

Improvement in Mood and Fatigue after Dehydroepiandrosterone Replacement in Addison's Disease in a Randomized, Double Blind Trial

PENELOPE J. HUNT*†, ELEANOR M. GURNELL*‡, FELICIA A. HUPPERT,
CHRISTINE RICHARDS, A. TOBY PREVOST, JOHN A. H. WASS,
JOSEPH HERBERT, AND V. KRISHNA K. CHATTERJEE§

Department of Endocrinology, University of Oxford, Radcliffe Infirmary (P.J.H., J.A.H.W.), Oxford, United Kingdom OX2 7JS; and Departments of Medicine (E.M.G., C.R., V.K.K.C.), Psychiatry (F.A.H.), Community Medicine (A.T.P.), and Anatomy (J.H.), University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom CB2 2QQ

ABSTRACT

Dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) are adrenal precursors of steroid biosynthesis and centrally acting neurosteroids. Glucocorticoid and mineralocorticoid deficiencies in Addison's disease require life-long hormone replacement, but the associated failure of DHEA synthesis is not corrected. We conducted a randomized, double blind study in which 39 patients with Addison's disease received either 50 mg oral DHEA daily for 12 weeks, followed by a 4-week washout period, then 12 weeks of placebo, or *vice versa*. After DHEA treatment, levels of DHEAS and Δ^4 -androstenedione rose from subnormal to within the adult physiological range. Total testosterone increased from subnormal to low normal with a fall in serum sex hormone-binding globulin in females, but with no change in either parameter in males. In both sexes, psychological assessment

showed significant enhancement of self-esteem with a tendency for improved overall well-being. Mood and fatigue also improved significantly, with benefit being evident in the evenings. No effects on cognitive or sexual function, body composition, lipids, or bone mineral density were observed. Our results indicate that DHEA replacement corrects this steroid deficiency effectively and improves some aspects of psychological function. Beneficial effects in males, independent of circulating testosterone levels, suggest that it may act directly on the central nervous system rather than by augmenting peripheral androgen biosynthesis. These positive effects, in the absence of significant adverse events, suggest a role for DHEA replacement therapy in the treatment of Addison's disease. (*J Clin Endocrinol Metab* 85: 4650–4656, 2000)

DEHYDROEPIANDROSTERONE (DHEA) and its sulfate ester DHEAS are the most abundant circulating steroids. First characterized in the 1930s (1), their role as important precursors of peripheral steroid (androgen and estrogen) biosynthesis has been well established. However, more recently, their added potential action as centrally acting neurosteroids has evoked interest. Animal work has shown that DHEA(S) is concentrated within the hippocampus (2), and further studies indicate that it enhances neuronal survival *in vitro* (3, 4) and improves long term memory *in vivo* (3, 5). Elevated glucocorticoid levels are associated with cognitive impairment (6) and hippocampal atrophy in rodents and humans (7, 8) as well as mood disturbance (9). DHEA(S) exerts a powerful antiglucocorticoid effect, although the precise mechanism is unclear (10, 11). Therefore, a fall in circulating levels of DHEA(S) results in a state of relative glu-

corticoid excess that might adversely influence neural function, including effects on cognition, memory, and mood.

The fetal adrenals synthesize significant quantities of DHEA(S), which then decline during childhood before rising again with adrenarche to reach a peak in young adulthood (12), followed by a relentless age-related decline (13). DHEA(S) is the only known steroid to show such decline in both sexes, and the fall in circulating levels has been implicated in some of the catabolic and neurodegenerative changes of aging, including increased cardiovascular mortality (14), malignancy (15), and risk of osteoporosis (16). Conversely, oral DHEA replacement in normal elderly individuals, which restores circulating serum levels of DHEA(S), and its metabolite Δ^4 -androstenedione, to a young adult level, has been associated with improvement in psychological well-being (17). Other replacement studies in this population have shown variable beneficial effects on body composition, with enhanced lean body mass (18, 19), changes in circulating insulin-like growth factor I (17, 18, 20), improved bone mineral density (BMD) and markers of bone turnover (21), and decreased insulin resistance (19). A recent study also suggests an antidepressant effect of DHEA therapy (22).

Addison's disease, or primary adrenal failure, occurs in about 1 in 25,000 individuals. It is characterized by chronic glucocorticoid and mineralocorticoid deficiency, which requires life-long oral replacement. Despite optimized therapy

Received July 17, 2000. Revision received August 21, 2000. Accepted August 27, 2000.

Address all correspondence and requests for reprints to: Prof. Krishna Chatterjee, Department of Medicine, Level 5, Addenbrooke's Hospital, Hills Road, Cambridge, United Kingdom CB2 2QQ. E-mail: kkc1@mole.bio.cam.ac.uk.

* P.J.H. and E.M.G. are joint first authors.

† Supported by a Wellcome Trust Overseas Postdoctoral Fellowship and the Health Research Council of New Zealand.

‡ Wellcome Trust Clinical Research Fellow.

§ Supported by the Wellcome Trust.

with these steroids, patients with Addison's disease report a reduced quality of life compared with normal individuals, often complaining of persistent fatigue and reduced well-being (23, 24). We surmised that these symptoms are at least in part due to the associated failure of adrenal DHEA synthesis, which is not corrected. Furthermore, we hypothesized that such DHEA deficiency, accompanied by unopposed glucocorticoid action in the central nervous system, might result in specific cognitive and memory impairment. We, therefore, undertook a randomized, double blind, placebo-controlled cross over study of oral DHEA replacement in Addison's disease. We assessed its effects on well-being, quality of life, and cognitive function and included measurement of biochemical indexes, circulating hormones, body muscle and fat masses, and BMD. We postulated that this patient cohort would be ideal for assessing DHEA replacement therapy for two reasons: first, as DHEA deficiency in this disorder is near absolute, the greater magnitude of change in circulating DHEA(S) levels after treatment would better demonstrate a beneficial change; and second, as patients are generally young, any detrimental effects of DHEA deficiency are less likely to be confounded by the multifactorial process of aging.

Subjects and Methods

Trial participants

Forty-four subjects were recruited from the Endocrine Clinics in Oxford and Cambridge, United Kingdom, together with some individuals from the United Kingdom Addison's Disease Patient Self-Help Group. The diagnosis of Addison's disease was substantiated by documented hypocortisolemia associated with either raised serum ACTH or hyperpigmentation and, where available, positive adrenal antibodies. A minimum 4-yr duration of Addison's disease was an inclusion criterion. Exclusion criteria were age less than 18 yr or greater than 70 yr, pregnancy, and any intercurrent significant medical or psychiatric condition. All patients took their usual glucocorticoid and mineralocorticoid hormone replacement, with both dosage and timing of administration being kept unchanged for 3 months before and throughout the study, except in three patients during brief intercurrent illness. Patients were also instructed not to alter their diet or exercise habits. The project had local ethical committee approval, and prior informed consent was obtained from all participants.

Study design

We recruited as many patients as possible who fulfilled the entry criteria. However, as Addison's disease is an uncommon disorder, the total number of subjects studied was limited. We therefore adopted a double blind, placebo-controlled, cross-over protocol to enhance the likelihood of detecting true change in outcome measures after DHEA treatment. A total of 44 patients were initially recruited from the 2 centers. Of those randomized to DHEA first, 2 patients failed to attend their initial assessment, and no further contact was made, and 1 patient was withdrawn after the development of insulin-dependent diabetes mellitus and subclinical hypothyroidism. Of those randomized to placebo first, 1 patient failed to attend for assessment, and 1 withdrew after initial assessment. Thus, 39 subjects (15 males, aged 33–56 yr; 24 females, aged 26–69 yr), of whom only 4 were over 50 yr, completed both arms of the study, and their results were subsequently analyzed. Further details regarding patient characteristics are listed in Table 1. Each patient was randomly assigned to consecutive 3-month treatment periods of either micronized DHEA (New Way International, Inc., Rockville, MD; 50 mg daily, orally) followed by lactose-containing placebo tablets of identical appearance or placebo followed by DHEA administration. A washout interval of 1 month separated the 2 treatment phases. Randomization of patients stratified by age and sex was performed pro-

TABLE 1. Trial participants

Characteristics	
Total no.	39
Median age, yr (range)	40 (25–69)
Sex (M/F)	15/24
Addison's disease	
Median duration, yr (range)	14 (4–46)
Adrenal antibody positive	23/39
Associated endocrinopathies	
Hypothyroidism	13
Type 1 diabetes mellitus	3
Premature ovarian failure	7
On hormone replacement therapy	5
Postmenopausal	
On hormone replacement therapy	1

spectively by an independent statistician, with half receiving DHEA first and the other half receiving placebo. Patient allocation details were coded and kept confidential until the trial was completed.

Measurements

Patients were assessed at three points: baseline and after each treatment (DHEA or placebo) phase. On every occasion, fasting blood samples and a 24-h urine collection were obtained, with assessment of cognitive and psychological function and morphological measurements. In addition, patients completed a 15-item Profile of Mood State questionnaire, which covers 6 subscales of mental health: tension, depression, anger, vigor, fatigue, and confusion. This profile was obtained each morning and evening for 2 days before baseline and at the end of each treatment phase, with simultaneous saliva samples for hormone measurements.

Serum DHEAS, testosterone, Δ^4 -androstenedione (Diagnostic Products, Gwynedd, UK), sex hormone-binding globulin (SHBG; Wallac, Inc., Milton Keynes, UK), lipids (Bayer Corp., Newbury, Berks, UK), insulin-like growth factor I (IGF-I), IGF-binding protein-3 (IGFBP-3) (25), free T_4 , TSH, vitamin B12, estradiol, bone alkaline phosphatase, and osteocalcin (Metra Biosystems, Palo Alto, CA) were measured by specific immunoassays in a single laboratory, with all samples from an individual patient analyzed in the same assay. Estradiol was only measured in males, because the hormonal status of females was variable (some were postmenopausal and/or receiving exogenous estrogen replacement therapy). Salivary cortisol and DHEA were measured by enzyme-linked immunosorbent assay or RIA, respectively, as described previously (26, 27). The intra- and interassay coefficients of variation were less than 10% throughout. Insulin resistance was quantified using homeostatic model assessment (HOMA) of fasting glucose and insulin (28).

Cognitive function and psychological symptoms were assessed by structured interview. Subjects were asked questions about their general health, mental function, recent life events, sleep, and possible adverse effects of treatment. These were followed by a series of cognitive tests of episodic verbal memory (recall of a word list, recall of a list of names and a paired associate recognition test), semantic memory (retrieval of words from a semantic category), and spatial memory (recall of spatial location of objects). All of the memory tests were available in parallel versions, and a different set of items was used on each occasion of testing to avoid practice effects. Executive function was assessed using a letter cancellation task, the Stroop Color-Word Test, and tests of simple and choice reaction time. Psychological symptoms were assessed by self-completion of the General Health Questionnaire (GHQ-30) of Goldberg (29), which includes five subscales of mental health: anxiety, self-esteem, depression, difficulty coping, and social dysfunction (30). The GHQ was scored using a Likert scale. Sexual function was assessed using a self-completion questionnaire derived from the Golombok Rust Inventory of Sexual Satisfaction (31).

Morphological measurements included body mass index and waist to hip ratio as well as assessment of body composition. Measurement of the latter, together with lumbar and femoral BMD, was performed by dual energy x-ray absorptiometry using either QDR 2000 or QDR 4500 scanners (Hologic, Inc., Waltham, MA), with individual patients as-

essed on the same machine throughout. The coefficients of variation of BMD measurements at spine and femur on both instruments were 1%.

Based on previous studies in aging, we anticipated a rise in circulating DHEA(S) and androgen levels together with psychological changes during DHEA administration and designated these primary outcome measures. Secondary end points included changes in body composition, BMD, and cognitive function.

Statistical analysis

For both primary and secondary end points, data were analyzed by comparison of differences between mean values postplacebo treatment *vs.* post-DHEA using a paired *t* test. For each parameter, significant period effects were adjusted for, and treatment by period interactions were found not to be significant by the use of further *t* tests (32) (SPSS, Inc., Chicago, IL). The 5% and 1% levels of significance were used in tests involving primary and secondary outcomes, respectively.

Results

Hormonal changes

After 50 mg oral micronized DHEA, serum DHEAS rose markedly from grossly subnormal to levels within the physiological range for young adults in both male and female subjects [males: postplacebo, $1.06 \pm 0.13 \mu\text{mol/L}$ (mean \pm SEM); post-DHEA, $5.43 \pm 0.43 \mu\text{mol/L}$; $P < 0.0001$; females: postplacebo, $0.13 \pm 0.01 \mu\text{mol/L}$; post-DHEA, $4.62 \pm 0.88 \mu\text{mol/L}$; $P < 0.0001$; Fig. 1a]. Salivary DHEA and DHEAS measurements at 1 and 3 months confirmed these findings;

DHEA was essentially absent with placebo, but during DHEA treatment, salivary levels were similar to those in normal individuals (morning DHEA: postplacebo, $0.07 \pm 0.01 \text{ ng/mL}$; post-DHEA, $1.34 \pm 0.55 \text{ ng/mL}$; $P < 0.001$; morning DHEAS: postplacebo, $0.37 \pm 0.08 \text{ ng/mL}$; post-DHEA, $4.51 \pm 0.48 \text{ ng/mL}$; $P < 0.001$). As expected there was, a similar rise in Δ^4 -androstenedione, the DHEA metabolite (males: postplacebo, $2.19 \pm 0.30 \text{ nmol/L}$; post-DHEA, $4.57 \pm 0.56 \text{ nmol/L}$; $P < 0.0001$; females: postplacebo, $1.08 \pm 0.28 \text{ nmol/L}$; post-DHEA, $4.41 \pm 0.69 \text{ nmol/L}$; $P < 0.0001$; Fig. 1b). The associated changes in circulating androgens and SHBG were also analyzed according to the patient's gender. In females, serum total testosterone increased from subnormal to low normal levels (postplacebo, $0.24 \pm 0.02 \text{ nmol/L}$; post-DHEA, $0.46 \pm 0.07 \text{ nmol/L}$; $P = 0.003$) in conjunction with a fall in circulating SHBG (postplacebo, $82.0 \pm 9.53 \text{ nmol/L}$; post-DHEA, $67.4 \pm 7.55 \text{ nmol/L}$; $P < 0.001$). However, there was no significant change in either SHBG or total testosterone (Fig. 1, c and d) or estradiol (postplacebo, $95.23 \pm 7.24 \text{ nmol/L}$; post-DHEA, $99.38 \pm 7.32 \text{ nmol/L}$; $P = 0.45$) in males. Salivary cortisol levels were measured in the morning and evening, and there was no difference in profiles after DHEA *vs.* placebo (morning cortisol: postplacebo, $98.5 \pm 38 \text{ nmol/L}$; post-DHEA, $97.4 \pm 30 \text{ nmol/L}$; $P = 0.84$; evening cortisol: postplacebo, $12.7 \pm 4.4 \text{ nmol/L}$; post-

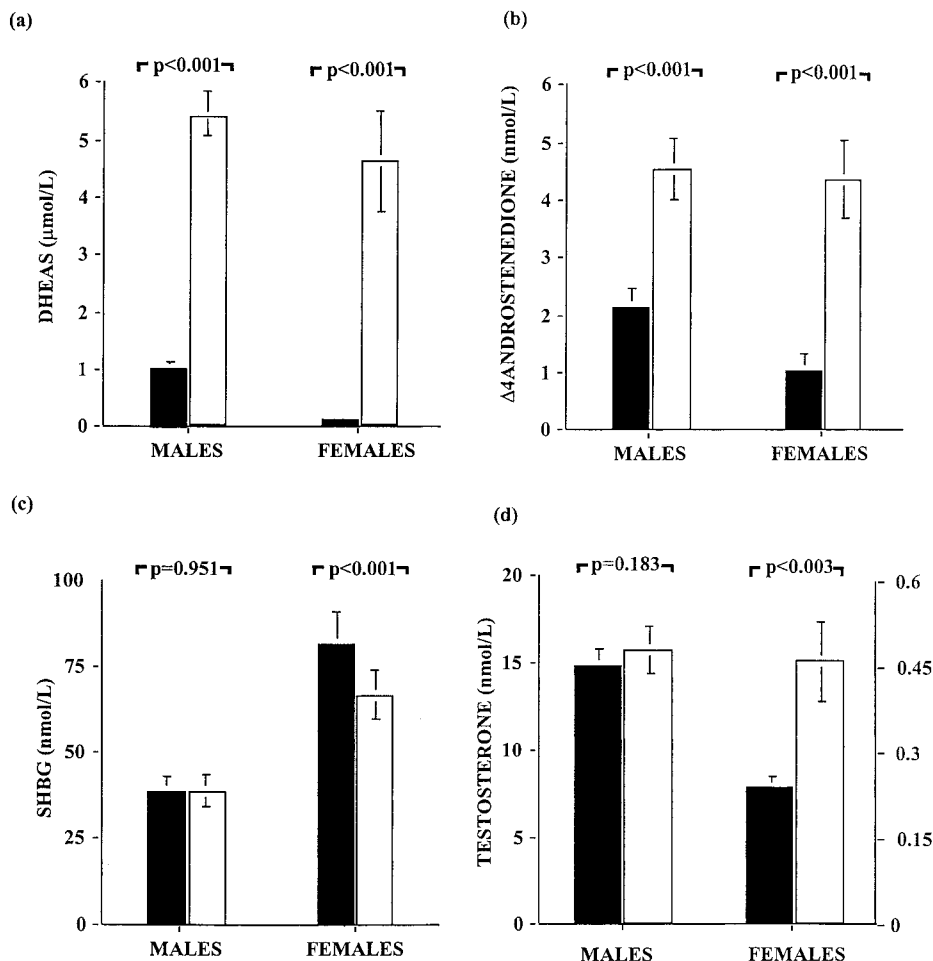


FIG. 1. Hormone and biochemical changes in males and females after DHEA treatment. a, Serum DHEAS levels after 50 mg oral DHEA (\square) or placebo (\blacksquare). The normal adult reference ranges for the median age (40 yr) of our patients are: females, 1.9–6.3 $\mu\text{mol/L}$; and males, 3.8–8.1 $\mu\text{mol/L}$. b, Serum Δ^4 -androstenedione after DHEA (\square) or placebo (\blacksquare); normal adult reference range in either sex, 3–12 nmol/L. c, Serum SHBG after DHEA (\square) or placebo (\blacksquare); normal adult reference range: males, 14–103 nmol/L; females, 18–117 nmol/L. d, Serum total testosterone after DHEA (\square) or placebo (\blacksquare); normal adult reference range: males, 8–32 nmol/L; females, 0.2–3 nmol/L. Note the different y-axes for males (left) and females (right).

DHEA, 13.2 ± 3.3 nmol/L; $P = 0.95$). All patients had normal vitamin B12 levels, and thyroid function remained unchanged throughout the study.

Well-being, mood, and fatigue

Well-being was assessed using the GHQ, which comprises 5 subscales (anxiety, depression, self-esteem, coping, and social dysfunction) together with a total score. The higher the score, the more symptoms are present. Table 2 shows scores for each category in 858 control subjects [calculated from age- and sex-matched participants in the Health and Lifestyle Survey (30, 33)] together with values in patients at baseline and after placebo or DHEA treatment. Figure 2 represents the difference between symptom scores in the control sample and patients at each time point. At baseline, although scores for overall GHQ as well as the individual subscales of anxiety, self-esteem, and social dysfunction appeared worse than those in the control group, these differences did not achieve statistical significance. For each GHQ subscale, there was a tendency for greater improvement after DHEA replacement than after placebo. This effect was particularly evident with self-esteem, which was significantly enhanced with DHEA treatment [post-DHEA, 7.3 ± 1.45 (mean \pm SD); postplacebo, 8.4 ± 1.44 ; $P < 0.001$]. The net overall GHQ score also showed greater improvement after DHEA, with the effect just failing to achieve statistical significance ($P = 0.08$; Table 2).

Patients completed a profile of mood state questionnaire in the morning and evening on 2 consecutive days, and the aggregate scores for mood and fatigue at each time point are shown in Table 3. After DHEA treatment there was a tendency for a beneficial response, with lower overall mood and fatigue scores in both the morning and evening. Interestingly, for both parameters, the effect was most evident and statistically significant at the end of the day [evening mood: post-DHEA, 67.5 ± 15.21 (mean \pm SD); postplacebo, 73.0 ± 16.4 ; $P = 0.018$; evening fatigue: post-DHEA, 23.97 ± 5.73 ; postplacebo, 27.03 ± 6.56 ; $P = 0.002$].

Cognitive and sexual function

Table 4 shows the scores at baseline and after placebo or DHEA for tests of memory and executive function. In contrast to the results of psychological symptoms, where scores uniformly improved more after DHEA than after placebo, cognitive tests did not show a consistent trend. Some parameters (e.g. letter cancellation and choice reaction time)

were marginally better after placebo than after DHEA, with others (e.g. spatial location recall, name recall, and color-word test) showing the opposite effect. Indeed, the only significant change (word list immediate recall) showed greater improvement after placebo than after DHEA. None of the other differences between DHEA and placebo on tests of verbal memory (episodic or semantic) or spatial memory or on any of the measures of executive function, whether measured in terms of accuracy or speed of processing, were significant.

Our sexual behavior questionnaire assessed interest and arousal, frequency of intercourse, erectile dysfunction, and lubrication. There was no significant difference in any of these indexes after DHEA *vs.* placebo.

Body composition and BMD

There was no difference in either mean lumbar vertebral (L2–L4) or femoral neck BMD after placebo or DHEA treatment (Table 5). This was also reflected by no change in serum osteocalcin or bone alkaline phosphatase, which are indexes of bone turnover. There was no significant change in body mass index after DHEA (data not shown), and measurement of body composition with quantitation of either overall lean and fat mass or analysis at different sites (limb and trunk) showed no significant change in either sex. Serum IGF-I and IGFBP-3 levels were also unaltered.

Compared with the effect of placebo, there were no changes in serum cholesterol, triglycerides, or lipoproteins (high and low density lipoproteins) or in tissue insulin sensitivity measured by HOMA after DHEA treatment (data not shown).

Adverse events

On direct questioning, the most common side-effect elicited was mild facial acne, affecting 8 of 24 females and 1 of 15 males during DHEA replacement, but this symptom was also reported by 4 females and 1 male who received placebo treatment. Mild excess facial hair growth was only reported in 2 females, 1 receiving DHEA and the other placebo. A single male subject reported increased facial hair growth after DHEA. However, no subject withdrew from the study due to these or other adverse effects. Serial hepatic enzyme measurements showed no effect of DHEA treatment.

TABLE 2. Well-being scores in control and Addison's disease subjects

	Mean score ^a (SD)				Difference in scores after placebo <i>vs.</i> DHEA	
	Controls ^b	Addison's disease			Difference (95% confidence interval)	<i>t</i> test <i>P</i> value
		At baseline	After placebo	After DHEA		
GHQ total	55.1 (10.6)	56.74 (8.12)	55.97 (9.31)	52.59 (9.25)	3.38 (−0.37, 7.14)	0.076
GHQ anxiety	14.4 (5.0)	15.67 (4.07)	14.74 (3.69)	14.56 (4.12)	0.18 (−1.08, 1.44)	0.78
GHQ depression	7.3 (2.5)	6.82 (1.50)	6.77 (1.81)	6.41 (1.45)	0.36 (−0.25, 0.97)	0.24
GHQ self-esteem	7.6 (1.6)	7.97 (1.46)	8.36 (1.44)	7.26 (1.45)	1.10 (0.46, 1.74)	<0.001
GHQ coping	9.8 (2.1)	9.56 (1.41)	9.62 (2.10)	8.87 (2.04)	0.74 (−0.17, 1.66)	0.11
GHQ social dysfunction	6.0 (1.1)	6.18 (0.94)	6.10 (1.14)	5.72 (1.23)	0.38 (−0.17, 0.94)	0.17

^a For each scale, a higher score denotes more symptoms.

^b GHQ reference data from 858 controls matched by sex and age (30, 33).

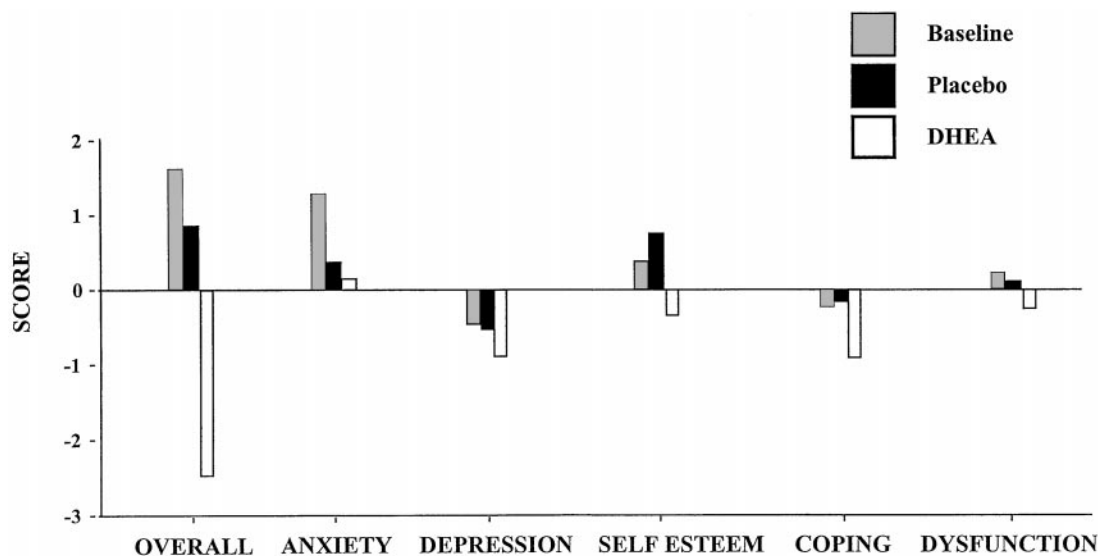


FIG. 2. Deviation in GHQ symptom scores from controls in Addison's disease patients. For each scale, the difference between values in patients vs. control subjects is shown at baseline (■) and after placebo (■) or DHEA (□) treatment.

TABLE 3. Mood and fatigue scores in Addison's disease

	Mean score ^a (SD)			Difference in scores following placebo versus DHEA	
	At baseline	After placebo	After DHEA	Difference (95% confidence interval)	<i>t</i> test <i>P</i> value
Mood total a.m.	68.39 (14.55)	67.61 (14.97)	65.53 (16.34)	2.42 (-2.74, 7.58)	0.35
Mood total p.m.	69.91 (13.84)	73.05 (16.40)	67.50 (15.21)	5.66 (1.02, 10.30)	0.018
Fatigue a.m.	23.42 (5.82)	22.45 (5.93)	21.58 (6.16)	0.97 (-1.28, 3.22)	0.39
Fatigue p.m.	25.97 (5.44)	27.03 (6.56)	23.97 (5.73)	3.16 (1.29, 5.03)	0.002

^a For each scale, a higher score denotes more symptoms.

TABLE 4. Cognitive function in Addison's disease

	Mean score (SD)			Difference in scores after placebo vs. DHEA	
	At baseline	After placebo	After DHEA	Difference (95% confidence interval)	<i>t</i> test <i>P</i> value
Word list immediate recall (no. correct)	7.59 (1.39)	8.21 (1.38)	7.64 (1.51)	0.56 (0.07, 1.06)	0.026
Word list delayed recall (no. correct)	5.77 (1.99)	6.54 (1.98)	6.18 (2.20)	0.36 (-0.23, 0.95)	0.22
Names immediate recall (no. correct)	6.21 (2.04)	6.62 (1.99)	6.79 (1.75)	-0.18 (-0.92, 0.56)	0.63
Names delayed recall (no. correct)	4.82 (1.88)	5.08 (1.94)	5.62 (1.79)	-0.54 (-1.21, 0.13)	0.11
Paired associates (no. correct) ^a		14.14 (2.47)	13.56 (3.16)	0.58 (-0.47, 1.64)	0.27
Spatial location immediate recall (no. correct)	7.85 (2.15)	8.00 (2.28)	8.36 (1.83)	-0.36 (-0.96, 0.24)	0.23
Spatial location delayed recall (no. correct)	7.15 (2.52)	7.56 (2.90)	7.54 (2.30)	0.03 (-0.83, 0.88)	0.95
Letter cancellation (no. correct)	22.23 (4.52)	23.54 (5.14)	23.38 (5.63)	0.15 (-0.73, 1.04)	0.73
Category fluency (no. correct)	22.15 (4.95)	18.00 (4.78)	18.15 (4.37)	-0.07 (-1.63, 1.49)	0.93
Simple reaction time mean (ms)	248.5 (43.4)	253.6 (37.6)	254.2 (36.4)	-0.61 (-9.42, 8.21)	0.89
Choice reaction time mean (ms)	533.6 (74.1)	529.2 (57.7)	524.4 (62.2)	4.77 (-6.49, 16.03)	0.40
Color-word test time difference (s)	56.22 (12.39)	50.62 (11.51)	50.84 (13.50)	-0.29 (-2.81, 2.24)	0.91

^a As only two parallel versions are available, this test was only administered after placebo and DHEA.

Discussion

Before treatment our patients with Addison's disease had markedly subnormal DHEAS and DHEA levels. We have shown that 50 mg DHEA corrects this deficiency, achieving mean circulating DHEAS levels of 4.93 $\mu\text{mol/L}$ in our cohort, which were sustained throughout the replacement period, falling back to baseline after the washout interval. These levels are within the physiological range for the median age of our patients. Salivary levels of DHEA, which correlate well with those in blood, were also normalized. The rise in

DHEAS was associated with normalization of its metabolite Δ^4 -androstenedione. Our observations suggest that 50 mg represents an optimum daily dose. Indeed, in other studies, higher oral doses of DHEA ranging from 100–200 mg have been shown to induce supraphysiological levels of DHEAS (34, 35). In conjunction with these hormonal effects we have documented significant improvement in some aspects of psychological function. Using well validated psychometric instruments, we found significantly enhanced self-esteem with a tendency for improved overall well-being with DHEA

TABLE 5. Secondary outcome measures

Parameters	DHEA		Placebo		P value
	Mean	SEM	Mean	SEM	
BMD					
Hip	0.94	0.03	0.93	0.02	0.51
Spine	1.00	0.02	1.00	0.02	0.28
Osteocalcin (ng/mL)	6.8	0.3	7.2	0.4	0.10
Bone alkaline phosphatase (U/L)	23.4	1.1	23.4	1.2	0.91
Body composition					
Lean (g)	44,768	1,704	44,104	1,715	0.51
Fat (g)	11,108	2,056	13,018	2,603	0.57
IGF-I (nmol/L)	22.6	1.1	21.6	1.1	0.12
IGFBP-3 (μ g/mL)	6.8	0.23	6.6	0.19	0.19

replacement. We also observed significant changes in mood and fatigue after DHEA, with evidence of diurnal variation in benefit, the most marked improvement being in the evening.

Persistent tiredness despite glucocorticoid replacement is described in Addison's disease (23, 24). One explanation for our observations might be that DHEA treatment either delays cortisol clearance or augments its action in our patients. However, a previous study showed no change in serum cortisol profiles after DHEA in aging males (36), and we found no differences in morning or evening saliva cortisol levels in our patients after DHEA or placebo. Furthermore, there is strong evidence that DHEA is a potent antiglucocorticoid, antagonizing corticoid-induced thymic involution (37), enzyme induction (38), and hypertension (10). Another explanation might be that DHEA may affect the hypothalamic-pituitary-thyroid axis, but as thyroid function remained unchanged throughout the study, this seems unlikely. It is of interest that DHEA has a greater benefit on mood and fatigue in the evenings. Unfortunately, there are no good data on the diurnal pattern of tiredness in Addison's disease. Although morning fatigue may be considered more specific in the diagnosis of organic disease, clinical endocrinologists will recall patients with Addison's disease receiving standard steroid replacement therapy who complain of fatigue at all times of the day. Demonstrating a significant change in psychological variables in any small study is difficult in view of the numerous factors affecting such parameters. It may be that since both fatigue and mood were slightly worse in the evenings compared with the mornings, it was easier to document an improvement in the evening scores. With a larger study group, we may also have seen a significant improvement in the morning, but this remains speculative. Nevertheless, it is pertinent to note that all measures of well-being (GHQ scores) as well as the mood and fatigue scores moved in a beneficial direction after DHEA therapy, suggesting the potential value for such treatment in this disease context.

Another study of DHEA treatment in 24 women with Addison's disease that was reported recently has also shown a rise in circulating adrenal androgens together with significantly improved well-being and sexuality (39). Our study supports their observations, but extends their findings in one major respect: we also observed psychological benefit in male patients. Furthermore, this effect in males was not associated with any significant increase in circulating testos-

terone or estradiol levels. In females, serum testosterone only rose slightly into the lower end of the normal range, with an associated fall in SHBG. These modest changes are consistent with the relative lack of androgenic side-effects (acne and hirsutism) after DHEA in our female patients, although we cannot discount the possibility that they might have developed after longer term treatment. It may also provide an explanation for our inability to demonstrate a positive effect of DHEA on libido and sexual function in females, as has been previously documented after testosterone supplementation in postmenopausal women (40), in whom circulating testosterone levels are restored to the upper end of the normal range. In our study the effects of DHEA treatment appeared independent of menopausal status or hormone replacement therapy. In view of the small size of our study group, subgroup analysis of female patients on or off exogenous estrogen replacement was not feasible. Together, these findings favor a central nervous system rather than a peripheral androgen-dependent effect of DHEA in patients.

In aging, cognitive decline has been known to be associated with lower circulating DHEAS levels (41), suggesting that such function might also be altered in Addison's disease. We found no impairment of memory or higher executive function at initial assessment in our patients, nor any improvement after DHEA. Nevertheless, we cannot completely discount a link between DHEA and cognition for two reasons: first, baseline scores of cognitive function in our patients were already high, making it difficult to measure further improvement; and second, as we tested cognitive function in the morning, it is possible that a beneficial effect later in the day (as seen with mood and fatigue) was missed.

Treatment with DHEA for 12 months has been shown to increase femoral BMD and reduce markers of bone turnover in postmenopausal females (21), and another recent study in 280 elderly subjects showed enhanced femoral bone density in women less than 70 yr of age and enhanced radial bone density in women above 70 yr of age (42). Accordingly, in our study the lack of effect of DHEA on bone metabolism after only 3 months of treatment was not unexpected. However, our patients do have abnormally low BMD (mean z-scores: lumbar spine, -0.39 ; femoral neck, -0.37), suggesting that longer term assessment of DHEA treatment is indicated. The short duration of exposure to DHEA is also likely to explain its lack of effect on body composition in contrast to that reported previously in older subjects (18–20). In keeping with the variable effects of DHEA on IGF-I and its binding

proteins reported in the literature (18–20, 38), we found no change in serum levels of IGF-I or IGFBP-3 in our study population.

In summary, we found that oral DHEA replacement in Addison's disease is biochemically effective, well tolerated, and associated with improvement in psychological well-being, mood, and fatigue. Importantly, two thirds of our patients at the end of the study wished to continue DHEA replacement therapy. With beneficial effects in males as well as females, we propose that its psychological action may be centrally mediated as a neurosteroid rather than be androgen dependent. Our observations suggest a significant physiological role for DHEA in humans, and its addition to existing steroid replacement therapy in Addison's disease should be considered further.

Acknowledgments

We thank Bente Jackson for administrative assistance, and the staff at the Acland Hospital for facilitating assessment of patients. We also thank Helen Shiers and Sarah Cleary for hormone assays, and Shirley Love for bone density measurements.

References

- Butenandt A, Danenbaum H. 1934 Isolierung neuen, physiologisch unwirksamen Sterinderivates aus Mannerharn, Seine Verknupfung mit Dehydroandrosterone und Androsteron. *Z Physiol Chem.* 229:192–195.
- Robel P, Bourreau E, Corpechot C, et al. 1987 Neuro-steroids: 3β -hydroxy- Δ^5 -derivatives in rat and monkey brain. *J Steroid Biochem.* 27:649–655.
- Roberts E, Bologna L, Flood JF, Smith GE. 1987 Effects of dehydroepiandrosterone and its sulfate on brain tissue in culture and on memory in mice. *Brain Res.* 406:357–362.
- Bologa L, Sharma J, Roberts E. 1987 Dehydroepiandrosterone, its sulfated derivative reduce neuronal death and enhance astrocytic differentiation in brain cell cultures. *J Neurosci Res.* 17:225–234.
- Flood JF, Smith GE, Roberts E. 1988 Dehydroepiandrosterone, its sulfate enhance memory retention in mice. *Brain Res.* 447:269–278.
- Newcomer JW, Craft S, Hershey T, Askins K, Bardgett ME. 1994 Glucocorticoid-induced impairment in declarative memory performance in adult humans. *J Neurosci.* 14:2047–2053.
- Landfield P, Waymire J, Lynch G. 1978 Hippocampal aging and adrenocorticoids: quantitative correlations. *Science.* 202:1098–1102.
- Lupien SJ, de Leon M, de Santi S, et al. 1998 Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat Neurosci.* 1:69–73.
- Starkman MN, Scheingart DE. 1981 Neuropsychiatric manifestations of patients with Cushing's syndrome: relationship to cortisol and adrenocorticotropic hormone levels. *Arch Intern Med.* 141:215–219.
- Shafagaj Y, Opuku J, Quereshi D, Regelson W, Kalimi M. 1992 Dehydroepiandrosterone prevents dexamethasone-induced hypertension in rats. *Am J Physiol.* 263:E210–E213.
- Kimonides VG, Spillantini MG, Sofroniew MV, Fawcett JW, Herbert J. 1999 Dehydroepiandrosterone (DHEA) antagonises the neurotoxic effects of corticosterone, translocation of SAPK 3 in hippocampal primary cultures. *Neuroscience.* 89:429–436.
- Parker LN, Sack J, Fisher DA, Odell WD. 1978 The adrenarche: prolactin, gonadotropins, adrenal androgens and cortisol. *J Clin Endocrinol Metab.* 46:396–401.
- Orentreich N, Brind JL, Rizer RL, Vogelmann JH. 1984 Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *J Clin Endocrinol Metab.* 59:551–555.
- Barrett-Connor E, Khaw K-T, Yen SSC. 1986 A prospective study of dehydroepiandrosterone sulfate, mortality and cardiovascular disease. *N Engl J Med.* 315:1519–1524.
- Ebeling P, Kiovisto VA. 1994 Physiological importance of dehydroepiandrosterone. *Lancet.* 343:1479–1481.
- Sambrook P, Birmingham J, Champion D, et al. 1992 Postmenopausal bone loss in rheumatoid arthritis: effect of estrogens and androgens. *J Rheumatol.* 19:357–361.
- Morales AJ, Nolan JJ, Nelson JC, Yen SSC. 1994 Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *J Clin Endocrinol Metab.* 78:1360–1367.
- Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SSC. 1998 The effect of six months treatment with a 100mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. *Clin Endocrinol (Oxf).* 49:421–432.
- Diamond P, Cusan L, Gomez J-L, Belanger A, Fabrie F. 1996 Metabolic effects of 12-month percutaneous dehydroepiandrosterone replacement therapy in postmenopausal women. *J Endocrinol.* 150:S43–S50.
- Casson PR, Santoro N, Elkind-Hirsch K, et al. 1998 Postmenopausal dehydroepiandrosterone administration increases free insulin-like growth factor-1 and decreases high-density lipoprotein: a six month trial. *Fertil Steril.* 70:107–110.
- Labrie F, Diamond P, Cusan L, Gomez JL, Belanger A, Candau B. 1997 Effect of 12-month dehydroepiandrosterone replacement therapy on bone, vagina and endometrium in postmenopausal women. *J Clin Endocrinol Metab.* 82:3498–3505.
- Wolkowitz OM, Reus VI, Keebler A, et al. 1999 Double-blind treatment of major depression with dehydroepiandrosterone. *Am J Psychiatry.* 156:646–649.
- Reidel M, Weise A, Schurmeyer TH, Brabant G. 1993 Quality of life in patients with Addison's disease: effects of different cortisol replacement modes. *Exp Clin Endocrinol.* 101:106–111.
- Baker SJK, Hunt PJ, Wass JAH. 1997 Assessing the potential for finetuning the management of Addison's disease/steroid replacement therapy [Abstract]. *J Endocrinol.* 155(Suppl):P2.
- Cheetham TD, Holly JM, Baxter RC, et al. 1998 The effects of recombinant human IGF-1 administration on concentrations of acid labile subunit, IGF binding protein-3, IGF-1, IGF-II and proteolysis of IGF binding protein-3 in adolescents with insulin-dependent diabetes mellitus. *J Endocrinol.* 157:81–87.
- Goodyer IM, Herbert J, Altham PME, Pearson J, Secher SM, Shiers HM. 1996 Adrenal secretion during major depression in 8- to 16- year olds. Altered diurnal rhythms in salivary cortisol and dehydroepiandrosterone (DHEA) at presentation. *Psychol Med.* 26:245–256.
- Guazzo EP, Kirkpatrick PJ, Goodyer IM, Shiers HM, Herbert J. 1996 Cortisol, dehydroepiandrosterone (DHEA), DHEA sulfate in the cerebrospinal fluid of man: relation to blood levels and the effects of age. *J Clin Endocrinol Metab.* 81:3951–3960.
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. 1985 Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 28:412–419.
- Goldberg DP. 1978 Manual of the General Health Questionnaire. Windsor.
- Huppert FA, Walters DE, Day N, Elliott BJ. 1989 The factor structure of the General Health Questionnaire (GHQ-30): a reliability study on 6317 community residents. *Br J Psychiatry.* 155:178–185.
- Rust J, Golombok S. 1986 The GRISS: a psychometric instrument for the assessment of sexual dysfunction. *Arch Sex Behav.* 15:157–165.
- Pocock SJ. 1983 Clinical trials: a practical approach. Chichester: Wiley & Sons.
- Cox BD, Blaxter M, Buckle ALJ, et al. 1987 The Health and Lifestyle Survey: preliminary report of a nationwide survey of the physical and mental health, attitudes and lifestyle of a random sample of 9003 British adults. London: The Health Promotion Research Trust.
- Arlt W, Justl H-G, Callies F, et al. 1998 Oral dehydroepiandrosterone for adrenal androgen replacement: pharmacokinetics and peripheral conversion to androgens and estrogens in young females after dexamethasone suppression. *J Clin Endocrinol Metab.* 83:1928–1934.
- Young J, Couzinet B, Nahoul K, et al. 1997 Panhypopituitarism as a model to study the metabolism of dehydroepiandrosterone (DHEA) in humans. *J Clin Endocrinol Metab.* 82:2578–2785.
- Arlt W, Haas J, Callies F, et al. 1999 Biotransformation of oral dehydroepiandrosterone in elderly men: significant increase in circulating estrogens. *J Clin Endocrinol Metab.* 84:2170–2176.
- May M, Holmes E, Rogers W, Poth M. 1991 Protection from glucocorticoid induced thymic involution by dehydroepiandrosterone. *Life Sci.* 46:1627–1631.
- Wright BE, Porter JR, Browne E, Svec F. 1992 Antiglucocorticoid action of dehydroepiandrosterone in young obese Zucker rats. *Int J Obesity.* 16:579–593.
- Arlt W, Callies F, van Vlijmen JC, et al. 1999 Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med.* 341:1013–1020.
- Davis SR, Burger HG. 1996 Clinical review: androgens and the postmenopausal woman. *J Clin Endocrinol Metab.* 21:227–236.
- Kalmijn S, Launer LJ, Stolk RP, et al. 1998 A prospective study on cortisol, dehydroepiandrosterone sulfate and cognitive function in the elderly. *J Clin Endocrinol Metab.* 83:3487–3492.
- Baulieu EE, Thomas G, Legrain S, et al. 2000 Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge Study to a sociobiomedical issue. *Proc Natl Acad Sci USA.* 97:4279–4284.