nmol/L (ng/dL)</th>
<th>Mass Free T, nmol/L (ng/dL)</th>
<th>DHT, nmol/L</th>
<th>3α-Diol G, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>8</td>
<td>5.6 ± 1.1</td>
<td>11.2 ± 1.9</td>
<td>1.4 ± 0.3 (41.5 ± 8.8)</td>
<td>0.4 ± 0.1 (13.0 ± 3.8)</td>
<td>0.7 ± 0.1</td>
<td>5.0 ± 0.6</td>
</tr>
<tr>
<td>No acne</td>
<td>10</td>
<td>2.8 ± 0.5</td>
<td>6.3 ± 0.5</td>
<td>0.7 ± 0.2 (20.8 ± 5.2)</td>
<td>0.2 ± 0.02 (4.6 ± 0.5)</td>
<td>0.4 ± 0.05</td>
<td>3.7 ± 0.7</td>
</tr>
</tbody>
</table>
P†        | .02 |               | .02                     | .03                     | .03                          | .18         |                 |
| Men      |     |               |                         |                        |                             |            |                 |
| Acne     | 8   | 7.8 ± 1.7     | 8.0 ± 1.2               | 15.7 ± 1.6 (452.0 ± 46.1) | 7.8 ± 1.0 (225.0 ± 28.6) | 1.2 ± 0.1  | 10.2 ± 1.5      |
| No acne  | 10  | 5.6 ± 0.7     | 8.0 ± 1.0               | 17.1 ± 3.9 (493.0 ± 112.4) | 7.3 ± 1.8 (211.0 ± 51.9) | 1.2 ± 0.2  | 7.9 ± 1.2       |
P‡        | .25 |               | .93                     | .76                     | .82                          | .84         | .25             |

* DHEAS indicates dehydroepiandrosterone sulfate; T, testosterone; DHT, dihydrotestosterone; and 3α-diol G, 3α-androstanediol glucuronide. Values are given as mean ± SEM. Reference ranges are as follows: DHEAS: men, 4.1 to 12.2 µmol/L; women, 2.7 to 9.8 µmol/L; androstenedione: men, 1.8 to 7.0 nmol/L; women, 1.4 to 8.4 nmol/L; total T: men, 8.7 to 31.2 nmol/L (251-899 ng/dL); women, 0.7 to 2.8 nmol/L (20-81 ng/dL); free T: men, 3.8 to 12.5 nmol/L (110-360 ng/dL); women, 0.04 to 5.2 nmol/L (1.2-150 ng/dL); DHT: men, 1.0 to 5.2 nmol/L; women, 0.35 to 2.1 nmol/L; and 3α-diol G: men, 3.4 to 22 ng/mL; women, 0.5 to 5.4 ng/mL.

† Unpaired t test, men with vs without acne.

‡ Unpaired t test, women with vs without acne.
are no hormonal therapies available that specifically block androgen-metabolizing enzymes within the SG. Such therapies may be beneficial in treating acne if sebum production is mediated by locally produced androgens. Whether sebum production is modulated by systemic androgens, locally produced androgens, or a combination of both still remains to be determined. This is one research question that will most likely be answered in the clinical setting as specific inhibitors of androgen-metabolizing enzymes become available.

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REFERENCES