

## Long-Term DHEA Replacement in Primary Adrenal Insufficiency: A Randomized, Controlled Trial

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**Context:** Dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) are the major circulating adrenal steroids and substrates for peripheral sex hormone biosynthesis. In Addison's disease, glucocorticoid and mineralocorticoid deficiencies require lifelong replacement, but the associated near-total failure of DHEA synthesis is not typically corrected.

**Objective and Design:** In a double-blind trial, we randomized 106 subjects (44 males, 62 females) with Addison's disease to receive either 50 mg daily of micronized DHEA or placebo orally for 12 months to evaluate its longer-term effects on bone mineral density, body composition, and cognitive function together with well-being and fatigue.

**Results:** Circulating DHEAS and androstenedione rose significantly in both sexes, with testosterone increasing to low normal levels only in females. DHEA reversed ongoing loss of bone mineral density at the femoral neck ( $P < 0.05$ ) but not at other sites; DHEA enhanced total body ( $P = 0.02$ ) and truncal ( $P = 0.017$ ) lean mass significantly with no change in fat mass. At baseline, subscales of psychological well-being in questionnaires (Short Form-36, General Health Questionnaire-30), were significantly worse in Addison's patients vs. control populations ( $P < 0.001$ ), and one subscale of SF-36 improved significantly ( $P = 0.004$ ) after DHEA treatment. There was no significant benefit of DHEA treatment on fatigue or cognitive or sexual function. Supraphysiological DHEAS levels were achieved in some older females who experienced mild androgenic side effects.

**Conclusion:** Although further long-term studies of DHEA therapy, with dosage adjustment, are desirable, our results support some beneficial effects of prolonged DHEA treatment in Addison's disease. (*J Clin Endocrinol Metab* 93: 400–409, 2008)

Synthesis of dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) is by the zona reticularis of the adrenal gland. Levels decline dramatically after birth, gradually increasing again during adrenarche to reach peak levels in young adulthood. Unlike the other major steroids secreted by the adrenal, serum DHEA(S) levels then follow a progressive age-related decline (1, 2). A large body of epidemiological data from cross-sectional correlational studies has documented an association between the decline in DHEAS levels and various age-related

disorders, including increased risk of cardiovascular events (3), malignancy (4), and osteoporosis (5). In concert with these findings, positive effects of DHEA replacement have been described on psychological well-being (6), body composition (7, 8), and bone mineral density (BMD) (9) in older, normal adults.

It is not clear whether DHEA(S) has its effect via direct action on target tissues and/or as a precursor for the biosynthesis of other steroids, including gonadal steroids such as testosterone. In the brain, DHEA(S) may act directly on neural tissue and thus

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Abbreviations: BMD, Bone mineral density; DEXA, dual-energy x-ray absorptiometry; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; GHQ-30, General Health Questionnaire; MFI-20, Multidimensional Fatigue Inventory; SF-36, Short Form-36.

qualify as a neurosteroid (10, 11). In the hippocampus, it has been found to be neuroprotective to injury (12–14) and to enhance memory and neurogenesis in the adult brain (15). It can also act as an antiglucocorticoid, antagonizing both glucocorticoid-induced thymic involution (16, 17) and the suppressive actions of corticosterone on the proliferation of progenitor cells in the dentate gyrus of the hippocampus (15). Although its cellular mode of action is unknown and a specific cell surface or nuclear receptor for DHEA has not been identified hitherto, microarray studies show that it induces a pattern of gene expression distinct from glucocorticoid or testosterone, further supporting a distinct mechanism of action (18).

Deficiencies of glucocorticoid and mineralocorticoid in primary adrenal insufficiency (Addison's disease) are well recognized and require lifelong replacement. However, the associated deficiency of DHEA(S) has been investigated only recently, and its possible clinical significance remains controversial. Patients with Addison's disease on optimal glucocorticoid and mineralocorticoid replacement therapy still report a reduced quality of life when compared with normal individuals (19) and score significantly worse than age- and sex-matched population controls on validated psychological tests that measure well-being (20, 21).

Several short-term studies of DHEA supplementation in adrenal insufficiency have now been reported: Young *et al.* (22) validated the efficacy of oral DHEA treatment in restoring physiological circulating levels of DHEA(S) in 10 adults with panhypopituitarism and showed some biotransformation of DHEA into sex steroids. Arlt *et al.* (23) studied 24 women, 14 of whom had primary adrenal insufficiency, in a randomized, placebo-controlled, double-blind crossover trial for 4 months. In addition to the expected changes in levels of DHEA(S) and its metabolites, the authors reported enhanced well-being and sexuality. Our previous placebo-controlled 3-month crossover trial of 39 patients (including 15 males) with primary adrenal insufficiency showed similar biochemical changes and enhanced psychological well-being, independent of gender (20). Johannsson *et al.* (24) demonstrated behavioral changes, reported by their partners, in 38 panhypopituitary females after 6 months of DHEA(S) replacement. No changes in body composition, BMD or cognition were demonstrated in any of these short-term studies of DHEA replacement. A 9-month, parallel group trial of DHEA replacement in 39 patients showing no benefit in health status (25) may have been underpowered (26).

We therefore undertook a 12-month trial of DHEA replacement therapy, with primary end points being to determine whether there were positive effects on bone mineral density (BMD), body composition, or effects on cognitive function, which might be related to the neuroprotective action of DHEA. We also wanted to confirm that the changes in biochemistry, well-being, and fatigue observed in our previous short-term trial (20) could be replicated and maintained with more protracted administration of DHEA, and these parameters were designated as secondary end points. A final objective of this longer-term trial was to assess the possible emergence of side effects that might not have been apparent in the shorter-term.

## Subjects and Methods

### Trial participants

Subjects were recruited from the Endocrine clinics in Cambridge, Oxford, St. Bartholomew's Hospital, London, UK, and Christchurch, New Zealand, together with individuals from the U.K. Addison's Disease Patient Self-Help Group. The diagnosis of Addison's disease was substantiated by documented hypocortisolemia associated with either raised serum ACTH (>100 ng/liter) or hyperpigmentation and, where available, positive adrenal antibodies. Duration of Addison's disease for at least 1 yr was an inclusion criterion. Exclusion criteria were age younger than 18 yr or older than 65 yr, pregnancy, past personal history of hormone-dependent malignancy, and any intercurrent significant medical or psychiatric condition (*e.g.* epilepsy, depression) requiring neuroactive medication. All patients took their usual glucocorticoid and mineralocorticoid hormone replacement with dosage and timing of administration being unchanged for 3 months before and throughout the duration of the trial. 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

One hundred patients were required to power the study to detect changes in BMD, and we aimed to recruit at least this number of subjects who fulfilled the entry criteria, within a 3-month time interval. The trial was a double-blind, placebo-controlled, parallel group design. One hundred subjects (49 DHEA group, 51 placebo group) completed the study, and their results were subsequently analyzed. Twenty-three subjects had taken part in our previous, short-term trial of DHEA (20) but were distributed comparably across DHEA (n = 9) and placebo (n = 14) groups. Furthermore, after completion of this first study, all subjects had been off DHEA for 2 yr. Demographic and clinical characteristics of trial participants are shown in Table 1. Each patient was randomly assigned to a 12-month treatment period of either oral micronized DHEA (50 mg daily) or a lactose-containing placebo tablet of identical appearance (McPherson Labs, Inc., Stafford, TX). The randomization was stratified by age (18–34, 35–49, 50–65 yr) and gender and undertaken by an independent statistician. Treatment allocation details were coded and kept confidential until the trial was completed. Two female patients who were concerned about acne reduced their dose to half a study tablet after 6 months and continued at this dose until the end of the trial. A washout interval of 1 month followed each treatment arm.

### Measurements

Major assessments were undertaken at baseline and after 12 months of treatment (DHEA or placebo) at one of the two trial centers (Cambridge, UK, and Christchurch, New Zealand). On each occasion, fasting

**TABLE 1.** Demographics and clinical details of patients recruited into trial

	DHEA	Placebo
n	54	52
Males	24	20
Females	30	32
Median age (range), yr	46 (23–65)	46 (22–65)
Median disease duration (range), yr	11 (1–46)	10 (1–49)
Hydrocortisone dose, mg per 24 h	25	27
Autoimmune thyroid disease	20	14
Type 1 diabetes mellitus	4	1
Pernicious anaemia	3	1
Vitiligo	3	1
Premature ovarian failure (HRT)	9 (8)	3 (2)
Post menopausal (HRT)	9 (4)	11 (6)

HRT, Hormone replacement therapy.

blood samples were followed by a structured interview, with assessment of cognitive and psychological function. Body composition and BMD were then measured by dual-energy x-ray absorptiometry (DEXA).

### Structured interview and cognitive tests

Subjects were asked questions about their general health, mental function, recent life events, sleep, and possible adverse effects of treatment (second visit only). These were followed by a series of cognitive tests, which focused on memory and executive function. Memory is known to be dependent on hippocampal function, which may be compromised in Addison's disease (27), and there appears to be a particularly strong link between spatial memory and hippocampal function (28–30). Accordingly, we included tests of both verbal and spatial memory. The verbal memory tests were recall of a short story from the Wechsler Memory Scale (31) and recall of a 16-item word list from the California Verbal Learning Test (32). Spatial memory was assessed by a recently developed measure of spatial location memory (33), which involved recalling the location of 10 items randomly located on a grid containing 30 squares. Executive function was assessed in three ways: a verbal fluency task, which required the subject to name as many animals as possible in 1 min; a letter cancellation task, which required them to cross out two specified letters on a sheet containing random letters of the alphabet as quickly and accurately as possible in 1 min; and the Stroop Color-Word Test, which comprises a list of color names (the words red, green, blue) printed in ink of a conflicting color. The same tests were used at both interviews, because parallel versions were not available for all tests. Analysis assumes that practice effects would be equal in both study groups. The National Adult Reading Test was used as a measure of verbal ability at baseline only (34).

### Psychological symptoms

Aspects of psychological status were assessed using validated self-completion questionnaires at baseline, at 6 and 12 months, and after washout (at 13 months) in each treatment arm. The Short Form-36 (SF-36) questionnaire examined symptoms relating to physical and mental health and is a tool that has been validated in population studies (35, 36). The Multidimensional Fatigue Inventory (MFI-20) (37) was also used to quantify physical and mental fatigue, activity, and motivation. It was originally developed to assess symptoms in cancer patients undergoing radiotherapy and is suited to this study because it concentrates on fatigue, a common complaint in Addison's disease (19). General well-being was assessed by self-completion of the General Health Questionnaire (GHQ-30) by Goldberg (38), which includes five subscales of mental health: anxiety, self-esteem, depression, difficulty coping, and social dysfunction (39), and it was scored using a Likert scale. Sexual function was assessed using a self-completion questionnaire and visual analog scale, which had been used in a previous trial of DHEA in aging (40).

### Morphological measurements

Body composition together with lumbar, femoral, and radial BMD were measured at baseline and at 12 months by DEXA using QDR 4500 scanners (Hologic, Bedford, MA) at both trial centers, with individual patients being assessed on the same machine throughout. The precision of BMD measurements was less than 1 or 1% in lumbar spine and hip, respectively.

### Biochemical parameters

Serum DHEAS, testosterone, androstenedione, SHBG, lipids, free T<sub>4</sub>, TSH, IGF-I, testosterone, and estradiol were measured at baseline and 12 months, using previously described specific immunoassays (20) in a single laboratory with all samples from an individual patient being analyzed in the same assay. Estradiol was measured only in males because the hormonal status of females was variable, some being postmenopausal and/or on exogenous estrogen replacement therapy. The intra- and interassay coefficients of variation were less than 10% throughout. Liver

function was assessed by measurement of aspartate aminotransferase,  $\gamma$ -glutamyl transferase, and alkaline phosphatase.

### Statistical analysis

We aimed to recruit at least 100 patients to have 95% power to detect a 2.5% change in hip BMD and 80% power to detect a 1% change in spine BMD. BMD data were analyzed by comparing changes from baseline to 12 months between using an independent samples *t* test. For the other primary end points (body composition and cognitive function), values at 12 months in placebo *vs.* DHEA-treated groups were compared, adjusting for values at baseline. The rationale for this approach was that it enabled conclusions to be drawn about differences in 12-month values using baseline data to explain a large proportion of the between-subject variance, hence improving power. The effect of gender and the possibility of differential effects within genders were investigated using ANOVA.

For secondary end points (biochemical parameters, well-being, fatigue), changes in parameters at intermediate time points after DHEA or placebo treatment were also analyzed, adjusting for values at baseline. For data that were not normally distributed (*e.g.* cognitive function data) the Mann Whitney *U* test was substituted. Categorical variables were analyzed using  $\chi^2$  and Fisher's exact test. Five and 1% levels of significance were used for primary and secondary end points, respectively.

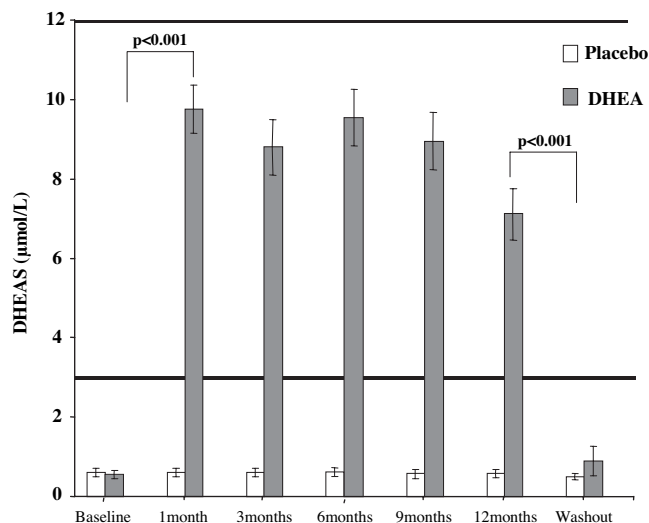
### Results

One hundred six patients were recruited initially. Of the 52 randomized to DHEA, three patients failed to complete the study: one young man did not want to risk being on placebo, one man was lost to follow-up, and one woman started antidepressants and was removed from the trial. Fifty-four patients were randomized to placebo and three individuals in this arm failed to complete the study: one young man was lost to follow-up, one man felt unwell on what he perceived was DHEA, and an older woman was dissuaded by her family practitioner. The data analysis are thus based on 49 subjects receiving DHEA and 51 receiving placebo who completed the study (Table 1).

### Hormonal and biochemical changes

In those receiving 50 mg oral micronized DHEA, serum DHEAS rose markedly within 1 month from grossly subnormal to levels within the physiological range for young adults in both male and female subjects. These levels were maintained throughout the 12-month period, signifying compliance with treatment. One month after discontinuing treatment, DHEAS levels fell back to baseline low levels, confirming satisfactory washout of the active study treatment (Fig. 1).

Table 2 illustrates changes in serum androstenedione, testosterone, SHBG, and lipid profiles in males and females and estradiol in males. As expected, there was a similar rise in androstenedione during DHEA treatment in both sexes. The associated changes in circulating androgens and SHBG were also analyzed according to the patient's gender. In females taking DHEA, serum total testosterone increased from subnormal to low normal levels (after placebo 0.13 *vs.* after DHEA 0.41 nmol/liter,  $P < 0.001$ ), but there was no associated change in circulating SHBG. In males there was no significant change in SHBG, total testosterone, or estradiol during DHEA treatment. Circulating fasting lipid profiles were unchanged as was thyroid function (data not



**FIG. 1.** Mean ( $\pm$  SEM) serum DHEAS levels in DHEA (shaded bars) or placebo-treated (open bars) groups throughout the 12-month trial and after treatment washout. The bold horizontal lines denote the normal laboratory reference range for DHEAS (not adjusted for age or gender).

shown), and changes in serum IGF-I in females reached border-line significance ( $P = 0.01$ ) (Table 2).

**Body composition and BMD**

At baseline, mean BMD was generally low in all Addison’s disease patients. Using World Health Organization T-score criteria, in the lumbar spine, 39% of males and females were osteopenic and 7% of males and 5% of females osteoporotic; in the femoral neck, 39% of males and females were osteopenic and 2% of females were osteoporotic. During the 12 months of the study, there was progressive diminution in BMD at most sites in patients. In those receiving DHEA, there was a marked and significant reversal of this trend in the femoral neck [mean (SEM) BMD (grams per square centimeter) changes: after DHEA,

0.0039 (0.004) vs. after placebo,  $-0.0068(0.003)$  g/cm<sup>2</sup>,  $P < 0.046$ ] but not at any other site (Fig. 2). Analyses by gender showed a differential effect only at the proximal radius, with significant enhancement of BMD after DHEA in men but not women [mean (SEM) BMD (grams per square centimeter) changes: males: after DHEA, 0.0046 (0.0046) and after placebo,  $-0.0136$  (0.006)  $P = 0.025$ ; females: after DHEA,  $-0.0091$  (0.0036) and after placebo,  $-0.0062$  (0.0037),  $P = 0.583$ ].

Overall there was no effect of DHEA treatment on body mass index (data not shown). However, when body composition in individual compartments was analyzed, DHEA increased lean mass, both total and truncal, with no effect on fat mass (Table 3). Analysis by gender showed that this effect was more marked in females, who showed greater changes in total body lean mass than their male counterparts [mean (SEM) lean mass (grams) changes: females, after DHEA, 869 (211) and after placebo, 183 (269),  $P = 0.034$ ; males, after DHEA,  $-117(247)$  and after placebo,  $-399(258)$ ].

**Cognitive function**

The National Adult Reading Test, as a measure of verbal IQ, showed no difference at baseline between the two randomized groups. There were no significant differences between the DHEA and placebo groups for any parameter of cognitive function with no differences at its conclusion between those who received DHEA or placebo (Table 4). Data analysis was repeated on subjects (27 placebo, 30 DHEA treated) aged 45 yr or older to determine whether there might have been selective effects of DHEA in this subgroup, but again DHEA had no significant effect on cognitive measures (data not shown).

**Well-being, fatigue, and sexual function**

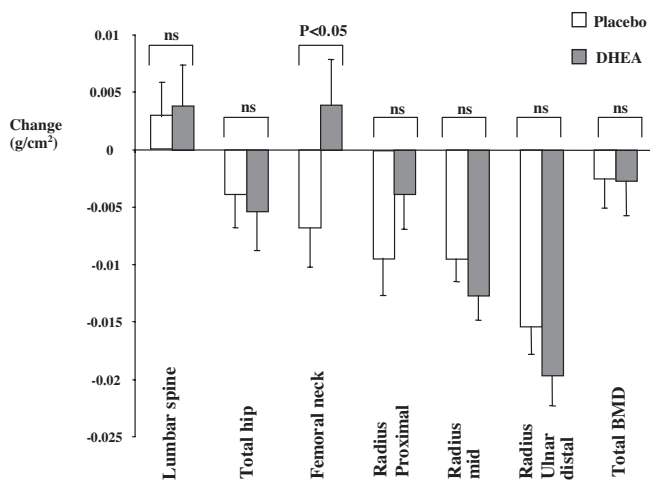
In comparison with normative data from a U.K. population (39), subjects with Addison’s disease showed a higher total GHQ-30 score, denoting worse mental health status at baseline,

**TABLE 2.** Changes in biochemical parameters between baseline and 12 months in placebo and DHEA-treated groups

Parameter	DHEA		Placebo		P value <sup>a</sup>
	Baseline	12 months	Baseline	12 months	
Androstenedione (nmol/liter)	1.56 (0.2)	4.2 (0.3)	1.68 (0.2)	1.6 (0.3)	<0.001
Testosterone (nmol/liter)					
Male	17.8 (1.3)	16.5 (1.2)	16.2 (1.1)	14.2 (0.9)	0.39
Female	0.21 (0.03)	0.41 (0.05)	0.14 (0.02)	0.13 (0.02)	<0.001
Estradiol (nmol/liter)					
Male	118.9 (6.8)	109.6 (6.3)	105.5 (4.3)	102.9 (4.3)	0.95
SHBG(U/liter)					
Male	35.7 (3.0)	38.8 (3.2)	36.0 (3.6)	38.4 (3.8)	0.90
Female	67.9 (7.9)	63.7 (7.2)	78.9 (7.7)	81.7 (7.4)	0.33
Lipids (nmol/liter)					
Cholesterol	4.45 (0.22)	4.62 (0.16)	4.63 (0.19)	4.57 (0.18)	0.36
Triglycerides	1.23 (0.14)	1.30 (0.12)	1.43 (0.14)	1.56 (0.15)	0.38
HDL	1.27 (0.08)	1.43 (0.06)	1.26 (0.07)	1.36 (0.06)	0.27
LDL	2.57 (0.15)	2.65 (0.12)	2.78 (0.15)	2.55 (0.14)	0.15
IGF-I (nmol/liter)					
Male	26.8 (1.8)	25.2 (1.9)	25.0 (2.0)	23.7 (1.7)	0.64
Female	23.7 (1.6)	25.0 (1.9)	22.5 (1.5)	20.9 (1.3)	0.01

Data shown are mean (SEM).

<sup>a</sup> P value relates to the comparison of 12-month values, adjusted for baseline, between DHEA and placebo groups.



**FIG. 2.** Mean ( $\pm$  SEM) change in BMD at 12 months in DHEA (shaded bars) or placebo-treated (open bars) groups. The *P* value ( $<0.05$ ) relates to comparison of mean absolute changes in BMD between DHEA and placebo-treated groups. ns, Not significant.

particularly on the anxiety and self-esteem subscales (Table 5). During DHEA treatment, either total GHQ-30 scores (Fig 3A) or for the self-esteem subscale (Fig 3B) declined (signifying improvement), with a rise in scores after washout, but comparison with the placebo group showed that these changes were not statistically significant (DHEA *vs.* placebo scores: total GHQ 6 months,  $P = 0.55$ , 12 months,  $P = 0.32$ , after washout,  $P = 0.23$ ; self esteem 6 months,  $P = 0.17$ , 12 months,  $P = 0.037$ ; after washout,  $P = 0.75$ ). As with GHQ status, using the SF-36 questionnaire as a tool to assess a broad range of physical symptomatology as well as psychological morbidity, the Addison's disease subjects had lower scores at baseline, denoting worse health status than a normal U.K. population (36) (Table 6). Interestingly, they exhibited an identical profile of deficits in particular dimensions of health (role physical, general health, vitality, role emotional) as a Norwegian population of Addison's disease patients studied independently by another group (21) (Table 6). During the trial, spider plots of the SF-36 scores at baseline, 6 and 12 months and after washout showed remarkable constancy in the placebo group, but some change during DHEA treatment (Fig. 4). In particular, the score for the role emotional dimension of health improved significantly at 12 months ( $P = 0.004$  for DHEA *vs.* placebo groups). Interestingly, after treatment washout, scores for both role physical and role emotional dimensions fell more markedly (denoting deterioration of health status) in the DHEA group, but the changes did not achieve statistical significance.

The MFI-20 covers dimensions that include physical fatigue, mental fatigue, reduced activity, and reduced motivation. Compared with the placebo group, there was a reduction (improvement) in scores for all dimensions in the DHEA group, but the changes only bordered on statistical significance for mental fatigue at the 6-month time point ( $P = 0.03$ ). After washout, fatigue scores in the DHEA-treated group rose back to levels comparable with placebo-treated patients (data not shown).

Using a questionnaire that had previously shown effects of DHEA in older normal subjects (40), we observed no significant changes in libido or sexual function in either gender (data not shown).

### Adverse events

An equivalent number of individuals in each arm guessed their treatment correctly, discounting the possibility that side effects had unblinded the study subjects. Female subjects receiving DHEA reported increased occurrence of skin spots, greasy skin, and axillary hair growth (Table 7). We measured sebum production using white adherent tapes (Sebutape; CuDerm Corp., Dallas, TX) applied to forehead skin at each assessment as described previously (41), but there was no difference in Sebutape scores between the placebo and DHEA groups (data not shown), despite the reported subjective symptoms.

### Discussion

This 12-month study of DHEA replacement in patients with Addison's disease both supports the improved well-being documented in our previous short-term study and adds new information on longer-term effects of DHEA. We report novel effects of DHEA on body composition (lean mass), femoral neck BMD, and particular psychological parameters (fatigue and self-esteem). Measures of cognitive function were not altered by DHEA therapy.

As expected, untreated Addison's patients had grossly subnormal DHEAS levels. Oral replacement with 50 mg micronized DHEA daily restored DHEAS blood levels to within the normal range for young adults. Because circulating DHEA levels decline with age (1, 2) and all subjects received the same dose of DHEA, there was a tendency for DHEAS levels to be above age-matched controls in those aged 50 yr or older. The hormone profile of DHEA-treated subjects was similar to that observed in our previous study (20) with significant increases in androstenedione in both sexes and testosterone in women but not in men. These

**TABLE 3.** Changes in body composition in DHEA and placebo-treated subjects

Parameter	DHEA		Placebo		<i>P</i> value <sup>a</sup>
	Baseline	12 months	Baseline	12 months	
Total body fat mass (g)	24,952 (1,484)	25,050 (1,522)	22,947 (1,218)	22,966 (1,250)	0.79
Truncal fat mass (g)	11,896 (754)	11,963 (768)	10,639 (673)	10,728 (686)	0.89
Total body lean mass (g)	46,021 (1,458)	46,839 (1,435)	45,784 (1,459)	45,850 (1,482)	0.022
Truncal lean mass (g)	23,165 (623)	23,419 (630)	23,208 (679)	22,992 (686)	0.017

Data shown are mean (SEM).

<sup>a</sup> *P* value relates to the comparison of 12-month values, adjusted for baseline, between DHEA and placebo groups.

**TABLE 4.** Changes in cognitive function in DHEA and placebo-treated groups

Tests	Maximum possible score	Baseline		12 months		P value <sup>a</sup>
		DHEA	Placebo	DHEA	Placebo	
Memory for story						
Immediate recall	25	14 (11, 17)	13 (9, 15)	16 (12, 18)	14 (13, 16)	0.15
Delayed recall	25	11 (10, 15)	11 (8, 14)	13 (11, 17)	14 (11, 16)	0.86
Memory for spatial location						
Immediate	10	6 (5, 9)	7 (5, 9)	7 (5, 9)	6 (4, 9)	0.41
Delayed	10	6 (4, 8)	6 (3, 8)	6 (4, 9)	5 (3, 8)	0.50
California Verbal Learning Test						
Trial 1	16	8 (7, 9)	8 (7, 10)	8 (7, 10)	8 (7, 10)	0.93
Trial 2	16	12 (10, 13)	11 (9, 14)	11 (10, 13)	12 (9, 13)	0.86
Trial 3	16	13 (10, 14)	12 (11, 14)	13 (11, 14)	12 (11, 14)	0.80
Short delay	16	11 (9, 12)	10 (8, 13)	11 (8, 13)	10 (8, 14)	0.73
Long-delay recall	16	10 (8, 12)	11 (7, 14)	11 (9, 14)	11 (9, 14)	0.94
Prospective memory	6	3 (2, 5)	5 (2, 5)	5 (2, 5)	5 (2, 5)	0.65
Verbal fluency		21 (17, 26)	20 (18, 23)	21 (19, 26)	19 (17, 23)	0.064
Visual search						
Accuracy	71	21 (18, 25)	22 (17, 25)	21 (19, 24)	21 (19, 24)	0.72
Speed						
Stroop effect						
Reading time (sec)		55 (46, 65)	58 (52, 66)	55 (48, 66)	59 (50, 68)	0.40
Color naming time (sec)		118 (104, 130)	119 (105, 150)	118 (100, 139)	119 (104, 138)	0.65

Data shown are median (interquartile range) values.

<sup>a</sup> P values are for comparison of DHEA vs. placebo at 12 months, and no statistically significant changes were observed.

changes are in accordance with DHEA being a sex steroid precursor. In men, higher basal testosterone levels are likely to have obscured the relatively small additional effect of administered DHEA. Although DHEA is converted to estradiol, the magnitude of this effect is insufficient to cornify the vaginal epithelium in rats (a sensitive assay) (42), and by analogy, we suggest that our observed lack of change in circulating estradiol levels in men receiving DHEA is not unexpected.

The low baseline BMD in Addison's subjects progressed, with diminution in bone density at most sites in placebo-treated subjects during the subsequent 12-month period. In this context, reversal of this trend with an observed increase in femoral neck BMD after DHEA therapy is notable. We suggest that such selective improvement in femoral neck BMD may be significant for two reasons: first, there is a correlation between reduced BMD at this site and low circulating DHEAS in several other contexts including hypopituitarism (43), aging and the postmenopausal state (5, 44, 45), and steroid-induced osteoporosis (46); second, other studies of DHEA therapy in postmenopausal women (9) or aging (40, 47) have also shown selective improvement in BMD at this site. Although the improvement in BMD is modest, compared with conventional therapies, this change may become sig-

nificant if compounded, as would be the case with long-term DHEA treatment of patients.

DHEA therapy increased both truncal and total body lean mass measured by DEXA. The improvement in lean muscle mass mirrors that seen in previous studies with DHEA supplementation in aging or postmenopausal women (7, 8). The mechanism by which increased lean muscle mass occurs is not known, but it is noteworthy that there was no associated diminution in fat mass as has been reported by other groups after DHEA supplementation (48, 49). Despite earlier reports suggesting changes in IGF-I with DHEA replacement, both our earlier short-term trial (20) and the present study showed no statistically significant change in circulating IGF-I levels, in agreement with another recent replacement study (50), arguing against a primary role of this hormone in mediating increases in lean muscle mass.

The effects of DHEA on psychological function were assessed both by comparing hormone and placebo-treated groups during 12 months of DHEA treatment and, in addition, determining whether any changes were reversed after washout in the DHEA-treated subjects. Because both the GHQ-30 and SF-36 tests have been validated and used on large populations of normal individuals, we were able to compare baseline scores in our Addi-

**TABLE 5.** Baseline GHQ-30 questionnaire scores in Addison's patients and comparison with normative data

GHQ-30	Total GHQ	Anxiety	Self-esteem	Depression	Coping	Social dysfunction
U.K. normative data <sup>a</sup>	55.1	14.4	7.6	7.3	9.8	6.0
Mean (SEM)	(0.4)	(0.2)	(0.05)	(0.09)	(0.07)	(0.04)
U.K. Addison's patients	58.7	16.3	8.1	7.2	10.3	6.0
Mean (SEM)	(1.09)	(0.5)	(0.14)	(0.21)	(0.25)	(0.11)
P value	<0.001	<0.001	0.002	0.69	0.02	0.60

Mean scores are shown with *higher values* denoting worse health status.

<sup>a</sup> GHQ-30 normative data from U.K. control population (36).

**TABLE 6.** Baseline SF-36 questionnaire scores in Addison's patients and comparison with normative data

SF-36	Physical functioning	Role physical	Bodily pain	General health	Vitality	Social function	Role emotional	Mental health
Norwegian normative data <sup>a</sup>	87.2	77.9	75.1	76.8	60	85.6	81.7	78.8
Mean (SEM)	(0.39)	(0.76)	(0.54)	(0.46)	(0.43)	(0.46)	(0.69)	(0.34)
Norwegian Addison's patients <sup>a</sup>	84.4	60.8	76.2	56.6	51.7	79.7	70.3	78.1
Mean (SEM)	(2.09)	(4.86)	(2.84)	(2.93)	(2.93)	(2.79)	(4.19)	(1.58)
<i>P</i> value <sup>a</sup>	0.13	<0.001	0.70	<0.001	0.001	0.024	0.003	0.70
U.K. normative data <sup>b</sup>	88.0	87.2	78.8	71.1	58.0	82.8	85.8	71.9
Mean (SEM)	(0.21)	(0.24)	(0.25)	(0.22)	(0.21)	(0.25)	(0.23)	(0.19)
U.K. Addison's patients	83.8	46.2	75.7	58.8	47.4	78.3	56.5	72.7
Mean (SEM)	(1.73)	(3.91)	(2.45)	(2.63)	(2.29)	(2.17)	(4.31)	(1.74)
<i>P</i> value	0.03	<0.001	0.17	<0.001	<0.001	0.049	<0.001	0.65

Mean scores are shown with *lower values* denoting worse health status.

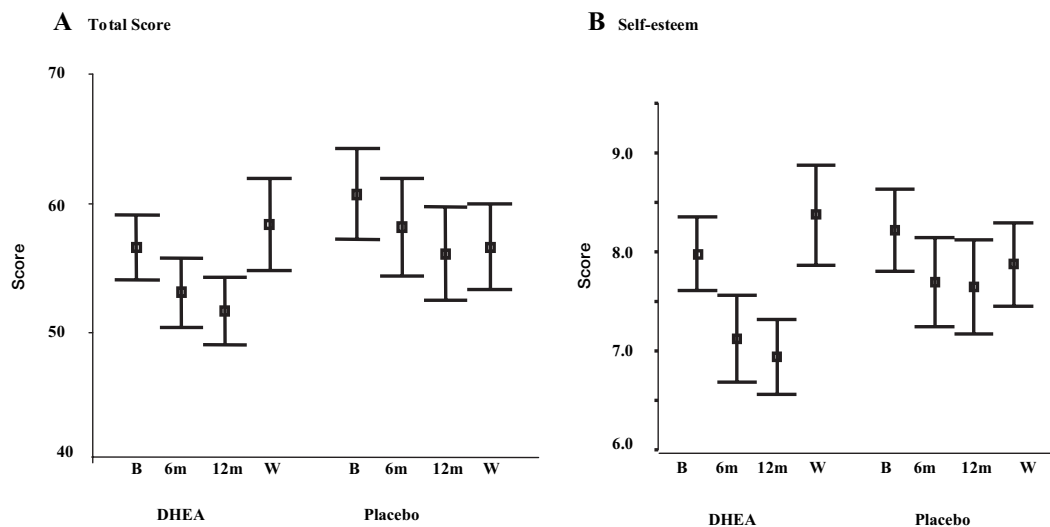
<sup>a</sup> Data published previously by Lovas et al. (21).

<sup>b</sup> SF-36 normative data from U.K. control population (34).

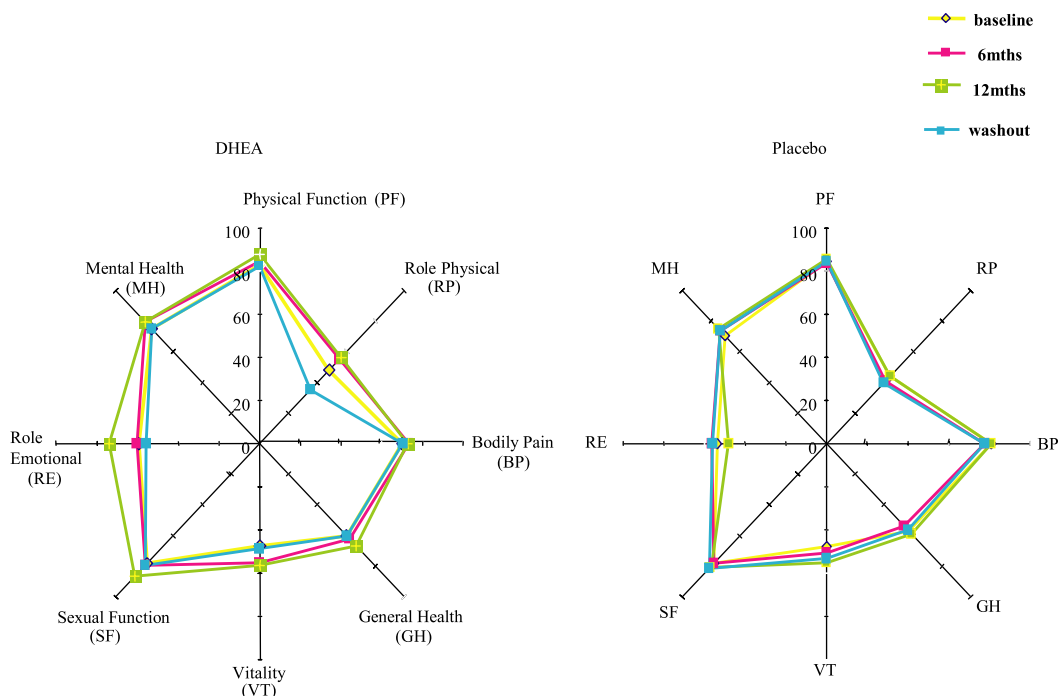
son's disease patients before hormone/placebo treatment with normative data. We recognize that these control subjects were not contemporaneous, making such comparison tentative. There were striking reductions in baseline scores for some subscales of GHQ-30 and dimensions of SF-36, compared with normal subjects drawn from a reference population. Interestingly, similar abnormalities in the self-esteem subscale of GHQ-30 occurred in both of our studies [this one and an earlier shorter-term replacement study (20)], and an identical pattern of abnormalities in baseline SF-36 scores were observed in another Addison's population from Norway (21), suggesting there may be a disorder-specific profile of psychological deficit in Addison's disease. During DHEA treatment, scores for the subscales of GHQ-30 and SF-36 improved and worsened more markedly (albeit nonsignificantly) after washout of DHEA. Furthermore, we observed a similar trend with physical and mental fatigue dimensions of the MFI-20 inventory (a prominent complaint in Addison's patients), with statistically nonsignificant improvement at 6 and 12 months during DHEA treatment, followed by deterioration of scores after washout. This pattern of initial early improvement in

well-being and fatigue followed by a rebound in scores after DHEA washout may be noteworthy. In a earlier 6-month study of DHEA treatment in hypopituitarism, beneficial effects on well-being were much more evident to partners of patients than study subjects (24). We speculate that the beneficial psychological effects of DHEA are most perceptible soon after starting treatment or after drug withdrawal, with diminished self-awareness of changes during longer-term continuation of therapy.

In contrast to the effects on well-being and fatigue, there were no significant changes in any of the wide range of cognitive functions assessed during DHEA therapy. This agrees with previous studies of DHEA supplementation in subjects with normal adrenal function (51, 52). Furthermore, a large cohort study on aging men failed to show any correlation between cognitive function and decreasing DHEA(S) levels (53). Several explanations are possible: although the study lasted 12 months, this may still be too brief for beneficial effects on cognitive function to become apparent; the possibility that there might have been selective effects on older patients, who would be expected to undergo some degree of



**FIG. 3.** Comparison of changes in mental health status, as assessed by GHQ-30 scores (mean and 95% confidence interval) at baseline (B), 6 months (6m), 12 months (12m), or after washout (W). Total score (A) and self-esteem subscale score (B) after placebo or DHEA treatment are shown. Higher scores denote worse health status.



**FIG. 4.** Spider plots showing the eight dimensions of health assessed by the SF-36 questionnaire at baseline, 6 months, 12 months, and after washout in DHEA- (left panel) or placebo-treated (right panel) groups. Lower scores denote worse health status. The only significant difference between groups was improvement of the role emotional dimension (RE;  $P = 0.004$ ) at 12 months after DHEA treatment.

cognitive decline under even normal circumstances, was examined by subgroup analysis of patients over 45 yr, but this also failed to show any significant DHEA effect (data not shown); effects on cognition may vary, depending on the duration of DHEA deficit, amount of glucocorticoid replacement, or some combination of these factors with age; there may be other ways of testing cognitive function that might reveal positive effects of DHEA. Finally, despite animal experimental data suggesting that DHEA has a neuroprotective effect, it may have no significant ameliorating effect on cognitive dysfunction in humans. Nevertheless, our data represent the most comprehensive evaluation of the effects of DHEA on cognition in Addison’s disease. We cannot discount the possibility that there may be subgroups of patients (e.g. related to age or gender) in whom DHEA might be particularly beneficial, but given our negative overall results, this remains speculative.

Finally, we observed no changes in sexual function after DHEA treatment, which is in keeping with observations in some short- (20, 48, 54) and longer-term trials (25) but differs from observations in women with primary or secondary adrenal failure (23, 24). Another androgen (testosterone) also improves sexual function in surgically menopausal women (55, 56). Accordingly, it is possible that beneficial effects of DHEA on sexual function are primarily androgen mediated, therefore being most evident in women with severe androgen deficiency. Future trials of DHEA in subjects with a combination of both Addison’s disease and ovarian failure could address this possibility.

This trial describes the longest duration of DHEA replacement therapy in a comparatively large number of patients with Addison’s disease and provides important additional informa-

tion on its effects and tolerability. Our results show that daily oral administration of DHEA in physiological dosage for 12 months normalizes serum DHEAS levels and does have positive psychological effects. Our study also suggests that patients with Addison’s disease may have a disorder-specific psychological deficit. By analogy with GH therapy in adult GH deficiency, it is possible that future development of an Addison’s disease-specific quality of life measure may provide a tool that better detects changes in well-being or better defines patients in whom DHEA therapy is indicated. Beneficial responses to DHEA treatment in lean body mass and femoral BMD were also observed, changes that if sustained in the long term, could reduce morbidity. Overall, DHEA therapy was generally well tolerated, although some females described androgenic side effects. In future trials, the dosage of DHEA may require adjustment in both sexes: older females may need only 25 mg daily; conversely, younger males

**TABLE 7.** Percentage of patient-reported side effects at 12 months after DHEA or placebo treatment

	Skin changes			Hair increase			
	None	Greasy	Spots	None	Pubic	Axillary	Facial
Males (40)							
DHEA (18)	66	11	17	0	0	0	7
Placebo (22)	68	9	0	0	0	0	5
Females (60)							
DHEA (31)	69	45 <sup>a</sup>	64 <sup>a</sup>	28	13	58 <sup>a</sup>	19
Placebo (29)	69	0	14	76	10	7	14

Patient numbers are in parentheses.

<sup>a</sup>  $P < 0.02$  where indicated for changes between placebo and DHEA-treated groups with other differences not being significant.



may require more than 50 mg to restore age-related circulating DHEAS levels.

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