SKIN DISEASES DUE TO INCREASED ANDROGEN SENSITIVITY

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Received: March 22, 1999

Key words: Androgenetic alopecia, estrogens, androgens, acne, 5α-reductase, finasteride, minoxidil, 17α-estrogen

Synopsis

In an inherited genetic hypersensitivity, normal levels of androgens may cause cosmetic disturbances or even dermatological diseases: acne and alopecia. The cosmetic dermatologist is called for help. Androgenetic stimulation leads to increased levels of sebum, to an imbalance of lipids on the skin surface, to follicular hyperkeratosis and, finally, to the formation of comedones. In those patients with hypersensitive sebocytes, only cosmetic disturbances are present at the beginning but a rapid progression towards an embarrassing skin disease with severe symptoms in the face is possible. An aggravation of Acne comedonica into Acne papulopustulosa and Acne conglobata has to be considered in each case. Therapy starts with adequate skin cleansing and comedonolytic skin care, e.g. with topical adpalene, and may continue in severe cases with oral isotretinoin. In females, antiandrogens may be given to reduce the androgenic stimulation of sebocytes.

Other patients reveal high levels of androgen receptors and testosterone-activating steroid-5α-reductase in the frontal areas and in the vertex of the scalp (balding areas). As a consequence, androgenetic alopecia develops. Although hair loss is generally regarded as a cosmetic disturbance, the patients afflicted from this disease suffer from their reduced self-esteem and their impaired psychological and social well-being. This matters for women and men, especially for young men. Androgenetic alopecia is a disease that needs help, from the doctor, from the pharmacist, and, on the first hand, from the cosmetic dermatologist. But only suppressive measures are known today. Topical minoxidil or topical 17α-estradiol will stop hair loss in the vast majority of cases. Life-long treatment may be necessary, however. Only recently, oral finasteride has been shown to be highly effective in suppressing hair loss in androgenetic alopecia. However, the undesirable actions of this drug warrant a most critical and cautious application.

Riassunto

Nella ipersensibilità genetica ereditata, i normali livelli di androgeni possono provocare lievi alterazioni cutanee o addirittura malattie dermatologiche di acne e perdita di capelli. Si ricorre, allora, all’aiuto del dermatologo-cosmetologo.
La stimolazione androgenica porta ad un aumento dei livelli di sebo, ad uno squilibrio dei lipidi della
superficie cutanea, alle ipercherosi follicolari ed infine, alla formazione di comedoni. Nei pazienti con sebociti ipersensibili, all'inizio si verificano soltanto lievi alterazioni cutanee, che possono rapidamente progredire verso una vera e propria patologia della pelle, con evidenti sintomi soprattutto sul viso. In ogni caso, ci si deve aspettare un'aggravarsi dall'acne comedonica all'acne papulo/pustulosa o all'acne conglobata.

La terapia comincia con un'adeguata pulizia della pelle e con un trattamento comedolitico, quale ad esempio l'adapalen topico, e può continuare, nei casi gravi, con isotretinolo orale. Nelle donne, possono essere somministrati antiandrogeni per ridurre la stimolazione androgenica dei sebociti.

Altri pazienti mostrano di avere alti livelli di recettori androgeni della 5α-reduttase che attiva il testosterone nei follicoli delle aree frontali e sulla sommità della testa (aree calve). Come conseguenza si sviluppa l’alopecia androgenetica.

Sebbene la perdita dei capelli generalmente sia ritenuta un disturbo di carattere cosmetico, i pazienti che ne sono colpiti soffrono di una ridotta autostima che minaccia il loro benessere psicologico e sociale. Ciò interessa l'uomo, la donna, ma specialmente i ragazzi.

L’alopecia androgenetica è un disturbo che richiede l’aiuto del medico, del farmacista e, in primo luogo del dermatologo-cosmetologo. Ma tutt’oggi sono conosciute soltanto metodologie soppressive. Minoxidil topico o il 17α-estradiolo topico sono in grado di fermare la caduta dei capelli nella maggioranza dei casi, senza però eliminare il problema. È necessario utilizzarli per tutta la vita. Solo di recente, il finasteride orale ha dimostrato di essere molto efficace nel sopprimere la caduta dei capelli provocata dall’alopecia androgenetica.

Comunque, gli effetti indesiderati di questo rimedio farmacologico richiedono una applicazione consapevole e cauta.
INTRODUCTION

Due to genetic factors, two types of skin cells may reveal an abnormally high sensitivity to androgens. Even normal levels of testosterone may provoke specific disturbances: the stimulation of sebocytes leads to acne, the stimulation of dermal papilla hair root cells causes androgenetic alopecia. In figure 1, the pathways of androgenetic stimulation of the two types of skin cells is depicted. Testosterone from testes, ovaries and adrenal glands must be converted into dihydrotestosterone in order to act on the androgen response element of nuclear DNA. This conversion is effected by a specific enzyme, the steroid-5α-reductase. Two isoenzymes exist (22): type I in skin and sebocytes, type II in hair root cells and prostatic glands. Inhibition of steroid-5α-reductase as well as the presence of antiandrogens protect sebocytes and hair root cells from androgenic stimulation. Both modalities are used for therapeutic purposes.

ACNE

Acne is one of the most frequent skin diseases, especially in the age group between 12 and 24 years (incidence rate 80%). The most important pathogenetic factor in acne is the androgen-induced increase in sebum production which leads to an imbalance of lipids on the skin surface (Figure 2). Furthermore, an abnormally high adherence of epithelial cells lining the follicles provokes follicular hyperkeratosis. Microcomedones and comedones are formed. In this anaerobic medium numerous Propionibacteria grow the products of which pass the follicular walls. Chemotactic factors, enzymes and antigenic proteins evoke dermal inflammation: acne papules develop. - "Body builder acne" following the ingestion of anabolic hormones is an excellent proof for the importance of androgens in the pathogenesis of acne. Stress aggravates acne by inducing the production of adrenal hormones. Therapy of acne in its four stages is directed against four pathogenetic factors: androgen-induced sebum production, follicular hyperkeratosis, bacterial growth, and inflammation (9, 10, 18).

In females, the oral administration of antiandrogens may reduce the high rate of sebum secretion due to androgenic stimulation. Cyproterone acetate or chloromadinone acetate were used preferably under the form of a contraceptive pill. It must be mentioned that cyproterone acetate inhibits steroid-5α-reductase in the sebaceous follicles (10). Spironolactone in daily doses between 100 and 200 mg is less effective in acne of females than the two other antiandrogens mentioned above. For the protection of a male fetus, females under antiandrogenic treatment must use an effective contraceptive. - So far, no positive results were obtained with topical applications of cyproterone acetate. Maybe the use of a liposomal lotion will improve the efficacy. Systemic administration of estrogens is ineffective in acne. Retinoids are the most potent and most widely used anti-acne drugs. They reduce sebum production to about 10% of its original value, sebaceous glands decrease dramatically in size, proliferation and differentiation of epithelial cells is normalized (action on α- and γ-retinoic acid receptors) (1, 22).

Furthermore, it has been shown that retinoids inhibit steroid-5α-reductase (20), another antiandrogen and antiacne effect of this class of drugs. In acne therapy, retinoids were used systemically and topically. 13-cis-retinoic acid is administered orally in doses of 5 mg/d/kg bodyweight over at least six months. In topical acne therapy adapalene has displaced all -trans-retinoic acid (tretinoin, vitamin A-acid). Adapalene exhibits far better tolerability, higher stability and somewhat more favorable biochemical-pharmacological actions than tretinoin. Adapalene is used as 0.1% gel (1, 22).

Steroid-5α-reductase is an important enzyme for the elicitation of androgenic effects. Inhibition of this enzyme is provoked by cyproterone acetate and by retinoids, both columns of antiacne treatment. Oral finasteride and 17α-estradiol (cf. later) have not been tried in acne.

ANDROGENETIC ALOPECIA

Androgenetic alopecia may occur in women and
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**Fig. 1. Androgenic Actions on Skin Cells**

- **TESTOSTERONE** (from testes, ovaries, and adrenal glands)
  - **INHIBITORS**
  - **SEBACEOUS GLANDS**
  - **ANTI-ANDROGENS**
  - **DIHYDROTESTOSTERONE**
  - **STERIOD-50-REDUCTASE**
  - **ANTI-ANDROGENS**

**Fig. 2. Pathogenesis of Acne**

- **GENETIC FACTOR**: androgen-susceptible sebocytes
- **STRESS**
- **INCREASED SEBUM SECRETION**
  - **IMBALANCE OF SKIN SURFACE LIPIDS**
  - **FOLLICULAR HYPERKERATOSIS**
  - **COMEDONES**
  - **COMEDOGENIC SUBSTANCES**
  - **INFLAMMATORY PAPULES**
  - **PUSTULES, NODULES, CYSTS**

BACTERIA

LOOSING OF FOLLICULAR WALLS, HYDRATION
men as a result of the effects of androgens on the genetically predetermined hair follicles. In Caucasians, the prevalence of this disease (“disease” according to the classification of the World Health Organization) approaches 100%. Although androgenetic alopecia is regarded as a normal variant of aging of most individuals, it causes psychological distress, especially in women and in young men. Hair root cells belong to the mitotically most active cells of the organism. The daily production of 20 to 30 m of hair is a great achievement. But on the other hand, hair root cells are classed with the most sensitive cells. The sensitivity against androgens leads to a gradual replacement of the large, pigmented hairs of the scalp by fine, insignificant hairs.

In recent years, this specific sensitivity of the balding hair dermal papilla cells has been the target of biochemical investigations. It was shown that these cells contain significantly higher androgen receptor levels than cells from non-balding areas (5, 22). Details are shown in figures 3 and 4. Furthermore, androgen-sensitive areas of the scalp possess more steroid-5α-reductase (type I and II) than the occipital regions where balding due to androgenetic alopecia never occurs (22). Details are shown in figure 5. It should be stressed that these biochemical differences between balding and non-balding areas are present in men and women.

Steroid-5α-reductase seems to play an important role in the pathogenesis of androgenetic alopecia:
- in men and women, balding areas of the scalp exhibit increased levels of steroid-5α-reductase
- in genetic deficiency of steroid-5α-reductase, no androgenetic alopecia develops. However, an analysis of the pertinent genes failed to show any association (2)
- a strong association was observed between male baldness and benign prostatic hyperplasia (12)
- inhibitors of steroid-5α-reductase may stop the continuous hair loss in men and women.

Finally, a last enzyme has to be mentioned which shows different activities in balding and non-balding areas, namely aromatase. This enzyme converts testosterone into estrogens. In men and in women with androgenetic alopecia, balding areas reveal significantly lower activities of aromatase (22). Details are shown in figure 6. – No therapeutic consequences resulted from this observation, so far.

The genes encoding the two steroid-5α-reductase isoenzymes are not associated with the appearance of androgenetic alopecia (2). A polygenic etiology should be considered, involving other enzymes and steroid receptors. Steroid-5α-reductase plays an important role as outlined above but the high activity of this enzyme can not be regarded as the only underlying cause of androgenetic alopecia.
THE HAIR CYCLE

Human hair grows in aperiodic cycles. Normal hair cycles last about seven years. The longest period of about six years is the anagen phase, the phase of active hair growth. After a short catagen phase, one year of telogen phase follows. This phase ends with hair loss. Then the follicle moves deeper into the dermis again, and another anagen phase starts (17, 19). In androgenetic alopecia, the hair cycles are becoming shorter and shorter, due to a shorter anagen phase, and visible hair loss occurs. The hair follicles continuously move towards the skin surface and undergo progressive miniaturization. Terminal hair is replaced by vellus hair and balding spots develop due to telogen hairs not replaced in time (4). In many instances, a complete atrophy of the hair follicles is the endpoint.

Fig. 4. Androgen receptors in Hair Follicles of Women and Men with Androgenetic Alopecia (22).

Fig. 5. Steroid-5α-reductase Type I and II in Hair Follicles of Men and Women with Androgenetic Alopecia (22).
In men, androgenetic alopecia causes the typical “male pattern baldness”. At the end of the second decade of life, the hairline recedes in the frontal and frontoparietal region; at the same time, vertex thinning starts. Hair loss progresses continuously, with short phases of arrest. At the age of 40 to 50 years, complete baldness may be present. However, the parietal and occipital regions remain unaffected of the balding process. As quoted above, these regions reveal lower levels of androgen receptors and steroid-5α-reductase, and higher levels of aromatase. This is the reason why hair transplants from the occipital region into balding areas never reveal hair loss but continuously grow hair.

In castrates or in individuals with steroid-5α-reductase deficiency androgenetic alopecia never occurs. The different stages of androgenetic alopecia in men were classified according to HAMILTON (figure 7).

**ANDROGENETIC ALOPECIA IN WOMEN**

Women with androgenetic alopecia generally have diffuse hair loss or hair thinning of the temporal and parietal areas with retention of the frontal hair line. In postmenopausal women, however, typical “male pattern baldness” may occur. The different stages of hair loss in women were classified according to LUDWIG (figure 7).

In women with higher levels of androgens, either idiopathic or symptomatic (tumors of the ovaries or of the adrenal glands; hormone therapy), hirsutism may develop: terminal hair grows on the face, on
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the body, and on the genital region as in males. In some instances, hirsutism may be accompanied by androgenetic alopecia. – In virilism, in addition to the symptoms of hirsutism, other signs of the male sex appear. In women with virilism, male pattern baldness may develop. In hirsutism and virilism, the causes for the hyperandrogenemia must be searched for.

(Hypertrichosis is characterized by an increased hair growth in women but the developing terminal hairs reveal the typical female distribution pattern. Hypertrichosis is generally due to genetic factors. No specific therapy is known, depilation in its different forms is the only advice that can be given to affected subjects (19). No hormonal deviations are present in hypertrichosis.)

TREATMENT OF ANDROGENETIC ALOPECIA

There are means for a successful treatment of androgenetic alopecia (stop of hair loss, increasing the mass of hair). No healing can be expected. Some hair loss is inevitable in aging, for both men and women. About balding, special anxiety develops in young men, and they seek medical advice. Until recently, doctors did not have much to offer (21). The situation has improved but it is important to state that only symptomatic treatment regimes are known. If the treatment is ended, massive balding comes back.

Topical applications of various products with irritants, konakion, rhodanides and others did not exert any significant influence on androgenetic alopecia in progression. Oral applications of vitamins, iron, zinc, selenium, gelatine, amino acids such as cystine, yeast extracts, biotin and others more may support hair regrowth in some instances. Significant effects in androgenetic alopecia were not recorded.

An effective treatment of androgenetic alopecia can be performed by topical applications of minoxidil, of estrogens, and of 17α-estradiol or by systemic administration of antiandrogens or finasteride.

MINOXIDIL

Minoxidil has been introduced into medical therapy as a powerful antihypertensive drug upon oral administration. Quite unexpectedly, patients taking this drug experienced massive hypertrichosis. This observation initiated clinical trials with 2 to 5% minoxidil for topical applications in various forms of hair loss. In androgenetic alopecia, such treatment proved to be effective (16). Details are shown in figure 8. It is still not known via which pharmacological mechanism minoxidil stops hair loss. As already stated,
minoxidil applications have to be continued as long as hair loss should be suppressed. In some rare instances, hypotensive effects have been evoked with topical minoxidil.

**TOPICAL ESTROGENS**

Topical applications of estrogens (e.g., 1% β-estradiol) arrested hair loss in androgenetic alopecia. However, the hormonal effects caused by systemically absorbed estrogen prohibit its use (12, 14, 15). In women, disturbances of the menstrual cycle developed, men experienced gynecomastia.

**ANTIANDROGENS**

Oral antiandrogens have successfully been used in androgenetic alopecia of women. Cyproterone acetate

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Fig. 9. The structural Formulas of 17β-Estradiol and its hormonally inactive Enantiomer 17α-Estradiol.

Fig. 10. The Metabolization of 14C-Testosterone in Liver Slices of Female Rats. The Influence of 17α-Estradiol.
Skin diseases due to increased androgen sensitivity was given either as monotherapy (10-50 mg/d) or, better, under the form of a contraceptive pill (3). Cyproterone acetate changes the configuration of the androgen receptor. Binding to the androgen-responsive-element of DNA is no longer possible. Prolonged treatment with antiandrogens should be considered with caution. For topical applications on the scalp, cyproterone acetate is not yet available. Topical applications of 3.3% spironolactone had no significant therapeutic action in androgenetic alopecia.

**17α-ESTRADIOL**

17α-Estradiol is the hormonally inactive enantiomer of the classical estrogen 17β-estradiol (figure 9). For the elicitation of estrogenic effects, the steric position of the substitutes on C-17 of the sterol skeleton is of great importance. A hydroxyl group in β-position on C-17 is necessary for estrogenic action. The same sterol with a hydroxyl group in α-position on C-17 lacks hormonal/estrogenic activity. Therefore, 17α-estradiol is only a steroid of the estradi type but not an estrogenic hormone.

In numerous biochemical and animal experiments, any relevant estrogenic activities of 17α-estradiol could be ruled out. The binding affinity of 17α-estradiol for the specific cytosolic estrogen receptor measured 0.8 to 9% of the affinity of 17β-estradiol. But in most experiments, no estrogenic activity of 17α-estradiol could be recorded, the compound was even used as negative control. A few tests revealed a very weak activity of 17α-estradiol with a maximum of 0.4% of 17β-estradiol. These data permit the conclusion that although 17α-estradiol binds to the specific receptor at a very weak degree, the resulting complex is not capable to react with the specific site on nuclear DNA.

As hormonal actions of 17α-estradiol could be ruled out, the question arose of how this steroid exerts its therapeutic action in androgenetic alopecia. In biochemical investigations, an inhibition of steroid-5α-reductase was recorded (24). For details see figure 10. This action could be confirmed in cell cultures, measuring growth of human hair matrix cells in the presence of testosterone, dihydrotestosterone, 17β- and 17α-estradiol (7). The incorporation of 17α-estradiol in this test system neutralized the growth decreasing action of testosterone but not that of dihydrotestosterone (details in figure 11).

After local application, 17α-estradiol penetrates into the epidermis and dermis (23). The incidence of undesirable topical effects is extremely low (0.0007%);
the slight burning sensation is caused by the solvent propanol/water in which 17α-estradiol is applied in a concentration of 0.025%. In contrast to 17β-estradiol (cf. above), 17α-estradiol never caused any systemic estrogenic effects not even on long term use over years. This observation confirms the fact that 17α-estradiol is not a hormone. Controlled clinical trials with topical 17α-estradiol have been performed in men and women over periods of at least one year. The uniform outcome of the

![Graph 1: Changes in Hair Morphology under Treatment with Topical 17α-Estradiol](image1)

**Fig. 12.** Changes in Hair Morphology under Treatment with topical 17α-Estradiol. 96 Patients, 1 Year (8).

![Graph 2: Hair Count Mean Change from Baseline Finasteride vs. Placebo](image2)

**Fig. 13.** Hair Count Mean Change from Baseline Finasteride vs. Placebo. Double-blind, 2 years, 1553 Men, Crossover after 12 months (6).
Studies were a decrease in telogen hairs (e.g., in one study by 63% in comparison to a placebo rate of 37%), and anagen hairs increased by 20% (8, 11, 13). For details see figure 12.

**FINASTERIDE**

Finasteride is a potent inhibitor of steroid-5α-reductase, mainly of type II which is found in prostatic glands and in hair root cells. For years finasteride has been used already in daily doses of 5 mg for the treatment of benign prostatic hyperplasia. Only recently, finasteride at daily doses of 1 mg was tested in androgenetic alopecia of men as steroid-5α-reductase has been shown to be of high pathogenetic importance in this type of hair loss. The clinical outcome of a large international trial was surprising: in controlled studies over two years, finasteride retained hair count in 83% of cases (placebo rate: 28%); a regrowth of natural visible hair was found in 66% of the patients (placebo rate: 7%). It can be concluded that undoubtedly finasteride is most effective in androgenetic alopecia of men. For details of the study outcome see figure 13 (6).

However, finasteride exerts major undesirable effects:

- finasteride is teratogenic
- finasteride may cause abnormalities of the external genitalia of a male fetus if the mother comes into contact with the drug. Therefore, women who are or who may be pregnant should not ingest finasteride nor should they handle crushed or broken tablets. The amount of finasteride in sperm of a sexual partner was reported to be too low to damage the male fetus after vaginal absorption.
- Finasteride even at low doses may decrease libido in men and may cause erectile dysfunction and ejaculatory disorders (incidence 1-2%). In some rare instances, gynecomastia was evoked.

Taking all those undesirable effects together finasteride should be recommended for the treatment of androgenetic alopecia only with utmost caution. One should never forget that finasteride as all the other in androgenetic alopecia effective measures acts only symptomatically and must, therefore, be used as long as hair loss should not come back. It goes without saying that the patient has to be informed about all the possible undesirable effects.
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