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Quantitative assessment of spironolactone treatment in women with diffuse androgen-dependent alopecia

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Synopsis

From a group of 12 Caucasian females with diffuse androgen-dependent alopecia, six were treated for 12 months with spironolactone (75 or 100 mg per day) and six remained untreated. In the untreated (control) group, mean values for total hair density ($P < 0.05$) and meaningful hair density ($P < 0.01$) were significantly lower 12 months later. In contrast to these findings, no significant change in total hair density or meaningful hair density could be found in treated subjects. In two women the initial dose of spironolactone was doubled, and treatment continued for a further 12 months; in both cases increases in total hair density and meaningful hair density were observed. The androgenic hormonal variables all decreased on treatment. However, dihydrotestosterone and 3α-androstanediol-glucuronide levels were almost 50% higher. Low-dose spironolactone, 75 to 100 mg per day, appears capable of stabilizing the course of diffuse androgen-dependent alopecia in women. Initially, dosages >150 mg per day may be necessary to improve hair quality and increase hair density. However, further long-term studies are required to confirm these findings.

INTRODUCTION

In women, thinning hair is predominantly a genetic condition (known as diffuse androgen-dependent alopecia, androgenic alopecia, androgenetic alopecia, common baldness, diffuse alopecia, diffuse hair loss, or female pattern baldness) that requires androgen-mediation for its phenotypic expression. The prevalence in women is frequently quoted to be around 30%, although precise epidemiological data are not available (1). The hair loss is typically diffuse, affecting the frontal and vertex areas with similar severity (2). Often a 1–2-cm band of denser hair is retained along the frontal hair line. A male-type pattern of hair loss, marked temporal or vertex recession, is less frequent (3). The major aesthetic change is the appearance of wider partings and a greater visibility of scalp through the hair. Changes in hair density may become apparent after

an episode of increased hair shedding, but for some an insidious and gradual change occurs over many years.

Diffuse alopecia in women has been associated with endocrine abnormalities, but a relationship cannot be established in all cases. Thirty per cent or more have no demonstrable endocrine abnormality (2,4–7). In Europe, the anti-androgen cyproterone acetate (CPA) has been available for many years and, in combination with ethinyl estradiol (EE_2), has been successfully employed to treat acne, androgen-dependent alopecia, and hirsutism. Cyproterone acetate has never been available within the USA, and therefore an alternative anti-androgen was sought. In the late sixties, the aldosterone antagonist spironolactone was reported to have anti-androgen activity (8–10). Subsequent studies demonstrated its usefulness in the treatment of hirsutism (11–15) and acne (16,17), but only anecdotal evidence exists for androgen-dependent alopecia (17,18).

Three fundamental hair variables—hair density, hair diameter, and hair length—can quantitatively characterize most scalp hair disorders. The unit area trichogram (19) is a technique capable of providing such information (20). This method has been employed to detail scalp hair changes during systemic anti-androgen therapy in women (21,22) and topical 2% minoxidil treatment in men with male pattern baldness (23). In view of the anti-androgen activity associated with spironolactone, we used the unit area trichogram to evaluate scalp hair in women with diffuse androgen-dependent alopecia treated for up to 24 months.

METHODS AND MATERIALS

SELECTION OF SUBJECTS WITH DIFFUSE ALOPECIA

Twelve premenopausal Caucasian females, mean age 37 years (range 30–45 years), with diffuse androgen-dependent alopecia, participated in this study. Each had noticed cosmetically thinner hair for at least 36 months prior to entering the study. All gave their informed consent. No subject had suffered any illness lasting longer than seven days, nor had they taken prescribed medications (including oral contraceptives) or applied products known to influence hair growth for six months prior to entering the study. None had been pregnant within the previous two years, and subsequent thyroid evaluations were all normal. None had been referred to an endocrine unit for obvious androgen excess or sought medical help for acne or hirsutism. Subjects with alopecia areata, cicatricial alopecia, or a history of thyroid dysfunction were excluded, as were those who exhibited alopecia of the male-type pattern.

ALLOCATION OF CONTROLS AND SUBJECTS TREATED WITH SPIRONOLACTONE

The treated group was comprised of six subjects, mean age 35 years (range 30–41 years), with total hair densities between 162 and 336 hairs per cm^2, who elected to undergo spironolactone therapy (75 or 100 mg per day) for 12 months. The control group was comprised of six subjects, mean age 38 years (range 30–45 years), matched for total hair density, who elected to remain untreated for 12 months. The duration of alopecia ranged from 3 to 16 years and was similar between and within the two groups. There was no significant difference between the mean age of control or treated subjects (unpaired

Student's t-test). After 12 months, two subjects from the treated group agreed to continue spironolactone therapy, employing higher dosages (150 or 200 mg per day), for a further 12 months.

THE UNIT AREA TRICHOGRAM AND REPRODUCIBILITY OF HAIR VARIABLES EMPLOYED

All subjects followed the same standardized shampooing procedure one month prior to sampling, which required the hair to be shampooed daily but not on the morning of sampling. Hair samples were obtained from the frontal area basally and, within 5 mm of the original sites, 12 or 24 months later. The mean area sampled was 56 mm^2 basally and 55 mm^2 after 12 months. From two unit area trichograms, separated by less than 25 mm (Figure 1), values for hair variables were obtained from each site. The generated data were pooled, and the difference (as a %) between this pooled value and an individual site provided a measure of the reproducibility. The sum of these differences gave a mean value for the group, which was $<5\%$ for each variable. The term *meaningful hair* was defined as all non-vellus hair. A vellus hair had been characterized previously as a hair $\leqslant 30$ mm in length having a diameter $\leqslant 40$ μm (23). The proportion of hair $\leqslant 80$ mm in length provided an estimate of the disturbance occurring to the hair cycle during the previous six months. The percentage of telogen hair $\leqslant 30$ mm in length was employed to assess complete hair growth cycles of less than six months. Where reference is made to hair length, this term relates to uncut hair only or cut hair above the pre-assigned limit. Dysplastic or dystrophic hair was classified as detailed previously (2), although their occurrence was less than 4%. Hairs in the catagen growth phase were grouped with the telogen population for data analysis. The mean number of hairs examined per unit

Figure 1. Two unit area trichograms separated by less than 25 mm.

area trichogram was 135 from controls and 141 from treated subjects. A total of 6624 hairs was examined in this study.

BIOCHEMICAL AND MEDICAL INVESTIGATIONS

Full medical, biochemical, haematological, and hormonal evaluations were undertaken in all subjects basally, on day 21 of the menstrual cycle and before 11.00 h following a 12-hour fast. Biochemical and haematological investigations were repeated after 6, 12, or 24 months as appropriate. All hormonal evaluations were undertaken by the Nichols Institute, San Juan Capistrano, California. The biochemical and hematological investigations were performed by MetPath, Teterboro, New Jersey.

STATISTICAL ANALYSIS

Group mean differences were compared statistically by Student's t-test for paired or unpaired samples as appropriate. All analyses were undertaken on an Apple Macintosh™ computer using the statistical program STATWORKS.™

RESULTS

Initially, in the treated group, irregular periods and mild hirsutism were noted in two subjects, while all six subjects had mild facial acne (two of whom suffered premenstrually). In the control group, two subjects had irregular periods, one had mild hirsutism, and two had mild facial acne (one premenstrually). None of these conditions were troublesome enough to warrant any subject seeking medical advice for these complaints. On treatment, two subjects with irregular cycles became regular, while two with regular menses developed irregular cycles. However, no subject withdrew from therapy because of any side effects.

COMPARISON BETWEEN BASAL HAIR VARIABLES AND THOSE OBTAINED AFTER 12 MONTHS IN CONTROL AND TREATED SUBJECTS

Mean baseline values for hair variables from controls and treated subjects were compared to values obtained from the same sites 12 months later (Tables I and II). In the control group, but not in the treated group, a significant decrease in total hair density ($P < 0.05$) and meaningful hair density ($P < 0.01$) was observed after 12 months (Figure 2). Subjective impressions supported these findings, particularly within the control group, where deterioration in hair quality was cause for concern.

BASAL BIOCHEMICAL AND HORMONAL EVALUATIONS FROM CONTROL AND TREATED SUBJECTS WITH DIFFUSE ANDROGEN-DEPENDENT ALOPECIA

Basal hematological and non-hormonal biochemical values were all within the reference range of the laboratory. The principle androgenic hormones, androstenedione, dehydroepiandrosterone-sulphate (DHEA-S), and total testosterone were also within their

Table I
Comparisons Between Hair Variables From the Frontal Area of Untreated Controls Basally and After 12 Months: Mean ± SD and Range (in parentheses)

Variable	Control group (n = 6)		
	Basal		12 Months
Total hair density (Hair per cm^2)	231 ± 57 (157–317)	*	206 ± 72 (120–303)
Meaningful hair density (Non-vellus hair per cm^2)	191 ± 67 (116–278)	**	169 ± 74 (80–268)
(%) Anagen hair	79.4 ± 9.3 (61.0–84.7)	ns	75.3 ± 12.4 (56.9–93.8)
(%) Meaningful anagen hair	85.9 ± 4.5 (81.5–94.2)	ns	79.0 ± 10.7 (65.5–93.6)
(%) Hair ≤80 mm in length	68.4 ± 24.0 (25.9–89.0)	ns	74.5 ± 14.9 (50.0–89.1)
(%) Vellus hair	17.9 ± 16.4 (2.0–46.3)	ns	19.2 ± 16.8 (2.0–50.8)
(%) Telogen hair ≤30 mm in length	11.7 ± 11.1 (2.0–32.9)	ns	11.2 ± 9.1 (0.0–27.7)

ns = Not significant: $P > 0.05$; *$P < 0.05$; **$P < 0.01$ (paired Student's t-test).

respective reference ranges. The peripheral markers for hyper-androgenism were raised in six (50.0%) for free testosterone, in two (16.7%) for 3α-androstanediol-glucuronide (3α-A-diol-G), and in one (8.3%) for dihydrotestosterone (DHT). However, no correlation between individual or grouped hormonal values with any hair value could be established.

TRICHOLOGICAL AND HORMONAL CHANGES IN TWO SUBJECTS WHO CONTINUED WITH SPIRONOLACTONE THERAPY FOR A FURTHER 12 MONTHS

One subject who initially received 75 mg of spironolactone per day was increased to 150 mg per day, and one initially receiving 100 mg per day was increased to 200 mg per day. After 12 months of treatment with these higher dosages, both had increases in total hair density and meaningful hair density and a corresponding decrease in the percentage of vellus hair and telogen hair ≤30 mm in length (Table III). Comparisons between basal hormonal levels and those observed after 24 months showed a substantial reduction in the androgenic hormones. However, both DHT and 3α-A-diol-G levels were inexplicably elevated.

DISCUSSION

The major initiating feature of androgen-dependent alopecia in men and women is the action of androgens upon the pilo-sebaceous unit (2,7,24,25), the associated dermal/sub-dermal tissue (26), and the receptor-binding phenomenon within the hair cell (27).

Table II
Comparisons Between Hair Variables From the Frontal Area Basally and After 12 Months of Spironolactone (75 or 100 mg per day) Treatment: Mean ± SD and Range (in parentheses)

Variable	Treated group (n = 6)		
	Basal		12 Months
Total hair density (Hair per cm^2)	256 ± 78 (162–336)	ns	239 ± 72 (145–313)
Meaningful hair density (Non-vellus hair per cm^2)	197 ± 67 (123–276)	ns	189 ± 51 (131–256)
(%) Anagen hair	78.5 ± 5.1 (72.9–84.8)	ns	79.8 ± 4.3 (74.8–84.7)
(%) Meaningful anagen hair	81.2 ± 6.0 (70.2–86.2)	ns	79.5 ± 9.9 (63.7–91.2)
(%) Hair ≤80 mm in length	56.9 ± 16.6 (37.6–80.8)	ns	56.1 ± 18.8 (33.0–82.9)
(%) Vellus hair	23.2 ± 6.0 (16.5–30.3)	ns	19.6 ± 8.5 (9.6–33.3)
(%) Telogen hair ≤30 mm in length	10.3 ± 2.9 (6.8–13.9)	ns	10.9 ± 5.6 (6.4–21.4)

ns = Not significant: $P > 0.05$ (paired Student's t-test).

Compounds with anti-androgen activity would therefore appear essential in the treatment of androgen-dependent alopecia (25), and studies employing CPA in combination with EE_2 support this view (21,23). For spironolactone, however, no quantitative data for alopecia were available; consequently, we employed dosing regimens established in acne and hirsutism. In moderately hirsute women, 50 mg of spironolactone per day was reported to regress terminal hair to vellus hair within six months of starting treatment (14). Good results had also been reported for dosages between 150 mg and 200 mg per day in acne (16) and hirsutism (13,17,28). However, with dosages >100 mg per day, side effects began to appear, and several studies reported drop-out rates in excess of 25% (12,15).

In our study, subjects treated with spironolactone (75 or 100 mg per day) had stabilized total and meaningful hair densities 12 months later (Table II), while in untreated controls a significant decrease was observed at this time (Table I). Subjective impressions supported these findings, particularly within the control group, where deterioration in hair quality was cause for concern. When the dosage was doubled, increases in total and meaningful hair densities were recorded in the two subjects so treated (Table III). Both were aware of an improvement in hair quality. In comparison to these findings for spironolactone, low-dose CPA-EE_2 studies suggest that CPA dosages ≤50 mg per month are unable to prevent further expression of the alopecia, whereas CPA dosages ≥500 mg per month are able to do so. Whether the degree of improvement achieved with high-dose spironolactone is similar to that obtained with high-dose CPA is the subject of an ongoing study.

One of the major problems in treating androgen-dependent alopecia is the difficulty in

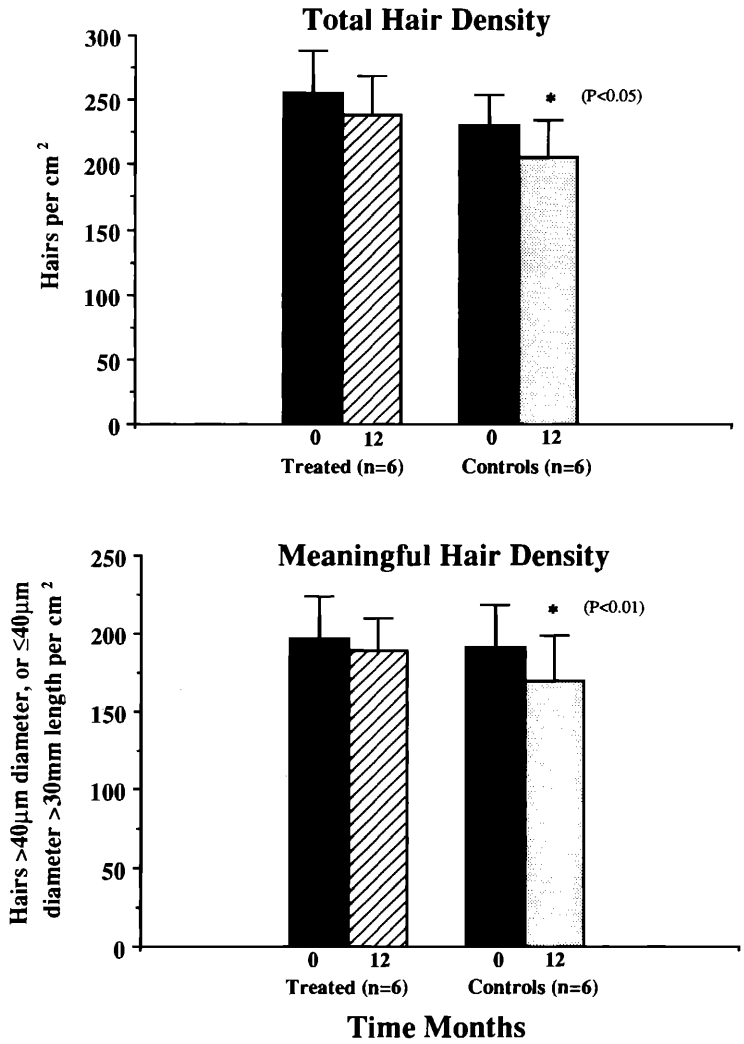

Figure 2. Changes in total and meaningful hair densities (mean ± SEM) in controls and subjects treated with spironolactone (75 or 100 mg per day). *Significance level (paired Student's t-test).

predicting what effective regimen is required for a specific group or individual. Circulating hormonal levels do not provide any reliable information about the rate of change occurring in scalp hair or the dosage required to treat it (2). This is of considerable importance since the treatment time required may be several years. Moderate dosages of spironolactone (75 or 100 mg per day) appear capable of stabilizing the course of androgen-dependent alopecia, at least in these women, without any significant side effects. Initially, higher dosages may be necessary to improve hair quality and achieve increases in hair density. However, further long-term studies are required to confirm these findings. Our data for spironolactone supports the role of androgens as a mediating factor in genetic hair loss in women.

Table III
Comparisons Between Basal Hair Variables and Those Obtained After 12 and 24 Months of Spironolactone Treatment

	Subject One			Subject Two		
Spironolactone (mg per day)	|---100---|---200---|			|---75---|---150---|		
Time (months)	0	12	24	0	12	24
Hair variable						
Total hair density per cm^2	310	303	349	162	145	173
Meaningful hair density per cm^2	258	267	293	130	131	147
(%) Anagen hair	72.9	76.6	86.6	79.4	84.0	77.6
(%) Meaningful anagen hair	79.5	78.6	86.5	85.6	84.7	80.2
(%) Vellus hair	16.5	16.5	11.9	19.6	9.6	15.0
(%) Telogen hair ≤30 mm	13.2	6.2	2.6	11.2	6.4	7.5

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REFERENCES

(1) A. Rook and R. P. R. Dawber, *In Diseases of the Hair and Scalp* (Blackwell Scientific Publications, Oxford, 1982), pp. 95–98.
(2) D. H. Rushton, I. D. Ramsay, K. C. James, M. J. Norris, and J. J. H. Gilkes, Biochemical and trichological characterisation of diffuse alopecia in women, *Br. J. Dermatol.*, **123**, 187–197 (1990).
(3) E. Ludwig, Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex, *Br. J. Dermatol.*, **97**, 249–254 (1977).
(4) J. A. Miller, C. R. Darley, K. Karkavitsas, J. D. Kirby, and D. D. Munro, Low sex hormone binding globulin levels in young women with diffuse hair loss, *Br. J. Dermatol.*, **106**, 331–336 (1982).
(5) J. M. Kasick, W. F. Bergfeld, W. D. Steck, and M. K. Gupta, Adrenal androgenic female-pattern alopecia: Sex hormones and the balding woman, *Clev. Clin. Q.*, **50**, 111–122 (1983).
(6) W. Futterweit, A. Dunaif, H. C. Yeh, and P. Kingsley, The prevalence of hyper-androgenism in 109 consecutive female patients with diffuse alopecia, *J. Am. Acad. Dermatol.*, **19**, 831–836 (1988).
(7) L. Moltz, Hormonale diagnostik der sogenannten androenetischen alopezie der frau, *Geburtsh in Frauenheilk*, **48**, 203–214 (1988).
(8) R. F. Spark and J. C. Melby, Aldosteronism in hypertension, *Ann. Intern. Med.*, **69**, 685–691 (1968).
(9) S. L. Steelman, J. R. Brooks, E. R. Morgan, and D. J. Patanelli, Anti-androgenic activity of spironolactone, *Steroids*, **14**, 449–450 (1969).
(10) H. C. Erbler, Suppression by the spironolactone metabolite canrenone of plasma testosterone in man, *Arch. Pharmacol.*, **285**, 403–406 (1974).
(11) K. P. Ober and J. F. Hennessy, Spironolactone therapy for hirsutism in a hyperandrogenic woman, *Ann. Intern. Med.*, **89**, 643–644 (1978).
(12) G. Shapiro and S. Evron, A novel use of spironolactone: Treatment of hirsutism, *J. Clin. Endocrinol. Metab.*, **51**, 429–432 (1980).
(13) D. C. Cumming, J. L. Yang, R. W. Rebar, and S. S. C. Yen, Treatment of hirsutism with spironolactone, *JAMA*, **247**, 1295–1298 (1982).
(14) P. Ylöstalo, J. Heikkinen, A. Kanppila, A. Pakarinen, and P. A. Järvinen, Low-dose spironolactone in the treatment of female hirsutism, *Int. J. Fertil.*, **32**, 41–45 (1987).
(15) E. L. Helfer, J. L. Miller, and L. I. Rose, Side-effets of spironolactone therapy in the hirsute woman, *J. Clin. Endocrinol. Metab.*, **66**, 208–211 (1988).

(16) A. Goodfellow, J. Alaghband-Zadeh, G. Carter, J. J. Cream, S. Holland, J. Scully, and P. Wise, Oral spironolactone improves acne vulgaris and reduces sebum excretion, *Br. J. Dermatol.*, **111**, 209–214 (1984).
(17) B. M. Burke and W. J. Cunliffe, Oral spironolactone therapy for female patients with acne, hirsutism or androgenic alopecia, *Br. J. Dermatol.*, **112**, 124–125 (1985).
(18) H. Zaun, Indikation und grenzen der antiandrogenen therapie, *Z. Hautkr.*, **59**(16), 1090–1097 (1983).
(19) D. H. Rushton, K. C. James, and C. H. Mortimer, The unit area trichogram in the assessment of androgen-dependent alopecia, *Br. J. Dermatol.*, **109**, 429–437 (1983).
(20) D. H. Rushton, K. C. James, and M. J. Norris, Quantitative assessment of hair quality, *Proceedings of the 15th IFSCC Congress, London*, B499–B516 (1988).
(21) C. H. Mortimer, D. H. Rushton, and K. C. James, Effective medical treatment for common baldness in women, *Clin. Exp. Dermatol.*, **9**, 342–350 (1984).
(22) D. H. Rushton and I. D. Ramsay, The importance of adequate serum ferritin levels during oral cyproterone acetate and ethinyl-oestradiol treatment of diffuse androgen-dependent alopecia in women (in press).
(23) D. H. Rushton, W. P. Unger, P. C. Cotterill, P. Kingsley, and K. C. James, Quantitative assessment of 2% topical minoxidil in the treatment of male pattern baldness, *Clin. Exp. Dermatol.*, **14**, 40–46 (1989).
(24) D. H. Rushton, *Chemical and Morphological Properties of Scalp Hair in Normal and Abnormal States* (PhD Thesis, University of Wales, 1988).
(25) J. B. Hamilton, Male hormone stimulation is a prerequisite and incitant in common baldness, *Am. J. Anat.*, **71**, 451–480 (1942).
(26) H. Pinkus, Differential patterns of elastic fibres in scarring and non-scarring alopecias, *J. Cut. Path.*, **5**, 93–104 (1978).
(27) M. E. Sawaya, A. J. Mendez, L. A. Lewis, and S. L. Hsia, Two forms of androgen receptor protein in human hair follicles and sebaceous glands: Variation in transitional and bald scalp, *J. Invest. Dermatol.*, **90**, 606 (1988).
(28) J. H. Barth, C. A. Cherry, F. Wojnarowska, and R. P. R. Dawber, Spironolactone is an effective and well tolerated systemic antiandrogen therapy for hirsute women, *J. Clin. Endocrinol. Metab.*, **68**, 966–970 (1989).