Adrenal androgenic female-pattern alopecia: sex hormones and the balding woman[1]

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Nineteen white women (age range, 18–37 years) with a distinct pattern of diffuse alopecia, characterized by retention of the frontotemporal hairline and progressive loss of central scalp hair, were evaluated. The serum adrenal androgen dehydroepiandrosterone-sulfate (DHEAS) ranged from 2.2 to 5.8 μg/ml (mean, 3.9 ± 1.1 μg/ml). The normal female range is 0.3 to 3.2 μg/ml (mean, 2.0 ± 0.7 μg/ml). All women had a normal total serum testosterone level. Of two women with elevated levels of serum prolactin, one had a pituitary adenoma as revealed by computed tomography. Apparently, DHEAS is hydrolyzed to dehydroepiandrosterone (DHEA) and subsequently converted to more potent androgens. In the hair follicle, DHEA will inhibit glucose-6-phosphate dehydrogenase, a key enzyme of the pentose cycle that is essential for the synthesis of nucleic acids. The disruption of the growth of scalp hair may be due to this increased adrenal production as well as to the peripheral metabolism of DHEAS.

Index terms: Dehydroepiandrosterone-sulfate (DHEAS) • Hair loss • Hormones
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The medical literature provides little assistance for the understanding and management of the balding woman. Counseling women with progressive alopecia using such terms as "diffuse hair loss of young women," "common baldness," and "male-pattern baldness" increases the patient's anxiety and reflects the lack of scientific knowledge with regard to the pathogenesis of this condition. Most young women with chronic, diffuse, noncicatricial alopecia are not properly evaluated or appropriately diagnosed. Particularly unfortunate is the woman who is advised that

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this condition is male-pattern alopecia, which is genetically predetermined and irreversible.

From September 1, 1981, to September 30, 1982, 578 women with nonscarring hair loss were seen for the first time in the Department of Dermatology at the Cleveland Clinic. Of these, 105 women were diagnosed as having alopecia areata. For the others, a careful history was taken, and clinical and laboratory examinations were conducted to determine whether metabolic, endocrine, connective tissue, or other disorders were present. A distinct pattern of diffuse central alopecia with retention of the frontotemporal hairline, not known to be associated with any specific disorder, was observed repeatedly. A similar hair-loss pattern was identified in the classification of female androgenetic alopecia by Ludwig[1] as based on his observation of 468 patients, but a review by Rook and Dawber[2] did not mention the association of any endocrine abnormalities with this type of alopecia.

Our similar observations may be classified as follows:

Grade 1. Thinning of the central scalp hair with retention of the frontotemporal hairline was perceptible (*Figs. 1–3*).

Grade 2. Pronounced thinning of the central scalp hair and onset of hair loss from the parietal and occipital scalp were noted (*Figs. 4, 5*).

Grade 3. Full baldness (few sparse hairs) of the central scalp and progressive hair loss from the parietal and occipital scalp were apparent.

Ludwig[1] suggested that a relationship existed between the degree of androgenic stimulation and the type of androgenetic alopecia that develops in genetically predisposed women. He believed that moderately increased levels of circulating androgens correlate with the female type of diffuse alopecia, whereas the male type of baldness with deep frontotemporal recession develops in women with testosterone levels comparable to those of normal men. To determine the validity of this concept, the androgenic hormones of 19 white women with grades 1 and 2 female-pattern alopecia were studied.

Methods

Nineteen women had distinct, diffuse central scalp alopecia with retention of the frontotemporal hairline. Based on clinical signs of androgen stimulation, this group was divided into subgroups of 8 women with alopecia only and 11 women who had alopecia associated with hirsutism or acne. Simultaneous determination of total serum testosterone (T), testosterone-estradiol binding globulin (TeBG), and dehydroepiandrosterone-sulfate (DHEAS) was done by radioimmunoassay techniques (*Table*). As a control, the serum DHEAS levels were measured in 11 normal women. In addition, serum prolactin levels were determined for 14 of the women studied. The T to TeBG ratio was calculated and named the "androgenic index" (T/TeBG). A statistical analysis of the serum DHEAS levels and the T/TeBG was performed with Student's *t* test.

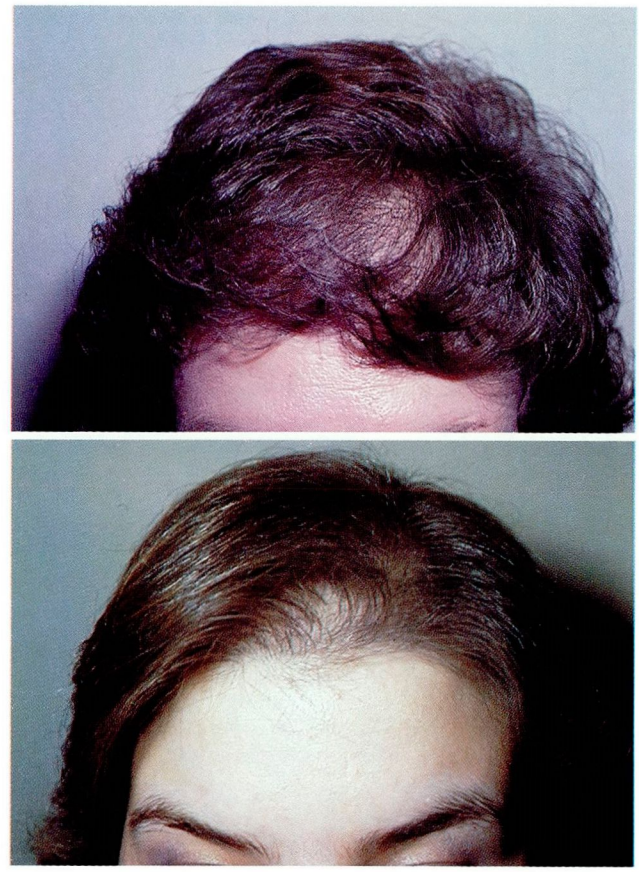
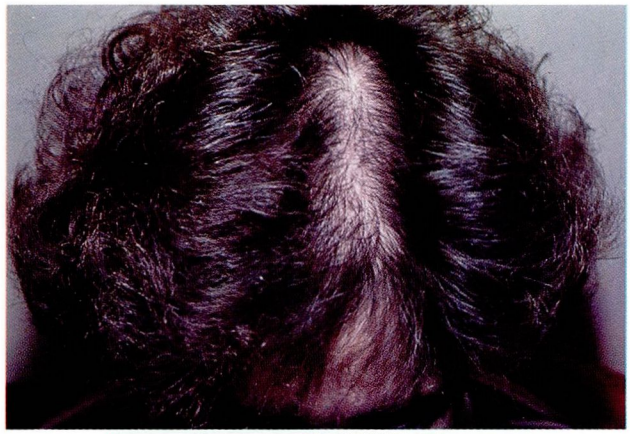


Figure 1. Grade 1 adrenal androgenic female-pattern alopecia with perceptible thinning of the central scalp hair.

Figure 2. Female-pattern alopecia with retention of the frontotemporal hairline.

Results

All 19 women had noted the progressive nature of their alopecia for at least one year before obtaining a medical evaluation. Three women had had their symptoms for 10 years before seeking consultation. Although the age range for the 19 patients was from 18 to 37 years (mean, 25 years), the onset of symptoms occurred at a mean age of 23 years. No significant difference in the mean age was apparent between the



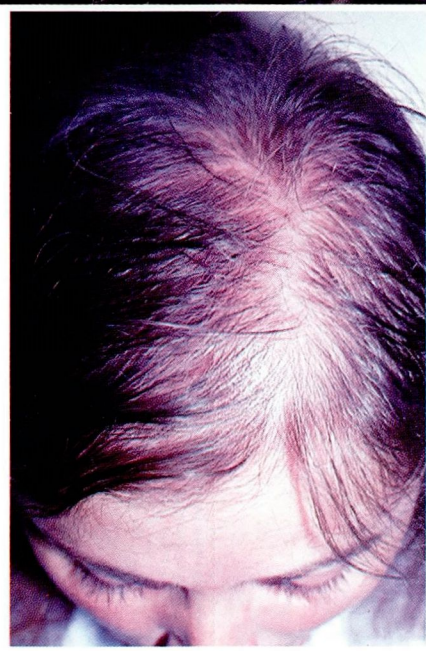


Figure 3. Progressive thinning of central scalp hair in grade 1 female-pattern alopecia.

Figure 4. Grade 2 androgenic alopecia with pronounced thinning of central scalp hair and onset of hair loss from the parietal scalp.

subgroup with alopecia only and those with alopecia, hirsutism, and acne.

The serum DHEAS levels ranged from 2.2 to 5.8 μg/ml (mean, 3.9 ± 1.1 μg/ml); the normal female values range from 0.3 to 3.2 μg/ml. For those with alopecia only, the range was 2.2 to 5.4 μg/ml (mean, 3.6 ± 0.9 μg/ml). For those with alopecia, hirsutism, and acne, the range was 2.3 to 5.8 μg/ml (mean, 4.2 ± 1.1 μg/ml). The 11 normal women had a mean serum DHEAS level of 2.0 ± 0.7 μg/ml. Therefore, the 19 women with alopecia had significant elevations of serum DHEAS ($p < 0.001$). No significant difference in the degree of elevation of serum DHEAS between the 8 women with alopecia alone and the

Figure 5. Scalp hair pluck, demonstrating thin and normal hair shaft diameters in adrenal androgenic female-pattern alopecia.

11 women with other signs of androgenic stimulation was noted.

For the 19 women with alopecia, T ranged from 45 to 147 ng/dl; the normal female values range from 30 to 170 ng/dl. The TeBG ranged from 0.5 to 2.9 μg dihydrotestosterone (DHT%); the normal female range is 0.6 to 2.4 μg DHT%. No significant abnormality of the T and the TeBG levels in the two subgroups was apparent. Nevertheless, when the T/TeBG ratio of those with alopecia (0.0445 ± 0.0214) was compared to the ratio of those with alopecia, hirsutism, and acne (0.0823 ± 0.0385) a significant difference was observed ($p < 0.025$). The T/TeBG ratio for normal women ranges from 0.014 to 0.068.

Table. Abbreviations

3 β-HSD	3 β-hydroxy-steroid dehydrogenase
5 α-DHT	5 α-dihydrotestosterone
17 α-HD	17 α-hydroxylase
17 β-HSD	17 β-hydroxy-steroid dehydrogenase or 17 β-hydroxy-steroid oxidoreductase
17-KS	17-ketosteroids
21-HD	21-hydroxylase
DHEA	dehydroepiandrosterone
DHEAS	dehydroepiandrosterone-sulfate
Free T	unbound serum testosterone
G-6-PDH	glucose-6-phosphate dehydrogenase
T	total serum testosterone
TeBG	testosterone-estradiol binding globulin
T/TeBG	androgenic index

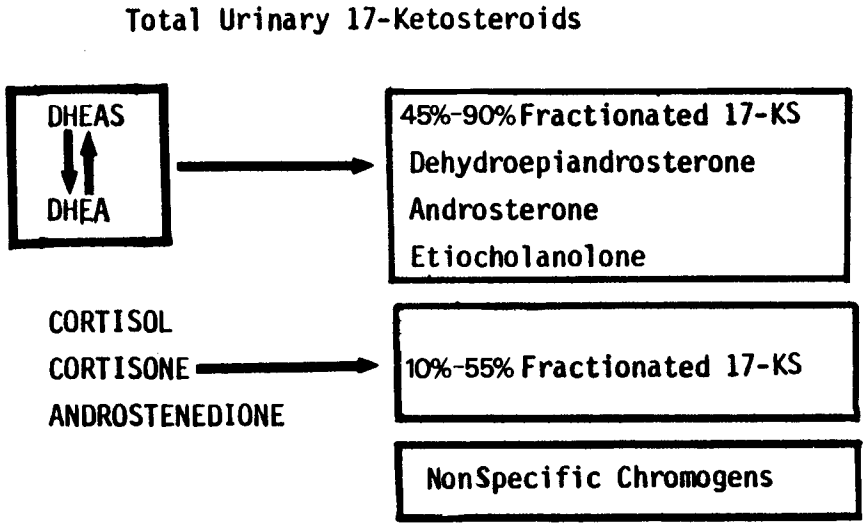


Figure 6. Hormones contributing to the total urinary 17-KS.

The serum prolactin levels of 12 of the 14 women tested (mean, 9.7 ng/ml) were within the normal range of 0.8 to 19.7 ng/ml (mean, 10.2 ± 4.7 ng/ml). The other 2 women had elevated levels of 37.4 ng/ml and 24.9 ng/ml; one underwent computed tomography, which revealed a small pituitary adenoma of the right lobe.

Discussion

The diffuse pattern of central scalp alopecia in young healthy women can be recognized clinically, and should be differentiated from the male pattern of frontotemporal recession and vertex thinning.[2] Previous reviews have not associated elevated androgen levels with this female pattern of alopecia.[2,3]

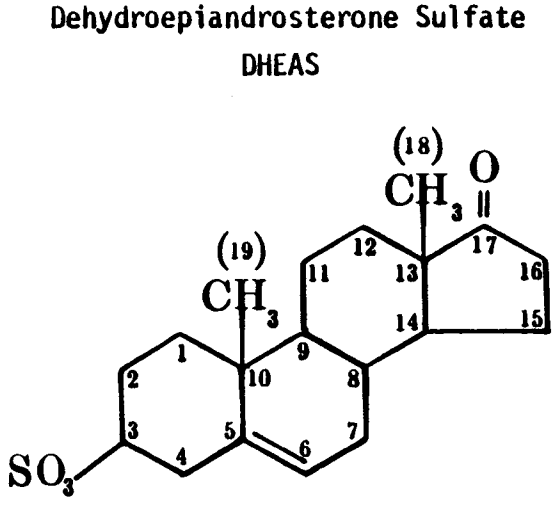


Figure 7. Molecular structure of the C_{19} adrenal androgen DHEAS.

Measurement of adrenal androgens: Usually, when evaluating the androgenic activity of women, the urinary 17-ketosteroids (17-KS) are measured, since this has been the only test available for determining androgen production. Unfortunately, this evaluation is limited since it measures androgen metabolites. Migeon[4] shows that the excretory levels of these metabolites and the circulating levels of active androgens do not always correlate well. The total urinary 17-KS measure the unconjugated and conjugated neutral C_{19} steroids with 17-ketone (Zimmerman reaction), but do not quantitatively evaluate biologically active androgenic hormones. Also, only a fraction of the metabolites are excreted as urinary 17-KS. Maroulis et al[5] demonstrated that urinary 17-KS determinations do not reliably identify patients with elevated serum androgens. The more potent androgens, testosterone and 5 α-dihydrotestosterone (5 α-DHT), contributed less than 1% to the total 17-KS. The major 17-KS being measured by the Zimmerman reaction consist of dehydroepiandrosterone (DHEA), androstenedione, androsterone, and etiocholanolone (*Fig. 6*). Of these, DHEAS, a steroid with 19 carbon atoms (*Fig. 7*) which characterizes the hormones with androgenic activity capable of stimulating male secondary sex characteristics, is the peripheral androgen in greatest concentration. DHEAS is only mildly androgenic.[6] The large pool of circulating DHEAS has a slow turnover rate and is not subject to diurnal variation.[7-9] Although circadian variations are evident, serum DHEA concentrations due to a long half-life show less synchrony with corticol secre-

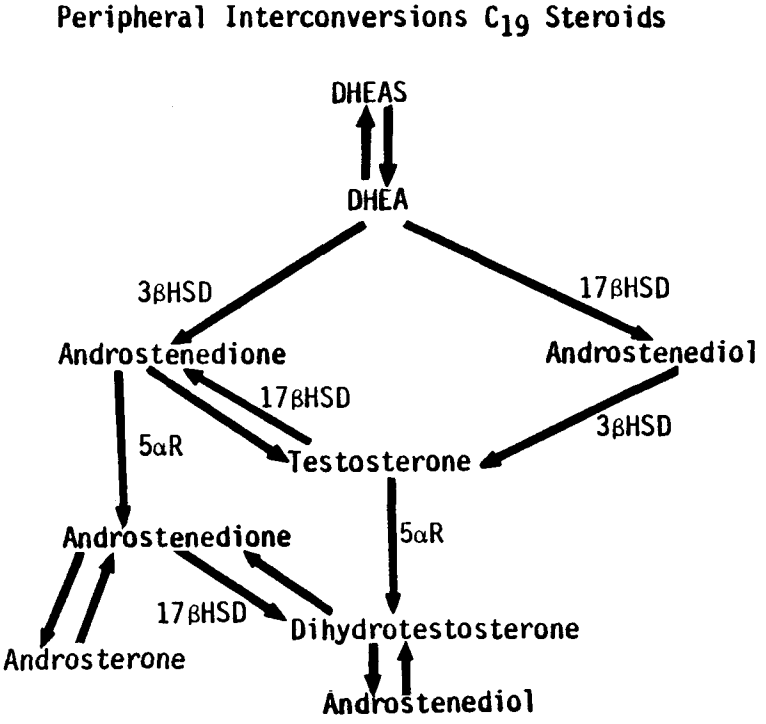


Figure 8. Peripheral metabolism of the C_{19} adrenal androgens.

tion.[10] The adrenal cortex contributes 80% of the serum DHEA and over 90% of the serum DHEAS.[11] Therefore, serum DHEAS is a useful marker for adrenal androgen secretion and can be measured by commercially available radioimmunoassay techniques requiring only 0.1 ml.[6]

Metabolism of DHEAS: Although the serum contains about 2 μg/ml of DHEAS and only about 3 ng/ml of DHEA,[9] the quantity of serum DHEA exceeds that of the T by at least 400 times.[12] The concentration of serum DHEAS begins to rise before puberty and augments sebum secretion.[13,14] In the sebaceous gland, 3β-hydroxy-steroid dehydrogenase $\Delta^{4,5}$ isomerase converts DHEA to androstenedione or testosterone through 5-androstene-3β, 17β-diol.[15] The rise of serum DHEAS associated with adrenarche is followed several years later by the appearance of pubic and axillary hair.[16,17] However, with aging, the events of adrenarche reverse, with decreasing serum concentrations of DHEA and DHEAS.[18]

Although the adrenocorticotropic hormone partially controls adrenal secretion of DHEA and DHEAS, suppression of the serum prolactin with bromocriptine produces a corresponding decrease in the serum concentrations of DHEAS.[19–21] Glickman et al[22] noted that of 21 women with hyperprolactinemia, 40% had an androgenic abnormality. Of these, 43% had an elevated unbound serum testosterone (free T) level, although the T was comparable. Depressed TeBG and high serum DHEAS levels were found with lesser frequency (in 19% compared to 21%). These authors postulated that prolactin may exert multiple effects on steroid secretion and metabolism.

The metabolism of DHEAS to DHEA proceeds via hydrolysis.[23] The ratio of serum DHEA to DHEAS in women less than 50 years of age is considerably higher than that of men.[18] Zumoff and Bradlow[24] reported that the conversion of DHEAS to DHEA has a greater effect in women than in men.

Serum DHEA, through hydrolysis of DHEAS, becomes an abundant precursor for a more potent androgen, androstenediol (androst-5-ene-3β, 17β-diol).[6] The production of androstenediol from DHEA is dependent upon the activity of 17β-hydroxysteroid dehydrogenase (17 β-HSD).[25] Further metabolism of androstenediol by 3β-hydroxysteroid dehydrogenase (3β-HSD) forms testosterone. Through 5α-reductase (5α-R) testosterone is converted to 5α-dihydrotestosterone (5α-DHT). Therefore, the peripheral metabolism of DHEAS appears to be dependent upon the rate of hydrolysis to DHEA and subsequent conversion to more potent androgens by

the activity of 17β-HSD. In normal human facial skin, where 17β-oxidation activity of 17β-HSD predominates over 17β-reduction, the 17-oxosteroids androstanedione and androsterone are the main products.[25] In normal axillary skin and, to a lesser degree, in pubic skin, where 17β-reduction predominates, 5α-DHT and other 17β-hydroxysteroids are the major metabolites of DHEAS.[25] Therefore, a metabolic pathway exists in axillary and pubic skin to allow female serum androgen levels of DHEAS to stimulate hair growth.

Normal female scalp skin minimally metabolizes DHEA, primarily to the weak androgens androstenedione, androstanedione, and androsterone.[25] Thomas and Oake[26] studied the metabolism of 7^{3}H-dehydroepiandrosterone in skin removed from the linea alba of hirsute and normal women. After four hours of incubation, between 13% and 25% of the DHEA was utilized in 5 normal women (mean, 19 ± (SE) 2.1%), and between 40% and 65% was utilized in 5 hirsute women (mean, 52 ± (SE) 4.0%). They noted increased peripheral metabolism of DHEA through testosterone and 5α-DHT which formed androstanediol in hirsute women. Testosterone metabolism was similar in the skin of hirsute and normal women, which suggested that the increased activity of 3β-HSD did not occur as a result of any increase in testosterone production. Therefore, the peripheral metabolism of DHEA varies with the site of the skin as well as with the enzymatic activity of 17β-HSD and 3β-HSD (*Fig. 8*).

Hirsutism and DHEAS: The clinical association of abnormal growth of facial hair, hirsutism, and elevated serum DHEAS levels has been observed.[27] Lobo et al[6] determined the mean serum DHEAS levels in 41 nonhirsute women with regular menstrual cycles and with normal prolactin levels (<20 ng/ml) to be 1.78 ± 0.1 μg/ml (SE) with a range of 0.3 to 2.8 μg/ml. In 52 hirsute women, of whom 49 had oligomenorrhea and 3 had regular ovulatory cycles, the mean serum DHEAS level was 3.36 ± 1.12 μg/ml (SE); 31 of the 52 women (59%) had serum DHEAS levels exceeding two standard deviations above the normal mean (>2.8 μg/ml). Hirsutism has previously been attributed to other gynecologic endocrinopathies such as polycystic ovary syndrome (PCO). In 23 of the 52 hirsute women studied by Lobo et al,[28] PCO was considered, based upon certain strict diagnostic criteria. Eight of these 23 women had serum DHEAS levels above 2.8 μg/ml, which suggests that adrenal hyperfunction is a component of PCO.

Roy et al[29] hypothesized that PCO was due to increased secretion of androgens like DHEA and androstenedione; in 42 female Sprague-Dawley rats given DHEA, 10 mg/kg body-weight, subcutaneously, cystic changes were produced in the ovaries of most of the animals. Therefore, adrenal androgen hypersecretion of DHEA and DHEAS might be a causative factor in polycystic ovarian changes and subsequent hirsutism.

Kirschner et al[30] studied the role of DHEAS and other potential C_{19} steroid prehormones of testosterone. In 20 women, all considered to have idiopathic hirsutism, the urinary 17-hydroxy-corticosteroid (17-OHCS) and basal serum cortisol concentrations were normal. In 5 of the 20 women, the urinary 17-KS concentrations were greater than 15 mg/day. In 12 of the hirsute women, the average serum DHEA values were approximately twice those obtained in 5 normal women. Of these 12, the peripheral concentrations of androstenediol were elevated twofold over those found in the normal women. Yet, approximately 5% of the serum DHEA was peripherally metabolized to androstenediol and 3% metabolized to androstenedione. Only 0.6% of the serum DHEA was eventually metabolized to testosterone, accounting for only 8% of the total testosterone production in these hirsute women. Thus, a marked increase of serum DHEA may result in elevated tissue and follicular levels of DHEA without significant metabolism to testosterone.

Hair follicles and DHEAS: Dehydroepiandrosterone influences the function and metabolism of scalp hair follicles.[31] The principal metabolites of DHEA in scalp follicles are (in order of magnitude): androstenediol, 7-hydroxy-dehydroepiandrosterone, 7-keto-dehydroepiandrosterone, 4-androstenedione, and 5-androstanedione. Fazekas and Sandor[31] reported that normal female occipital scalp follicles performed the same metabolic conversions as nonbalding male occipital follicles. However, four principal metabolites were formed from testosterone in male scalp hair follicles: androstenedione, 5α-DHT, 5α-androstanedione, and androsterone.[32] The conversion of androstenedione into testosterone and 5α-DHT was very limited. In two normal men, the principal metabolite of testosterone which affects the beard, scalp, and pubic hair follicles was

androstenedione.[32] The formation of androstenedione from testosterone was three times greater than from DHEA incubated at comparable concentrations in the male scalp hair follicle.[31] These findings suggest that androstenedione may be significant in the regulation of normal hair growth. This compound, like 5α-DHT, actively stimulates amino acid uptake and protein synthesis in intact human scalp hair follicles in vitro.[33]

In women who normally have reduced levels of T as compared to normal men, the role of other androgens may significantly affect the growth and distribution of scalp and body hair. In women, the serum concentration of DHEA is much greater than that of T.[12] Hair follicles form 100 times more androstenediol and 10 times more 7-hydroxy-DHEA from DHEA than does human skin incubated under similar conditions.[32] Therefore, the hair follicle, rather than the skin, seems to be the primary site for peripheral metabolism of DHEA.

A marked reduction in the formation of 5-androstenediol from DHEA (an average of about 9% of the control values) was measured in a study of the metabolism of hair follicles from the frontal scalp of two balding men.[31] The results suggested a decrease in the function of 17β-HSD, which resulted in decreased formation of 5-androstenediol. Fazekas and Sandor[32] examined the effect of DHEA and 5-androstenediol upon the activity of human hair follicle glucose-6-phosphate dehydrogenase (G-6-PDH). DHEA and epiandrosterone were the most effective inhibitors of human hair follicle G-6-PDH activity. Androstenediol, androstenedione, androstanedione, androsterone, and 5α-DHT had only marginal effects. Therefore, DHEA has a strong inhibitory effect on the activity of this important hair follicle enzyme. Adachi et al[34] reported that the activity of G-6-PDH increases most dramatically during the growing phase of the human scalp hair follicle. G-6-PDH is a key enzyme of the pentose cycle, which supplies building blocks for the synthesis of nucleic acids and is an important source of nicotinamide adenine dinucleotide phosphate (NADPH). The hair follicle concentrations of DHEA may be significant in regulating the activity of follicular G-6-PDH. Increased intracellular concentrations of DHEA may decrease the activity of G-6-PDH, interfering with the follicular pentose cycle and inhibiting hair growth.

The concentration of free DHEA in the hair follicle has not been reported. Physiologic serum concentrations of DHEA in normal women are 0.15 to 0.75 ng/dl.[8] At these concentrations the inhibition of the enzyme G-6-PDH may be 5% to 10%.[32] The actual intrafollicular concentration of DHEA may be much greater than the serum concentration, depending on the sulfatase activity of the follicle and surrounding tissue and the conversion of DHEAS to DHEA. More importantly, abnormally elevated levels of serum DHEAS may increase hair follicle DHEA levels, resulting in greater inhibition of G-6-PDH. A defect in the function of 17β-HSD decreases formation of 5-androstenediol from DHEA, thereby further increasing intracellular concentrations of DHEA. In summary, increased serum DHEAS concentrations and altered metabolism of DHEA within the hair follicle may result in abnormal hair growth.

Androgenetic alopecia: The concept of a relationship between the degree of androgenic stimulation and the type of androgenetic alopecia in genetically predisposed females as reported by Ludwig[1] was based upon variations in the level of circulating testosterone. Price[3] attempted to implicate increased local 5α-DHT conversion in the affected hair follicles in the biochemical genesis of androgenetic alopecia. Emphasis was directed toward the altered androgen metabolism of frontal scalp hair follicles in genetically predisposed individuals. These concepts of altered testosterone metabolism and the role of 5α-DHT in the pathophysiology of androgenetic alopecia in young women require critical reevaluation.

Female-pattern alopecia: The progressive diffuse central scalp alopecia in healthy young women is a distinct clinical entity, and should not be confused with male-pattern baldness. The main differentiation is retention of the normal hairline without frontotemporal recession in women. Jackson et al[35] recognized that this condition differed from hereditary pattern baldness. Their observation was based upon mean anagen hair diameter measurements in 58 women with diffuse hair thinning and without a detectable endocrine abnormality. Male-pattern alopecia has been characterized by a gradual regression of the hair, with measurement of hair diameter showing a gradual decrease.[36] In contrast, women with this diffuse alopecia showed a wide spread of anagen hair diameters, with two equal statistical peaks at 0.04 mm and 0.06 mm.[35] This

suggests the existence of two different types of hair in diffuse female alopecia. In contrast, in 2 women with diffuse alopecia and hypothyroidism, 80% of the hairs were approximately 0.04 mm thick, and virtually no hairs were of the normal average diameter (0.06–0.08 mm). In our patients, microscopic examination of hair plucks showed a distribution of anagen hairs into thin and nearly normal shaft diameters (*Fig. 5*). The thin hairs were not the dystrophic anagen hairs characteristic of diffuse alopecia areata.[37]

Diffuse female-pattern alopecia also differs from the diffuse thinning of hair limited to the vertex (skull-cap alopecia) observed by Ludwig[1] in postmenopausal women. Female-pattern alopecia is not associated with any inflammatory or cicatricial disorder of the scalp.

DHEAS and female-pattern alopecia: The 19 women in our study had a significant ($p < 0.001$) elevation of the serum adrenal androgen DHEAS compared to the 11 controls. The association of such an elevation level with a distinct pattern of diffuse alopecia implicates the adrenal gland as the source of excess androgen hormone production. Serum DHEAS itself does not directly cause this type of alopecia; however, it is significant as a marker hormone for adrenal androgen hyperexcretion and as the prehormone to the peripheral metabolism of more potent androgens. However, all patients with clinical signs of androgenic stimulation should be carefully evaluated, because serum DHEAS may not be abnormally elevated in all women with adrenal androgen hyperproduction.

The serum pool of DHEAS is dependent upon the rate of formation of DHEA, the rate of sulfoconjugation of DHEA to DHEAS, and the metabolic clearance rate of serum DHEAS. In our study, a 19-year-old woman with diffuse central scalp alopecia, acne, and facial hirsutism had a normal serum DHEAS level of 2.3 μg/ml. However, her urinary 17-KS were 21.1 mg/24 hours (normal range for females, 4–17 mg/24 hr.). The increased excretion of the urinary 17-KS may be the result of increased metabolic clearance of serum DHEAS. A normal serum DHEAS level alone is not a sufficient criterion to rule out adrenal androgen metabolic abnormalities.

Testosterone and female-pattern alopecia: The elevation of T was not identified by Ludwig[1] in female androgenetic alopecia. When women had elevations of T comparable to levels in normal men, the male type of alopecia with frontotemporal recession developed. All 19 women in our study had normal levels of T. No significant difference in the T levels of the 8 women who had alopecia alone and the 11 women who had additional signs of androgenic stimulation, including acne and hirsutism, was noted. In the study by Lobo et al[27] of 52 hirsute women, serum DHEAS alone was elevated in 33%, and T alone was elevated in 12%. However, 45% of the women had both elevated free T and serum DHEAS levels, while only 18% had both normal free T and serum DHEAS concentrations. Lobo et al[27] concluded that women with increased serum DHEAS levels tend to have elevated levels of free T.

T/TeBG ratio: The most significant sex steroid binding protein is the beta globulin TeBG. Hepatic production of TeBG may be altered by pregnancy, hyperthyroidism, liver disease, and certain drugs, including conjugated estrogens and oral contraceptives.[38–40]

Mathur et al[41] evaluated 39 hirsute women and noted that 31% had elevated serum DHEA levels, 41% had elevated androstenedione, 49% had elevated T levels, and 56% had elevated Free T. They also reported that 72% of the patients had suppressed TeBG levels, and 77% had an elevated T/TeBG ratio. This group of hirsute women had mean Free T levels approximately 175%, TeBG levels approximately 50%, and T/TeBG ratios approximately 300% of those observed in normal subjects. Mathur et al[41] concluded that both TeBG and T/TeBG provide better indices of hyperandrogenicity than does either T or free T.

In our study, 8 women with female-pattern alopecia only had a significantly lower T/TeBG ($p < 0.025$) than did the 11 women who had the signs of increased androgenic stimulation of acne and hirsutism. Further study may correlate the level of T/TeBG with the serum levels of Free T, androstenedione, and the ratio of DHEA/DHEAS, especially in those patients with normal or borderline increased T levels.

Prolactin and female-pattern alopecia: Vermeulen et al[20] recognized that serum DHEA and DHEAS levels were significantly higher than normal ($p < 0.001$) in women with elevated prolactin levels. This may be attributed to pituitary hypersecretion, chronic treatment with psychotropic drugs, or to prolactinoma. Specific binding sites for prolactin have been identified in the

adrenal gland.[42] Vermeulen et al[20] suggested that prolactin can stimulate the secretion of adrenal androgens, such as DHEAS, by the adrenal cortex independently of the adrenocorticotropic hormone (ACTH). Lobo et al[21] noted that a 60% reduction in serum prolactin produced an approximately 30% decrease in serum DHEAS. Kandeel et al[43] studied hyperprolactinemic women who were treated with ACTH. They observed greater increases in circulating DHEAS than in Δ^4 steroids such as testosterone and cortisol and hypothesized that a disturbance in the 3β-HSD enzyme system increases the production of Δ^5 steroids such as DHEA and 5-androstenediol. Through the enzymatic activity of 17β-HSD, DHEA is derived from 17α-hydroxy-pregnenolone, and 5-androstenediol is derived from DHEA.

Serum prolactin levels were abnormally elevated in 2 of our 14 alopecia patients. Because pituitary adenoma was revealed by computed tomography in one of these 2 patients with hyperprolactinemia, it is possible that a subset of women with female-pattern alopecia due to adrenal androgen excess may have an acquired progressive form of alopecia related to a prolactin-secreting adenoma. In an unselected autopsy series of 120 persons who did not have any clinical evidence of pituitary disease, 43 microadenomas were found in 32 pituitaries (incidence, 27%); and 41% of the tumors, when stained, revealed the presence of prolactin.[44] The incidence of prolactinomas did not differ between men and women. This indicates that more than one in 10 persons in the general population dies with a prolactinoma. Sherman et al[45] studied 42 women with hyperprolactinemia due to pituitary adenomas, of whom 74% had onset of amenorrhea following childbirth or took estrogen-containing oral contraceptives. Noting that microadenomas of the pituitary probably occur in 5% to 10% of the population, Sherman et al[45] postulated that in some women the estrogen of pregnancy or of oral contraceptives may be enough to stimulate growth of a microadenoma to a critical size, which would lead to persistent hyperprolactinemia. In the evaluation of androgenic female-pattern alopecia with or without hirsutism, the possibility of hyperprolactinemia due to a pituitary adenoma should not be overlooked.

Adrenal androgenic female-pattern alopecia: Elevation of serum DHEAS is a marker for a clinically recognizable type of hair loss that is due to increased adrenal C_{19} androgen production in young women. This type of alopecia may be associated with alteration of the hair shaft diameters, acne, and hirsutism. In young women, this disease is called adrenal androgenic female-pattern alopecia.

The pathogenesis of this pattern is unclear, although it may be the result of several different disorders of adrenal metabolism. A genetic basis for adrenal hyperproduction of DHEA or a deficiency of the 17β-HSD or 3β-HSD enzyme systems in adrenal or peripheral tissue cannot be ruled out. Acquired abnormalities of increased DHEA production through hyperprolactinemia secondary to pituitary adenomas, through adrenal cortical hyperplasia, or through adrenocorticosteroid-producing tumors must also be considered. The most significant abnormality may reside within the hair follicle itself as a result of the intracellular metabolism of DHEA and inhibition of G-6-PDH of the pentose cycle. Hair growth is dependent upon shifts in glucose metabolic pathways.[34] Compared with that in resting follicles, glucose utilization in active anagen follicles increases 100%; glycolysis, 200%; activity of the pentose cycle, 800%; and metabolism by other pathways, 150%. Active anagen follicles generate more nicotinamide adenine dinucleotide phosphate (NADPH) through these metabolic pathways than resting follicles. Therefore, DHEA inhibition of G-6-PDH in the pentose cycle and reduced production of NADPH may interfere with anagen follicle development and hair growth.

Milder forms of congenital adrenal hyperplasia (CAH) have been observed in adults. Lobo and Goebelsmann[46] identified 5 women with partial 21-hydroxylase deficiency (21-HD) after ACTH stimulation testing of 25 hirsute oligomenorrheic women. Following a bolus of ACTH, 0.25 mg, administered intravenously, a much larger increase in serum 17-hydroxyprogesterone (17-HP) was noted in the 5 CAH patients than in the controls and the other hirsute women. These 5 CAH patients, clinically indistinguishable from women with PCO and hirsutism, had basal serum measurements of DHEAS, androstenedione, and T within the 95% confidence limits established for hirsute women, although 3 of the CAH patients had serum C_{19} androgen steroid levels (DHEAS) above those seen in normal women.

The proper evaluation of alopecia in young

women is dependent upon a complete history and clinical examination in order to identify etiologic factors. The hair pluck technique is useful for the examination of anagen and telogen hairs, dysplastic hair shafts, and dystrophic hairs of diffuse alopecia areata.[47] Laboratory evaluation for androgenic alopecia should initially include determination of the serum DHEAS and T levels, TeBG (for the T/TeBG ratio), and serum prolactin amounts. An additional investigation would depend on the correlation of the initial clinical examination and the laboratory results.

Treatment: The prospect of successfully treating diffuse female-pattern alopecia is improved by the identification of an adrenal androgen abnormality. Several recent reports have indicated that spironolactone is a highly effective and safe agent for the treatment of hirsutism. Shapiro and Evron[48] gave 100 mg of spironolactone twice daily from the fourth to the 22nd day of the menstrual cycle to each of 30 hirsute women. Improvement became evident in 23 of the 30 women, usually three to five months after the beginning of treatment. The texture of the hair became softer and less coarse. Although a decrease in hair density was an average of 64% of the initial value, the appearance of the hair was still abnormal compared to the nonhirsute control women. Side effects reported in the first few weeks of spironolactone therapy included polyuria and polydipsia in 8 women; headache in 2; weight gain in 2, increased appetite in 2; and weakness, tiredness, and exhaustion in 6. Cummings et al[49] studied 20 women treated with spironolactone (200 mg/day) for moderate to severe hirsutism. They reported a reduction in the quantity and an improvement in the quality of facial hair growth in 19 of the patients. Nielsen[50] evaluated the effect of spironolactone (50 mg/day) on 21 hirsute women for an average period of seven months. The frequency of hair removal by mechanical and chemical methods was reduced by one half in 57% of these patients. Side effects noted were tenderness of the breasts in 48% of patients and menstrual irregularities in 19%.

Based on these reports, we prescribed a low dose of 25–50 mg to be taken twice daily for 8 of the 19 patients with adrenal androgenic alopecia for periods ranging from 3 to 12 months. Three of four women treated for more than nine months had an increased growth of scalp hair with a decrease in the amount of daily hair loss. Two women treated with spironolactone, 50 mg twice daily for nine and 12 months, had a reduction of serum DHEAS from 4.3 to 2.3 μg/ml and 5.8 to 2.4 μg/ml, respectively. We have not prescribed spironolactone to pregnant women, and have avoided its use in women with a familial history of breast carcinoma.

Menard et al[51] studied the biochemical effect of spironolactone on the progesterone 21-HD and 17α-HD enzyme system, which is dependent upon the adrenal microsomal cytochrome P-450. Their findings show that the presence of the sulfur atom at the carbon 7-α position on the spironolactone molecule is required for the breakdown and loss of heme and apoproteins from the adrenal cytochrome P-450, thereby decreasing steroid hydroxylase activities in the adrenal gland. The reduction of 17α-HD parallels the destruction of cytochrome P-450 by spironolactone. The loss of 17α-HD activity results in decreased production of 17α-hydroxy-pregnenolone from pregnenolone. Ultimately this leads to a decrease in concentration of the serum C_{19} androgens DHEAS and testosterone as well as serum cortisol. No loss of cytochrome P-450 occurs in tissues in which steroid 17-α-HD activity is low or absent. These studies suggest that the greater the activity of 17α-HD, the greater the effect of spironolactone on the loss of heme from the adrenal cytochrome P-450, resulting in decreased adrenal androgen production.

Spironolactone also functions as an antiandrogen within the target organ. Corvol et al[52] demonstrated that spironolactone is able to compete in vivo and in vitro with 5α-DHT for intracellular androgen receptor sites. The affinity of spironolactone for the androgenic 8 S cytosolic receptor is about one twentieth that of 5α-DHT.

Spironolactone appears to exert its effect both centrally, by reducing adrenal C_{19} androgen production, and peripherally, by interfering with androgen affinity to hair follicle cytosolic receptors.

Summary

The association of increased levels of the serum adrenal C_{19} androgen DHEAS with a distinct pattern of progressive central scalp alopecia in healthy young women is called adrenal androgenic female-pattern alopecia. A hypothesis for the pathogenesis of this alopecia is based on the inhibition of follicular G-6-PDH of the pentose cycle by intracellular DHEA, resulting in the alteration of the growth of anagen hair.

The T levels were normal in 19 women studied

with this pattern of alopecia. Other manifestations of androgenic stimulation, such as acne and hirsutism, were associated with an increased T/TeBG ratio.

The oral administration of spironolactone is an effective treatment for hirsutism. This drug inhibits adrenal C_{19} androgen production by disrupting the 17α-HD-dependent adrenal microsomal cytochrome P-450 enzyme system, is an androgen antagonist because it competitively binds with the androgen cytosolic receptor sites of the hair follicle, and may inhibit the effect of androgens in women with adrenal androgenic female-pattern alopecia.

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