

Low Dose Dehydroepiandrosterone Affects Behavior in Hypopituitary Androgen-Deficient Women: A Placebo-Controlled Trial

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Thirty-eight women, aged 25–65 yr, with androgen deficiency due to hypopituitarism were treated with oral dehydroepiandrosterone (DHEA; 30 mg/d if <45 yr of age and 20 mg if ≥45 yr of age) for 6 months in a randomized, placebo-controlled, double blind study, followed by a 6-month open treatment period. The administration of DHEA raised the serum levels of DHEAS to normal age-related reference ranges and increased androstenedione and T to subnormal levels. Androgen effects on skin and/or pubic and/or axillary hair were observed in 84% (32 of 38) of the women after all received 6 months of DHEA treatment. No such effects were observed after the placebo treatment. These effects after 6 months were correlated with the serum levels of DHEAS ($r = 0.37$; $P = 0.03$), androstenedione ($r = 0.42$; $P = 0.01$), and T ($r = 0.37$; $P = 0.03$). The percentages of partners who reported improved alertness, stamina, and initiative by their spouses were 70%, 64%, and 55%,

respectively, in the DHEA group and 11%, 6%, and 11%, respectively, in the placebo group ($P < 0.05$). According to the partners, sexual relations tended to improve compared with placebo ($P = 0.06$). After 6 months of treatment, increased sexual interest or activity was reported by 50% of the women taking 30 mg DHEA, by none taking 20 mg DHEA, and by two women taking placebo ($P = \text{NS}$). Compared with levels after placebo administration, high density lipoprotein cholesterol and apolipoprotein A-1 levels decreased after DHEA. Serum concentrations of IGF-I, serum markers of bone metabolism, and bone density did not change.

In conclusion, oral administration of a low dose of DHEA to adult hypopituitary women induced androgen effects on skin and axillary and pubic hair as well as changes in behavior, with only minor effects on metabolism. (*J Clin Endocrinol Metab* 87: 2046–2052, 2002)

WOMEN WITH PITUITARY insufficiency have severe androgen deficiency due to a lack of both adrenal and ovarian androgen production (1, 2). Dehydroepiandrosterone (DHEA), which is the main steroid secreted from the adrenals, is sulfated to DHEAS, mainly in the adrenal gland, but also in the liver and other peripheral tissues. DHEA and DHEAS are further transformed in target tissues into more active steroids, such as androstenedione, T, DHT, and estrogens. These transformations depend on the tissue activity of steroidogenic and metabolizing enzymes such as 3β -hydroxysteroid dehydrogenase/ Δ^5 - Δ^4 -isomerase, 17β -hydroxysteroid dehydrogenase, 5α -reductase, and aromatase (3). The effects of DHEA are probably mediated through these peripheral transformations, although direct effects have been proposed through a specific receptor for DHEA that has not been identified.

The metabolic consequences of hypopituitarism in patients receiving adequate conventional hormone replacement therapy, except GH, are more marked in women than

in men in terms of abdominal obesity, lipoprotein profile (4, 5), osteopenia (6), and quality of life (7). Untreated severe androgen deficiency in women with hypopituitarism may contribute to these gender differences.

Recently, promising effects on well-being and libido were reported after DHEA administration to adult women with adrenal insufficiency, suggesting the importance of low androgen levels in these women (8, 9). In these studies the administration of 50 mg DHEA raised serum levels of DHEAS 24 h after intake to the upper normal range and increased androstenedione and T levels to the lower normal ranges. Young *et al.* (2), who studied the metabolism of DHEA in detail in patients with panhypopituitarism, found that 50 mg DHEA increased plasma DHEAS and T to levels observed in young women 4 and 3 h after intake, respectively, and increased androstenedione to levels in premenopausal women 3 h after intake. The 24-h urinary excretion of androstenedione glucuronide, an androgen metabolite regarded as a reliable marker of the pool of T (10), increased to levels seen in normal young women, in accordance with the report by Arlt *et al.* (8), who noted serum levels of this metabolite in the upper normal range 24 h after the intake of 50 mg DHEA. Collectively, the observations indicate that doses lower than 50 mg may be suitable for long-term treatment in hypoandrogenic women.

Abbreviations: apo, Apolipoprotein; CV, coefficient(s) of variation; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; HDL, high density lipoprotein; HL, hepatic lipase; HSCL, Hopkins Symptom Check List; ICTP, carboxyl-terminal cross-linked telopeptide of type I collagen; LPL, lipoprotein lipase; PAI-1, plasminogen activator inhibitor 1; PICP, carboxyl-terminal propeptide of type I procollagen; t-PA, tissue plasminogen activator.

We report our observations of 38 women with hypopituitarism who were given low age-adjusted doses of DHEA in a 6-month, placebo-controlled trial, followed by 6 months of open treatment. The primary end point was to study the effect on quality of life, well-being, and behavior. Secondary end points were to study the effects of DHEA treatment on skin, hair, glucose and lipid metabolism, body composition, bone metabolism, and safety.

Subjects and Methods

Patients

Forty women with hypopituitarism with both adrenocorticotrophic and gonadotropic insufficiency were enrolled in the study. The results are based on 38 patients who fulfilled the inclusion criteria and completed the study (Table 1). The pituitary insufficiency was acquired in adulthood in all but 1 patient. The replacement therapy had been stable for at least 12 months before inclusion and was not changed throughout the study period. All but 1 subject had GH deficiency that had been treated for a mean period of 5 yr (range, 1–9 yr). Four and six women in the DHEA and placebo groups, respectively, were not receiving estrogen replacement therapy. These women belonged to the older patient group and had previously experienced side effects of estrogen replacement therapy. The two study groups were similar in terms of age, duration of disease, cause of pituitary pathology, and replacement therapy (Table 1).

Study protocol

This was a two-phase trial with an initial 6-month, randomized, double blind, placebo-controlled period, followed by open treatment for 6 months. The randomization was performed centrally. The women were stratified into two equal age range groups, below and above 45 yr of age, and were given 15 and 10 mg DHEA/placebo twice daily, respectively. The production unit of the National Corporation of Swedish Pharmacies (Stockholm, Sweden) prepared capsules containing DHEA (Sigma, St. Louis, MO). The use of a low dose DHEA regimen designed to result in DHEAS levels in the mid-normal range was supported by our own preliminary unpublished observations of open treatment with DHEA in hypopituitary women.

Before treatment and at 6 and 12 months of follow-up, blood samples were taken in the morning after an overnight fast and approximately 12 h after the last DHEA dose. All samples except those for safety monitoring were stored at -20 or -80 C until being assayed. Body composition and muscle strength were assessed, and physical examination, including clinical assessment of body hair growth, was performed at baseline and at 6 and 12 months. Changes in skin (oiliness, moisture content, and elasticity) and pubic and axillary hair growth were discussed at each visit. The patients self reported changes in sexual interest and activity and responded to two quality of life questionnaires. Their spouses/

partners completed a questionnaire about their relationship with the patient after the 6-month blinded treatment period. Body weight was measured in the morning to the nearest 0.1 kg, and systolic and diastolic blood pressures were measured after 5 min of supine rest. Side effects were asked about on each visit, and safety was monitored every third month using biochemical measurements and an interview conducted by the managing physician.

Materials and Methods

A score for neutral body hair was calculated from the sum of the scores obtained from the forearm and leg (0–8 points), and a hormonal score was calculated from nine other skin areas (0–36 points) as described previously (11).

Biochemistry

DHEAS was measured with a solid phase RIA (Coat-A-Count, Diagnostic Products, Los Angeles, CA), androstenedione was measured using an RIA (Ortho-Clinical Diagnostics, Amersham Pharmacia Biotech, Poole, UK), and serum total T was measured using a competitive immunoassay (Diagnostic Products). The intraassay coefficients of variation (CV) and the detection limits for DHEAS, androstenedione, and T were 5% and 0.03 $\mu\text{mol/liter}$, 4% and 0.07 nmol/liter, and 7–20% and 0.10 nmol/liter, respectively.

Serum levels of SHBG were measured with time-resolved, noncompetitive, sandwich fluoroimmunoassays (AutoDELFLIA SHBG kit, Wallac, Inc., Turku, Finland), and serum concentrations of IGF-I and insulin were measured using competitive immunoassays from Nichols Institute Diagnostics (San Juan Capistrano, CA) and Pharmacia Diagnostika (Pharmacia Insulin RIA, Uppsala, Sweden), respectively. The intraassay CV was 4.6%, 7%, and 2.5–4.2% for SHBG, insulin, and IGF-I, respectively.

Serum concentrations of osteocalcin (CIS Biointernational, Oris Industries, Gif-Sur-Yvette, France), carboxyl-terminal cross-linked telopeptide of type I collagen (ICTP), and carboxyl-terminal propeptide of type I procollagen (PICP) were measured using RIAs (Orion Diagnostica, Espoo, Finland). Bone-specific alkaline phosphatase activity in serum was calculated from measurements of the enzyme activity in untreated serum and after extraction with wheat-germ lectin (Roche Molecular Biochemicals, Mannheim, Germany). The intraassay CV were 7%, 6%, 3%, and 7% for osteocalcin, ICTP, PICP, and bone-specific alkaline phosphatase, respectively.

Serum cholesterol and triglycerides were determined using fully enzymatic methods (Roche Molecular Biochemicals) with a Cobas Fara auto-analyzer (Hoffman-LaRoche Inc., Basel, Switzerland) that had within-assay CV of 0.9% and 1.1%, respectively. High density lipoprotein (HDL) cholesterol was determined after precipitation of apolipoprotein B (apoB)-containing lipoproteins with manganese chloride and heparin. The low density lipoprotein cholesterol concentration was calculated. ApoA-1 and apoB were determined by immunoturbidometric assays (UniKit Roche, Hoffman-LaRoche Inc.). Serum lipoprotein(a) was measured by RIA

TABLE 1. Clinical characteristics of the 38 hypopituitary women with androgen deficiency who received DHEA and placebo for 6 months, followed by 6 months of open DHEA treatment

Variable	DHEA treated	Placebo treated
Age; mean (range) (yr)	51 (25–65)	50 (25–65)
No. (≥ 45 / < 45 yr)	19 (14/5)	19 (15/4)
Duration of disease; mean (range) (yr)	11 (2–30)	18 (3–34)
Cause of pituitary deficiency		
Nonfunctional pituitary adenoma	7	9
Craniopharyngioma	3	5
Cushing's disease	3	1
Prolactinoma/acromegaly	3	1
Other	5	3
Replacement therapy		
GH; no. (mg/d)	19 (0.5 \pm 0.2)	18 (0.6 \pm 0.2)
Estrogen; no. (oral/transdermal)	17 (13/4)	13 (10/3)
L-thyroxine; no. (mg/d)	19 (0.11 \pm 0.03)	19 (0.12 \pm 0.03)
Cortisone acetate; no. (mg/d)	19 (26.7 \pm 7.0)	19 (28.0 \pm 8.4)

Values are mean \pm SD.

(Mercodia AB, Uppsala, Sweden). The intraassay CV of ApoA-1, apoB, and lipoprotein(a) were 2.3%, 1.9%, and 4.4%, respectively.

For the determination of postheparin plasma lipoprotein lipase (LPL) and hepatic lipase (HL) activity, heparin (100 U/kg BW) was given iv. Venous blood samples were drawn after 15 min into precooled Vacutainer tubes (BD, Franklin Lakes, NJ) containing heparin. The tubes were immediately placed in ice water, and plasma was recovered by centrifugation. The samples were frozen at -80°C pending assay as described previously (12). All measurements were made in triplicate. Lipase activity is expressed as milliunits per ml plasma, where 1 mU corresponds to the release of 1 nmol fatty acid/min at 25°C and pH 8.5.

Fibrinogen, tissue plasminogen activator (t-PA) antigen, and plasminogen activator inhibitor 1 (PAI-1) activity were measured as described previously (13).

Hemoglobin concentration, hematocrit, plasma glucose, glycosylated hemoglobin, electrolytes, creatinine, liver enzymes, and free T_4 were measured using routine in-house methods.

Body composition and handgrip

Bone mineral content and bone mineral density in total body, lumbar spine, and femoral neck; lean body mass and fat mass were determined using dual energy x-ray absorptiometry (DPX-L, Lunar Corp., Madison, WI).

The height from a firm bed to the umbilicus (sagittal diameter) was measured in the supine position using a digital sagittalometer.

Handgrip strength on the dominant side was measured using an electronic grip force measurement instrument, which measures the maximum momentary force and the mean force over a set period of 10 sec in Newtons (14). Verbal instructions were given to encourage maximum force production. The results from handgrip strength were compared with normal reference values adjusted for age and sex (15), and an observed/predicted ratio was calculated for each woman.

Questionnaires

The Hopkins Symptom Check List (HSCL) is composed of 56 items that cover psychiatric and somatic problems related to mental distress (16). The items can be gathered into 8 subscales: anxiety, depression, tension, cognition, inferiority, interpersonal sensitivity, somatization, and fearfulness. The Psychological General Well-Being index was also employed. This is another generic quality of life measure that assesses perceived health, anxiety, ability to cope, and depression (17). A 12-item questionnaire modified from that reported by Burman *et al.* (7) was developed to assess changes in mood and behavior in response to treatment. The husband or the patient's partner made the evaluation on completion of the placebo-controlled period.

The patients were asked to report changes in sexual interest and activity as reduced, unchanged, or increased. The reports were given anonymously at 6 and 12 months, and the numbers of reduced/unchanged *vs.* increased responses were subsequently computed.

Ethics

All subjects gave their informed consent to participate in the study. The study design was approved by the Swedish Medical Products Agency and the ethics committees at the Faculties of Medicine, Universities of Uppsala and Goteborg.

Statistical analysis

All descriptive statistical results are presented as the mean \pm SD, except for those with highly skewed data distribution, which are presented as the median and range. The overall within-group effect of treatment was analyzed using Friedman's ANOVA for repeated measurements. *Post hoc* analysis and the analysis of between-group levels and treatment effects during the placebo-controlled phase of the trial were performed using Wilcoxon's matched pairs, signed-rank sum test and the Mann-Whitney *U* test, respectively. Correlations were sought by calculating Spearman's rank coefficient, and Fisher's exact test was used in analyses of four-field tables. Statistical significance was considered been obtained if *P* was 0.05 or less.

Results

Thirty-eight women were eligible for efficacy analysis for the placebo-controlled period and the open 6-month treatment. At completion of the study, subnormal androgen levels were confirmed in all but one woman, who turned out to have partial pituitary insufficiency and normal serum adrenal androgen levels. She was excluded from analysis in the study. The exclusion did not change the results of the study. No severe side effects were recorded. One woman reported mild anxiety, and two women recorded restlessness, all while taking DHEA. One woman allocated to DHEA group discontinued treatment after the first visit as a result of oily skin and increased perspiration.

Serum androgens, SHBG, and IGF-I (Table 2)

Serum morning levels of DHEAS, androstenedione, and T increased markedly in the DHEA-treated group compared with placebo. Serum DHEAS 12 h after dosage and at trough levels reached normal concentrations. Androstenedione and T reached subnormal reference ranges. The serum androgen levels determined after 6 months of treatment were not statistically different in the women above and below 45 yr of age receiving 20 and 30 mg DHEA, respectively (DHEAS, 2.53 \pm

TABLE 2. Measurements of androgens, SHBG, and serum IGF-I concentrations during 6 months of DHEA or placebo, followed by 6 months of open DHEA treatment

Variable	Group	Baseline	6 months	12 months	<i>P</i> ^a
DHEAS (1.6–10.2 $\mu\text{mol/liter}$) ^b	DHEA	0.09 \pm 0.06	2.77 \pm 1.75 ^{c,d}	3.02 \pm 1.80 ^c	<0.001
	Placebo	0.10 \pm 0.08	0.10 \pm 0.07	2.65 \pm 1.42 ^c	<0.001
Androstenedione (1.6–9.0 nmol/liter) ^b	DHEA	0.08 \pm 0.06	0.45 \pm 0.32 ^{c,d}	0.49 \pm 0.36 ^c	<0.001
	Placebo	0.11 \pm 0.11	0.12 \pm 0.11	0.76 \pm 0.61 ^c	<0.001
T (0.14–2.80 nmol/liter) ^b	DHEA	0.09 \pm 0.02	0.15 \pm 0.11 ^{c,d}	0.14 \pm 0.85 ^c	<0.001
	Placebo	0.10 \pm 0.02	0.10 \pm 0.01	0.20 \pm 0.19 ^c	<0.001
SHBG (mmol/liter)	DHEA	55 \pm 26	59 \pm 36	58 \pm 35	0.6
	Placebo	73 \pm 44	67 \pm 40	60 \pm 35 ^c	0.02
IGF-I ($\mu\text{g/liter}$)	DHEA	165 \pm 51	167 \pm 51	186 \pm 82	0.2
	Placebo	163 \pm 58	154 \pm 58	167 \pm 64	0.6

^a Overall within-group treatment effects calculated with Friedman's ANOVA.

^b Normal ranges for adult females, as provided by the assay manufacturers. Values below the detection limit of the assays for T and androstenedione were assigned values corresponding to the detection limits. At baseline and after 6 months of active treatment, there were 29 and 2 and 37 and 19 such values for androstenedione and T, respectively.

^c *P* < 0.05 as compared with commencement of DHEA treatment; baseline in the DHEA group and 6 months in the placebo group.

^d *P* < 0.001 *vs.* changes in the placebo group between baseline and 6 months.

1.37 and $3.53 \pm 1.84 \mu\text{mol/liter}$; androstenedione, 0.54 ± 0.44 and 0.93 ± 1.36 ; T, 0.17 ± 0.13 and $0.20 \pm 0.20 \text{ nmol/liter}$, respectively).

Serum concentrations of IGF-I and SHBG were unchanged during the placebo-controlled period. In the group first allocated to placebo, SHBG decreased during the open extended phase when this group received treatment with DHEA, whereas the serum IGF-I concentration did not change.

Quality of life assessments and sexual interest/activity

The baseline total scores from each dimension obtained using the HSCL-56 and Psychological General Well-Being questionnaire were similar in the placebo and DHEA groups and did not change in response to treatment, apart from a small reduction, *i.e.* an improvement in quality of life in the total HSCL-56 score at 12 months compared with baseline in those initially randomized to placebo (86 ± 21 to 79 ± 23 ; $P < 0.01$).

The partner questionnaire revealed an overall improvement in 3.8 ± 2.7 items in the DHEA-treated group compared with 1.1 ± 1.8 in the placebo group ($P = 0.006$). Significant improvements in the response to DHEA treatment were obtained for “gets more done,” initiative, stamina, and alertness, whereas sexual relations tended to improve (Fig. 1).

Changes in sexual interest/activity were asked about in all women who had partners (7 of 9 in the 30 mg group and 22 of 29 in the 20 mg group). Changes were not detected during the controlled part of the study. After the subsequent 6 months of open treatment with DHEA, all those with partners receiving 30 mg and 9 (41%) of those receiving 20 mg reported increased sexual interest/activity.

Skin and hair

Sixteen of the 19 women receiving DHEA treatment experienced changes in skin or perspiration, and none of the women initially randomized to placebo ($P < 0.001$). Changes in skin (oily, moisture, and elasticity) after 6 months of DHEA treatment in the whole group were reported by eight

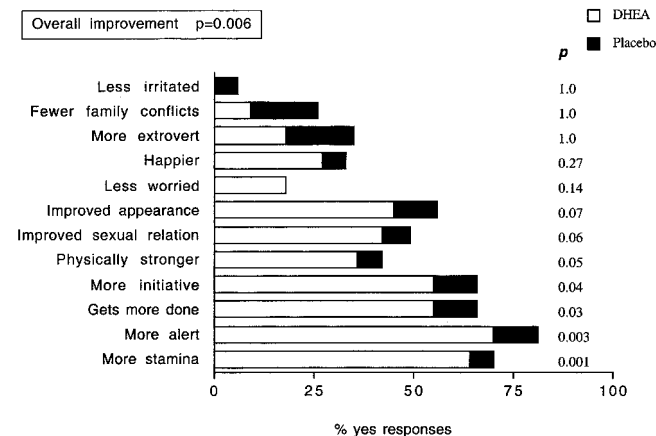


FIG. 1. Effects of DHEA treatment as determined by a spouse questionnaire at the end of the 6-month DHEA and placebo treatments. The white part and the black part of the columns represent the percentage of yes responders in the DHEA and placebo groups, respectively.

of nine (89%) receiving 30 mg and by 12 of 29 (41%) women receiving 20 mg, *i.e.* 21 of the 38 (53%) women developed skin changes after 6 months of active treatment. There was no significant difference between those receiving 20 and 30 mg DHEA. After 12 months of DHEA treatment, another seven women initially randomized to 20 mg DHEA had experienced androgenic skin effects. During the 12-month period, 24 (63%) women experienced increased perspiration on physical activity in response to the DHEA treatment.

An increase in or the reappearance of axillary and/or pubic hair was seen in all women given 30 mg DHEA and in 20 of 29 (69%) women receiving 20 mg DHEA, *i.e.* in a total of 76% of the women receiving active treatment. The baseline median hormonal body hair score was 1 (range, 0–12) and 0 (range, 0–6) in the DHEA and placebo groups, respectively, and the baseline neutral score was 1 (range, 0–4) and 1 (range, 0–4) in the DHEA and placebo groups, respectively. These scores did not change in response to treatment.

In total, 9 of 9 subjects taking 30 mg and 23 of 29 taking 20 mg DHEA, *i.e.* 32 of the 38 women (84%) in the study developed androgenic effects in skin and/or pubic and/or axillary hair after 6 or 12 months of DHEA treatment. The women who experienced androgenic effects on both skin and hair had increased serum concentrations of DHEAS, androstenedione, and T compared with the women without these effects (Fig. 2). Moreover, the androgenic score after 6 months was correlated with the serum levels of DHEAS ($r = 0.37$; $P = 0.03$), androstenedione ($r = 0.42$; $P = 0.01$), and T ($r = 0.37$; $P = 0.03$).

Glucose metabolism, lipoproteins, and coagulation (Table 3)

DHEA treatment reduced serum HDL cholesterol and apoA-1 concentrations compared with those during placebo administration. The within-group analysis after a further 6 months of treatment demonstrated that this effect was transient. Other lipids and lipoproteins were not affected by the treatment. LPL activity decreased and HL activity increased in the placebo group during the extended 6-month treatment. There was no correlation between changes in HDL cholesterol and HL activity during 6 months of active treatment ($r = -0.2$; $P = 0.2$). Plasma fibrinogen, PAI-1 activity, and

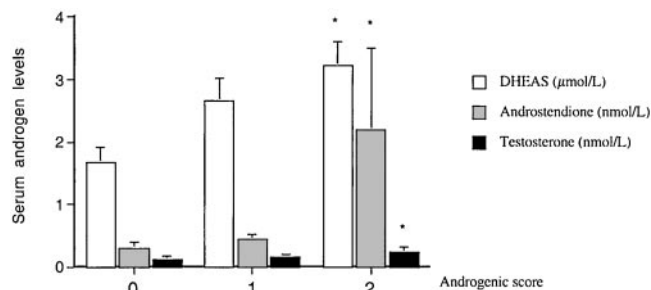


FIG. 2. Relationship between androgen action on the skin and/or hair and morning serum levels of DHEAS, androstenedione, and T after 6 months of DHEA treatment. Effects on the skin and hair were each assigned 1 point, effects on both were assigned 2 points. Six, 14, and 18 women scored 0, 1, and 2 points, respectively. *, $P < 0.05$ compared with androgenic score 1. Normal ranges for adult females are: DHEAS, 1.6–10.2 μmol/liter; androstenedione, 1.6–9.0 nmol/liter; and T, 0.14–2.8 nmol/liter.

TABLE 3. Measurements of serum lipids and lipoprotein concentrations during 6 months of DHEA or placebo, followed by 6 months of open DHEA treatment

Variable	Group	Baseline	6 months	12 months	<i>P</i> ^a
Total C (mmol/liter)	DHEA	5.5 ± 1.3	5.6 ± 1.3	5.7 ± 1.5	0.2
	Placebo	5.6 ± 0.9	5.8 ± 1.1	5.6 ± 0.9	0.2
Triglycerides (mmol/liter)	DHEA	1.66 ± 0.73	1.61 ± 0.72	1.61 ± 0.69	0.6
	Placebo	1.66 ± 0.69	1.68 ± 0.61	1.63 ± 0.56	0.6
HDL cholesterol (mmol/liter)	DHEA	1.31 ± 0.38	1.27 ± 0.36 ^b	1.30 ± 0.39	0.8
	Placebo	1.32 ± 0.46	1.41 ± 0.51	1.31 ± 0.45	0.09
LDL cholesterol (mmol/liter)	DHEA	3.45 ± 1.11	3.60 ± 1.17	3.71 ± 1.32	0.04
	Placebo	3.51 ± 0.68	3.68 ± 0.80	3.60 ± 0.66	0.6
apo A-1 (g/liter)	DHEA	1.55 ± 0.27	1.51 ± 0.28 ^{b,c}	1.54 ± 0.29	0.04
	Placebo	1.57 ± 0.35	1.65 ± 0.41	1.54 ± 0.38	0.1
apo B (g/liter)	DHEA	1.12 ± 0.27	1.18 ± 0.32	1.21 ± 0.37	0.2
	Placebo	1.16 ± 0.18	1.19 ± 0.20	1.18 ± 0.17	0.9
Lipoprotein (a) (g/liter) ^d	DHEA	239 (17–1781)	248 (17–1798)	176 (17–1815)	0.9
	Placebo	151 (17–1008)	193 (17–1142)	134 (17–974)	0.03
LPL (mU/ml)	DHEA	127 ± 46	132 ± 48	137 ± 51	0.1
	Placebo	138 ± 43	143 ± 48	124 ± 42 ^c	0.02
HL (mU/ml)	DHEA	128 ± 66	130 ± 59	142 ± 55	0.1
	Placebo	136 ± 81	123 ± 92	136 ± 104 ^c	0.02
t-PA antigen (ng/ml) ^d	DHEA	0.59 (0.13–1.65)	0.64 (0.12–1.67)	0.66 (0.10–4.70)	0.3
	Placebo	0.81 (0.10–1.65)	0.88 (0.18–1.81)	1.02 (0.10–3.32)	0.2
PAI-1 activity (U/ml) ^d	DHEA	5.3 (0.2–33.0)	3.2 (0.1–23.0)	3.0 (0.1–39.0)	0.4
	Placebo	2.7 (0.1–28)	2.2 (0.1–23.0)	2.4 (0.1–39.0)	0.1
Fibrinogen (g/liter)	DHEA	2.80 ± 0.51	2.92 ± 0.50	2.92 ± 0.68	0.5
	Placebo	2.87 ± 0.49	2.93 ± 0.67	2.88 ± 0.49	0.7

^a Overall within-group treatment effects calculated with Friedman's ANOVA.

^b *P* < 0.01 vs. changes in the placebo group between baseline and 6 months.

^c *P* < 0.05 as compared with commencement of DHEA treatment; baseline in the DHEA group and 6 months in the placebo group.

^d Values are median (range).

t-PA antigen were not affected by DHEA treatment. Fasting plasma glucose, glycosylated hemoglobin, and insulin concentrations did not change.

Body composition, handgrip strength, and bone metabolism

Lean body mass was not affected by DHEA treatment during the controlled phase of the trial. During the open treatment, lean body mass increased after 12 months of treatment within the DHEA group and after 6 months of active treatment in the original placebo group. Body weight, body fat mass, and central adiposity did not change significantly in response to treatment (data not shown).

Handgrip strength did not change during the 6 months of DHEA treatment compared with that during placebo administration. However, both peak and mean handgrip strength over 10 sec increased within the placebo group after 6 months of open DHEA treatment. A similar tendency was noted in the DHEA group during the overall treatment period (data not shown). Based on age- and sex-adjusted reference values, it was found that the study group at baseline had 79 ± 20% and 67 ± 23% of predicted values for peak and mean handgrip strength over 10 sec, respectively. These values had at 12 months increased to 83 ± 17% and 74 ± 23% (both *P* < 0.05).

The serum bone markers osteocalcin, PICP, and ICTP were not affected by the DHEA treatment, and no changes were seen in bone mineral density or bone mineral content in total body, lumbar spine, and femoral neck (data not shown).

Biochemical safety measures

In response to the first 6 months of treatment, small increases in the hemoglobin concentration, hematocrit, and

serum concentrations of aspartate aminotransferase, γ glutamyl transferase, and ALP was observed within the normal range in each treatment group. No statistically significant differences between the two treatment groups were seen.

Discussion

In this placebo-controlled trial of hypopituitary women with severe androgen deficiency, DHEA was used for androgen replacement therapy. Positive effects on behavior were observed, and although the dose of DHEA employed is the lowest reported, most women experienced the desired androgenic effects on hair and skin. Some anabolic effects were observed during the extended open phase of the trial, whereas only minor effects on lipid and glucose metabolism were detected.

DHEA has been defined as a neurosteroid (18, 19) with neurotropic effects that include increased neuronal excitability, γ -aminobutyric acid type A receptor antagonistic properties, and alterations in synaptic transmission in the hippocampus (19, 20). DHEA may therefore influence cognitive processes. Whether these actions of DHEA occur through a unique receptor or via intracellular conversion to androgens or estrogens is unknown.

In prospective studies of elderly women, the age-related decline in serum DHEAS concentration has been associated with a poor perception of health and life satisfaction (21), but not with any deterioration in cognitive status in men (22). In women with more severe androgen deficiency due to primary and secondary adrenal failure, DHEA treatment improved well-being (8), and in men and women with Addison's disease, self-esteem and afternoon mood and fatigue were improved (9). In the present study DHEA did not have

superior effect on quality of life compared with placebo, as assessed by two generic quality of life questionnaires. In contrast, the spouses reported few effects on behavior during placebo, but an overall improvement during treatment with DHEA. The discrepant perception of effects between the patients and their partners remains to be explained. It is conceivable that the partners, not being subjected to medical care, a factor that is likely to contribute to a positive change in perceived quality of life during a clinical trial, were more objective in this respect than the patients (7).

Serum free T has been shown to be positively correlated with sexual desire in women, and increased libido has been reported when T is combined with estrogen replacement therapy in postmenopausal women (23, 24). In patients with adrenal insufficiency, increased libido in response to DHEA treatment was seen in a study that comprised only women (8), whereas in a study of both men and women, libido was not affected by the treatment (9). In the present study DHEA treatment compared with placebo did not influence sexual interest and activity, whereas during the extended open phase an increase was reported by most women. The absence of effects on sexual interest and activity during the controlled phase of this trial argues against an impact of DHEA on libido at the doses administered. It cannot, however, be ruled out that changes would be detected with more specific and sensitive instruments.

Although the measured sebum production, skin hydration, and epidermal thickness are increased in response to DHEA treatment (25, 26), the self-perceived effects on skin and hair have varied considerably in previous trials. In elderly women receiving 50–1600 mg/d for 1–12 months, effects on skin/hair are seldom reported (26–30), whereas in women with Addison's disease receiving 50 mg DHEA, effects on skin/hair were experienced by 9 of 24 in 1 study and by 19 of 24 women in a second study (8, 9). In the present trial the majority of women experienced these androgenic effects. This treatment effect was related to the serum levels of DHEAS, androstenedione, and T, suggesting a dose-related effect. The majority of our patients reported increased perspiration, which has only been reported in a small trial of women with Addison's disease (31). It is possible that this androgenic effect has not been asked about in previous trials. The body hair scoring system used in this trial, which did not include axillary and pubic hair, was not able to detect any clinically significant changes in hair growth.

The tissue response to DHEA is probably organ specific and dependent on the intracellular enzymes that convert DHEA to more active androgens and estrogens (3). Previous studies suggest that the vaginal epithelium responds to DHEA as it does to estrogen, and breast tissue as it does to androgen, whereas the endometrium is not affected by DHEA (25, 32). This study suggests that the hepatic effects of DHEA are mainly androgenic. This is best observed by the reduction seen in serum apoA-1, HDL cholesterol, and SHBG concentrations. These changes were small and transient with continuing treatment. These effects have been seen in previous treatment trials with DHEA (8, 9, 25, 27, 29, 33), although not in all (9, 28, 30). The postheparin LPL activity decreased, and the HL activity only increased in the placebo group after 6 months of open DHEA treatment. These

changes reflect an androgen action on these lipolytic enzymes and were expected (34). However, they were not mirrored by changes in circulating lipids and lipoproteins, and their overall significance is therefore unclear.

Well known anabolic effects of androgens, such as increased muscle mass and strength, are infrequently reported in response to DHEA treatment (30, 33, 35). In the present study no changes in lean body mass and handgrip strength occurred during the placebo-controlled period of the trial, whereas a small, yet significant, increase was observed in lean body mass and handgrip strength in the placebo group when they received open DHEA treatment. This anabolic treatment response may reflect the profound degree of androgen deficiency in this group of women, as the dose of DHEA used is the lowest ever reported. It may also indicate that the markedly reduced muscle strength that we found in the hypopituitary women may be an effect of their lack of androgens even though they received adequate GH replacement (36).

An increase in serum IGF-I concentration was not observed in this trial compared with previous ones in healthy elderly and women with adrenal failure (8, 29, 30, 33). Androgen treatment enhances endogenous GH secretion (37) and GH deficiency, and the ongoing GH replacement therefore explains the lack of increased serum IGF-I and a plausible augmentation of the somatotrophic axis in this group of hypopituitary women. The ongoing GH replacement therapy may also have attenuated the effects on lipid and bone metabolism and body fat mass in response to the DHEA treatment.

Our selection of women with long-standing adrenocorticotrophic and gonadotropic insufficiency and thereby a more severe androgen deficiency than healthy elderly women, ovariectomized women, and women with primary adrenal insufficiency (1, 2) may explain the more marked androgenic action on skin/hair and perspiration than that previously reported despite the use of lower doses of DHEA.

In our view the present experience might argue in favor of androgen replacement in androgen-deficient hypopituitary women who have impaired well-being despite optimal replacement with other hormones, including GH and estrogen. It is not clear which androgen and which formulation should be used for replacement in women. In our experience DHEA, a pro-hormone metabolized locally to more potent sex steroids, might offer an effective and convenient mode of replacement. We suggest that the initial dose should be lower than that previously used in women with Addison's disease. The dose should be titrated individually to obtain normalization of morning serum levels of DHEAS and by monitoring clinical effects on hair and skin.

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