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Effects of Dehydroepiandrostenedione, Superimposed on Growth Hormone Substitution, on Quality of Life and Insulin-Like Growth Factor I in Patients with Secondary Adrenal Insufficiency: A Randomized, Placebo-Controlled, Cross-Over Trial

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To assess whether dehydroepiandrostenedione (DHEA) substitution, superimposed on GH substitution, improves quality of life of patients with secondary adrenal failure, we studied the effects of DHEA (50 mg/d, 16 wk) *vs.* placebo (16 wk) in GH- and ACTH-deficient men (n = 15; age, 52 ± 3 yr), and postmenopausal women (n = 16; age, 61 ± 2 yr) in a double-blind, placebo-controlled, crossover study. All patients were receiving stable hormone replacement therapy, including a fixed dose of human recombinant GH during the study. The men received testosterone substitution. The female patients did not receive estrogen substitution. At baseline, multiple parameters of quality of life were impaired compared with age- and sex-matched controls, especially in female patients. These parameters were not improved by DHEA treatment. DHEA only slightly improved the depression score (women) and health perception (women and men), although these parameters were not abnormal at baseline. DHEA increased serum IGF-I concentrations in female patients (by ~18%; $P < 0.001$), but not in male patients. In neither group did DHEA affect IGF-binding protein-3 levels. We conclude that DHEA, superimposed on GH substitution, does not substantially improve quality of life in patients with secondary adrenal insufficiency regardless of gender. In addition, DHEA increases IGF-I levels only in estrogen-depleted females, but not in testosterone-treated males, with secondary adrenal insufficiency. **(*J Clin Endocrinol Metab* 90: 3295–3303, 2005)**

GH DEFICIENCY (GHD) IS associated with impaired quality of life (1), and substitution with recombinant human GH (rhGH) improves quality of life (1–7). However, despite this beneficial effect of GH substitution and other pituitary hormones, these patients may still have significant impairments in multiple aspects of quality of life (8). It is likely, therefore, that other factors impair quality of life in these patients.

Many patients with GHD will also have secondary adrenal insufficiency and, therefore, decreased levels of dehydroepiandrostenedione (DHEA) (9, 10). DHEA has long been considered an inactive precursor of sex steroids. However, deficiency of DHEA due to adrenal insufficiency is associated with impaired quality of life, and treatment with DHEA in subjects with DHEA deficiency significantly improves quality of life (11–13) (see Table 1). In addition, beneficial effects of DHEA substitution have been reported on other parameters, such as insulin resistance and bone mineral density (14–20). These beneficial effects are attributed to the conversion of DHEA into androgens and estrogens. Previously, only one study focused on the effects of DHEA in female patients with secondary adrenal failure, and it showed that quality of life parameters improved (12). Remarkably, in that study quality of life parameters were assessed predominantly by the partners of the patients, rather than by the patients themselves.

Therefore, to assess whether DHEA substitution, superimposed on GH substitution, improves quality of life in male and female patients with secondary adrenal failure, we studied the effects of DHEA (50 mg/d, 16 wk) *vs.* placebo (16 wk) in GH- and ACTH-deficient men (n = 15) and in GH- and ACTH-deficient postmenopausal women (n = 16) in a double-blind, placebo-controlled, crossover study. All patients were receiving stable hormone replacement therapy, including a fixed dose of rhGH during the study. Because previous studies had not been controlled for estrogen status (Table 1), we chose to include only postmenopausal women without estrogen replacement therapy. Men were all receiving stable testosterone replacement.

There are indications that DHEA substitution may increase serum levels of IGF-I (Table 1). Because our study was well controlled for GH availability, and DHEA might affect IGF-I independently of GH secretion (21), we also evaluated the effects of DHEA on IGF-I levels in our study.

Patients and Methods

Patients

Patients with pituitary diseases and both ACTH and GH deficiencies were recruited from the Outpatients Clinic of the Department of

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Abbreviations: CV, Coefficient of variation; DHEA, dehydroepiandrostenedione; DHEAS, DHEA sulfate; GHD, GH deficiency; HADS, hospital anxiety and depression scale; IGFBP-3, IGF-binding protein-3; ILMA, immunoluminometric assay; MFI-20, Multidimensional Fatigue Inventory-20; rhGH, recombinant human GH; SF-36, Short Form-36.

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TABLE 1. Overview of studies on the effects of DHEA substitution in patients with primary and/or secondary adrenal failure

Study	n	Sex	Type of adrenal failure	Hormone status[a]	Design[b]	DHEA dose (mg)	Effect of DHEA on IGF-I	Effect of DHEA on quality of life [c]
Arlt *et al.* (11)	24	F	14 primary, 10 secondary (combined analysis)	ER or ED	Double-blind RCT, crossover design; DHEA *vs.* placebo treatment for 4 months, washout 4 wk, single center	50	Increased only in primary, but not in secondary adrenal failure	Symptom Checklist-90: + MDM Questionnaire: + VAS sex activity score +
Hunt *et al.* (12)	39	24 F 15 M	Primary	F, ER or ED; M, testosterone replete	Double-blind RCT, crossover design; DHEA *vs.* placebo treatment for 3 months, washout 4 wk, single center	50	No effect	GHQ-30: I+
Johannsson *et al.* (13)	38	F	Secondary	ER or ED; fixed rhGH substitution in 37 patients	Double blind RCT parallel control group, DHEA *vs.* placebo treatment for 6 months, multicenter	20 (age >45 yr) or 30 mg (age <45 yr)	No effect	Partner responses to: 1. Hopkins symptom check list:+ 2. Psychological general well-being index: +; partner questionnaire: +
Lovas *et al.*, (31)	39	F	32 primary, 6 secondary, 1 unknown (combined analysis)	ER or ED	Double-blind RCT, parallel control group, DHEA *vs.* placebo treatment for 9 months, multicenter	25	No effect	SF-36: = Fatigue scores: = Sexuality scores: =
Present study	31	15 F 16 M	Secondary	F, estrogen deficient; M, testosterone replete; fixed rhGH substitution	Double-blind RCT, crossover design; DHEA *vs.* placebo treatment for 4 months, washout 8 wk, single center	50	F: increase; M: no change	HADS: + SF-36: + MFI-20: = QOL-AGHDA: = Sexual function: =

[a] ER, Estrogen replete, including estrogen replacement therapy (with or without progestagen); ED, estrogen deficiency, *e.g.* postmenopausal or secondary hypogonadism.

[b] RCT, Randomized controlled trial.

[c] +, Improvement in one or more items; =, no effect; Symptom Checklist-90, the 90-item Checklist 90 (revised version); MDM Questionnaire, Multidimensional Mood Questionnaire; VAS, visual analogue scale; GHQ-30, General Health Questionnaires; MFI-20: Multidimensional Fatigue Inventory-20; QOL-AGHDA, quality of life assessment of GHD in adults.

Endocrinology and Metabolism of Leiden University Medical Center (LUMC). Recruitment of patients took place between October 2001 and April 2002. The LUMC is a large tertiary referral center for pituitary disorders. Inclusion criteria were GHD, proven by insufficient stimulation of GH secretion (GH, <7 mU/liter) during insulin-induced hypoglycemia (minimal glucose concentration after insulin administration, 2.2 mmol/liter) with stable replacement therapy with rhGH for at least 3 months before the start of the study, and ACTH deficiency, proven by insufficient cortisol secretion (cortisol, <0.55 μmol/liter) during insulin-induced hypoglycemia, with stable hydrocortisone replacement therapy for at least 3 months before the start of the study. In all subjects, IGF-I levels during treatment with rhGH were in the mean range of sex- and age-matched values. Deficiencies of other hormones of the anterior pituitary as well as antidiuretic hormone (ADH) were allowed, as long as stable substitution with T_4 and ADH were realized for at least 3 months before the study. T_4 was administered to obtain plasma free T_4 values in the upper 50% range of the normal reference values. The dose of T_4 was stable for at least 3 months before starting the study. For all male participants, stable testosterone replacement by transdermal testosterone application (50 mg/d) was required (Testoderm, Ferring Pharmaceuticals, Hoofddorp, The Netherlands). For female participants, estrogen replacement therapy was not allowed. Exclusion criteria were liver disease, malignant disease, or other severe system disease as well as the use of drugs that could potentially interfere with the assessment of study parameters, such as psychotropic drugs.

Study protocol

The study was a randomized, placebo-controlled, double-blind, crossover study, with two treatment periods of 16 wk separated by an 8-wk washout period. A block randomization scheme was used (n = 2),

with stratification for gender. The randomization schedule was prepared by the Department of Pharmacy. Patients received in random order 50 mg DHEA (Vito Fit Corp., Helmond, The Netherlands) or placebo capsules (containing cellulose). The purity and quantity of DHEA were verified by HPLC analysis at the Department of Pharmacy of LUMC. DHEA or placebo capsules were taken orally each morning. rhGH was injected before bedtime. Compliance for study medication and regular medication was verified at each visit. The treatment allocation was deblinded after all study data were authorized and introduced in a database, which was closed before deblinding.

The medical ethic committee of LUMC approved the study protocol, and all patients gave written informed consent.

Measurements

All visits took place at the outpatient clinic between 0800 and 1000 h.

Quality of life questionnaires

Quality of life investigation was performed with five validated questionnaires at baseline and at the end of each treatment period. The questionnaires are described in detail below. Questionnaires were completed in a quiet room in the morning. The baseline measurements were compared with those of an age- and sex-matched control group; for each participant in the DHEA study, two age- and sex-matched controls were selected from a group of 114 healthy relatives of GH-deficient patients from the Department of Endocrinology and Metabolism of LUMC (Table 4). The socioeconomic status (level of education, profession, marital state, and living area) of controls and participants was comparable.

Short Form-36 (SF-36)

The SF-36 comprises 36 items that record general well-being during the previous 30 d (22). The items are formulated as statements or questions and were scored as numbers. Eight parameters were calculated with a range of 0–100: physical problems, bodily pain, general health, vitality, social functioning, emotional role, and mental health. The first three parameters measure physical health, the last three parameters measure mental health, and the general health and vitality scales are sensitive to both physical and mental health outcomes. Higher scores represent better quality of life (23).

Quality of life assessment of GHD in adults

The quality of life assessment of GHD in adults is developed specifically to assess the impact of GHD and GH replacement in adults (24). The items are formulated as statements and were scored as numbers. Low scores represent better quality of life (24).

Multidimensional Fatigue Inventory-20 (MFI-20)

The MFI-20 records fatigue using 20 statements (25). Five parameters are calculated from the statements (general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue), with a maximum score of 20/parameter. A high score indicates a higher level of fatigue or impairment (26).

Hospital Anxiety and Depression Scale

The HADS consists of 14 items pertaining to anxiety and depression (27). Each item is scored as a number, with a maximal score for each subscale (anxiety or depression) of 21. Higher scores indicate more severe anxiety or depression. A score of 6 or higher on the depression scale or 7 or higher on the anxiety scale is considered abnormal (28, 29).

Eleven Questions on Sexual Function

The Eleven Questions on Sexual Function questionnaire is developed by the National Institute for Social Sexual Research (Rutgers Nisso Group, Utrecht, The Netherlands) with the Department of Sexuology of LUMC. It measures sexual experience during the previous 30 d using 11 questions. For all patients, three parameters were calculated from eight questions: sexual fantasies, libido, and general sexual satisfaction. For patients with partners, three additional parameters were calculated related to physical sexual functioning: problems with erection or lubrication, problems with orgasm, and pain or discomfort during sexual activities. The questions were scored from 1–7; a higher number indicated a higher degree of satisfaction.

Endocrine parameters

All blood samples were taken between 0800 and 1000 h, before regular medication and study drugs were administered, with the exception of cortisol replacement therapy.

Study parameters were serum measurements of IGF-I, IGF-binding protein-3 (IGFBP-3), DHEA, DHEA sulfate (DHEAS), testosterone, estradiol, estrone, SHBG, serum lipids, hemoglobin A_{1C}, and insulin. These measurements were performed at baseline and at the end of each study period. All blood samples were stored immediately at −80 C until measurement. Other study parameters were anthropomorphic measurements (weight, body mass index, and waist/hip ratio).

Safety parameters

A general health questionnaire was administered before the study. Laboratory safety parameters were serum levels of sodium, potassium, alanine aminotransferase, aspartate aminotransferase, γ-glucose transferase, alkaline phosphatase, and creatinine. Weight, heart rate, and blood pressure were recorded at every visit.

Laboratory assays

All analyses for each subject were analyzed in the same run. The total serum IGF-I concentration was measured by immunoluminometric assay (ILMA) after dissociation and blocking of the IGFBPs with IGF-II (Nichols Advantage, Nichols Institute Diagnostics, San Clemente, CA). The detection limit was 0.12 ng/ml (0.9 nmol/liter). The intraassay coefficient of variation (CV) ranged from 4.4–5.2%, and the interassay CV ranged from 5.7–7.4%. The plasma IGFBP-3 concentration was measured by RIA (Nichols Institute Diagnostics). The interassay CV was less than 6.8% at the concentrations measured in the present study. The limit of detection was 0.0625 mg/liter (2.8 nmol/liter). Normal values range from 46–122 nmol/liter in subjects aged 30–50 yr and from 49–112 nmol/liter in subjects aged 50–70 yr. GH concentrations were measured with a sensitive, time-resolved fluoroimmunoassay (Wallac, Turku, Finland) that was specific for 22-kDa GH. The standard was recombinant human GH (Genotropin, KabiVitrium, Uppsala, Sweden), which was calibrated against World Health Organization First International Reference Preparation 80/505. To convert milliunits per liter to micrograms per liter, divide by 2.6. The limit of detection (defined as the value 2 SD above the mean value of the zero standard) was 0.03 mU/liter. The intraassay CV ranged from 1.6–8.4% in the assay range from 0.26–47 mU/liter, with a corresponding interassay CV of 2.0–9.9%. DHEA was measured by RIA after extraction (DHEA-kit, Diagnostics Products Corp., Bad-Nauheim, Germany). The detection limit was 0.012 μg/liter (0.04 nmol/liter), the intraassay CV was 5.2–10.8%, and the interassay CV was 5.9–11.7%. DHEAS was measured by ILMA (Immulite, Diagnostics Products Corp., Los Angeles, CA). The detection limit was 148 μg/liter (0.4 μmol/liter), the intraassay CV was 7.0–9.5%, and the interassay variation was 8–15%. Androstenedione was measured by RIA (Diagnostic Systems Laboratories, Sinsheim, Germany), with a detection limit of 0.02 ng/ml (0.07 nmol/liter), an intraassay CV of 2.7–6.3%, and an interassay CV of 9.3–11.7%. Total testosterone was measured by RIA (Diagnostics Products Corp.), with a detection limit of 0.08 ng/ml (0.2 nmol/liter), and intra- and interassay CVs of 10–19%. Estrone was measured using RIA (Diagnostic Systems Laboratories, Veghel, The Netherlands), with a detection limit of 1.1 pg/ml (40 pmol/liter), an intraassay CV of 4.4–9.4%, and an interassay CV of 5–17%. SHBG was measured by ILMA (Immulite, Diagnostics Products Corp., Bad-Nauheim, Germany), with a detection limit of 0.34 mg/liter (4.0 nmol/liter), an intraassay CV of 4.1–7.7%, and an interassay CV of 4–20%. Estradiol was determined with the Elecsys E170 (Roche, Basel, Switzerland), with a detection limit of 1.36 pg/ml (5 pmol/liter), an intraassay CV of 1.6–2.0%, and an interassay CV of 1.6–2.7%. Hemoglobin A_{1C} was measured using the Bio-Rad Variant method (Bio-Rad Laboratories, Veenendaal, The Netherlands), with a detection limit of 3.6%, an intraassay CV of 1%, and an interassay CV of 1–2%. Serum insulin was

measured by immunoradiometric assay (BioSource, Etten-Leur, The Netherlands), with a detection limit of 0.1 mU/liter (0.6 pmol/liter), an intraassay CV of 2.1–4.5%, and an interassay CV of 3.1–4.3%. A Hitachi 747 autoanalyzer (Roche, Mannheim, Germany) was used to quantify serum concentrations of total cholesterol and triglycerides with enzymatic tests (all from Roche). High density lipoprotein cholesterol was measured with a homogenous enzymatic assay (Hitachi 911, Roche). Low density lipoprotein cholesterol concentrations were calculated with the Friedewald formula.

Statistics

The sample size was determined by a formal power analysis based on the rise in IGF-I in the study by Arlt *et al.* (11). In this study, a pooled SD of changes in IGF-I of 11% was found. It was calculated that with two groups of 15 patients each, a rise in IGF-I of 12% could be detected with 80% power and an α of 0.05. When no carryover effect was present, a minimal IGF-I rise of even 8% could be detected.

Data were analyzed on a per protocol base. Treatment effects were analyzed using univariate ANOVA. The model associated with the ANOVA had an intercept representing treatment effects. All data were presented separately for men and women. The effects of treatment were also measured by adjusting for carryover and time effects. The tests for carryover and time effects followed the procedures described by Hills and Armitage (30). Carryover and time effects were also tested. If no time or carryover effects were detected, data from both study periods were combined. Categorical data were analyzed with the χ^2 test. Data are presented as the mean ± SEM. SPSS for Windows version 11.0 (SPSS, Inc., Chicago, IL) was used for analysis, and a P value of 0.05 was considered significant.

Results

Clinical characteristics

Thirty-four patients were recruited, 17 women and 17 men (Fig. 1). One man was excluded before initiation of treatment, because he developed allergic reactions of the skin to transdermal testosterone replacement therapy. Therefore, 16 men and 17 women started the study. One female patient had progression of a nonendocrine pituitary adenoma, documented by magnetic resonance imaging during the first study period, and decided to withdraw from the protocol. One male patient died at home during the second phase of the study, probably because of an acute myocardial infarction, but the exact cause of death could not be verified because no autopsy was performed. Data from these two patients were not included in the analyses of the data (see Fig. 1). Thirty-one patients (16 women and 15 men) completed the study. The baseline characteristics of these patients are given in Table 2. No side effects, such as acne or greasiness of the skin, were observed in any patient. All women were postmenopausal, and none received estrogen replacement therapy. All men used transdermal testosterone replacement therapy. All patients had GHD that had been treated for a mean period of 5.2 ± 0.6 yr. The causes of pituitary insufficiency are given in Table 2.

Quality of life

Baseline values compared with values obtained in controls. Quality of life parameters of patients compared with controls are given in Table 3. Multiple parameters appeared to be worse in patients than in controls despite conventional hormonal replacement therapy. In general, women had more abnormal quality of life parameters than men.

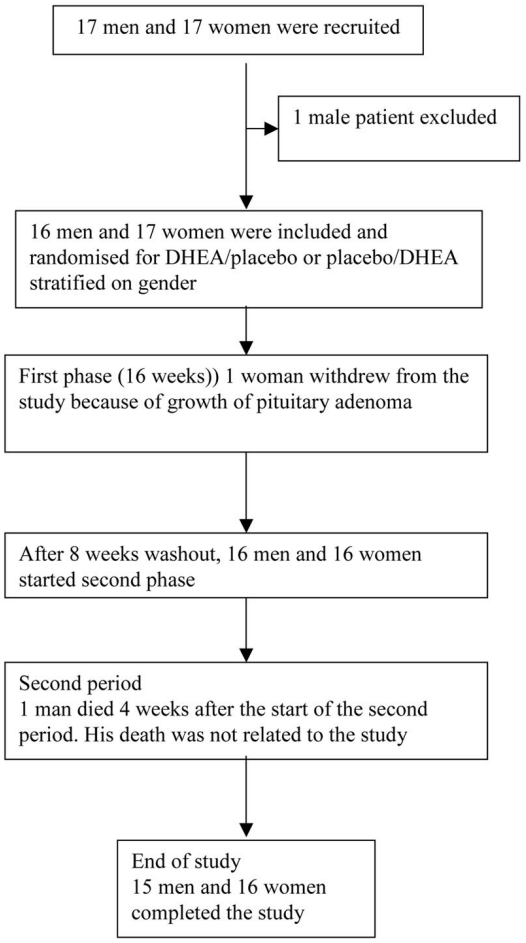

FIG. 1. Study flow chart.

Women scored significantly worse than age- and sex-matched controls in seven of 15 tested parameters, whereas men scored worse in three of 15 tested parameters than age- and sex matched controls. In women, physical functioning (SF-36), role limitations due to physical and emotional problems (SF-36), and general and physical fatigue (MFI-20) were worse than in controls. In men, general health perception was worse than in controls (MFI-20). In both men and women, social functioning (SF-36) and activity level (MFI-20) were worse than in controls.

Effects of DHEA vs. placebo. The effects of DHEA on the outcome of quality of life questionnaires in female and male patients are given separately in Table 4. There were no carryover or time effects for any of the study parameters. Remarkably, parameters that were abnormal at baseline compared with controls did not improve significantly upon treatment with DHEA. In women, a significant improvement in the depression score (HADS) was observed. In both women and men, change in health (SF-36) improved significantly. DHEA had no effect on the different dimensions of fatigue or on parameters of sexual functioning. Patients with partners showed no beneficial effect of DHEA on sexual performance, nor did the satisfaction about their sex life change.

TABLE 2. Baseline characteristics of 31 patients who were treated with 50 mg/d DHEA for 16 wk or placebo in a randomized cross-over design with 8-wk washout

F/M	16/15
Age: [mean (yr)]	57.2 ± 2.0
Men	52.6 ± 3.5
Women	61.5 ± 1.7
Duration of GH therapy	5.2 ± 0.6 (6 months to 17 yr)
Dose of GH therapy (mg/d)	
Men	0.41 ± 0.03
Women	0.45 ± 0.04
Cause of pituitary deficiency	
Nonfunctional pituitary adenoma	13
Cushing's disease	4
Prolactinoma	4
Craniopharyngioma	4
Other	6
Treatment	
Transsphenoidal surgery	14
Transcranial surgery	12
Radiotherapy	14
Surgery and radiotherapy	14
Radiotherapy and adrenalectomy	3
Other replacement therapy	
L-T_4	30
Cortisol	31
Estrogen/testosterone	0/15 (only men)

F, Females; M, males.

IGF-I and IGFBP-3 concentrations: effects of DHEA vs. placebo

DHEA treatment significantly increased serum IGF-I levels by approximately 18% in female patients compared with placebo treatment ($P < 0.001$; Table 5 and Fig. 2). In contrast, in male patients, there was no significant effect of DHEA, compared with placebo, on IGF-I levels (Table 5 and Fig. 2). DHEA did not influence IGFBP-3 levels in female or male patients.

Other plasma concentrations: effects of DHEA vs. placebo

DHEA treatment increased serum levels of DHEA, DHEAS, estrone, and androstenedione substantially in both men and women (Table 5). DHEA substitution increased estradiol only in women. Interestingly, after DHEA treatment, androstenedione and estrone levels in women reached the baseline levels in men.

Other parameters: effects of DHEA vs. placebo

BMI, waist, and waist/hip ratio were not influenced by DHEA treatment. Fasting serum lipid levels, glucose and insulin levels were not influenced by DHEA (data not shown).

Side effects of DHEA

There were no side effects reported during DHEA or placebo treatment. Some patients experienced an increase in perspiration, but this was not different between the groups. There were no differences observed between DHEA *vs.* placebo treatment in systolic or diastolic blood pressure, pulse rate, or safety laboratory parameters.

Discussion

The present study was performed to determine whether DHEA substitution, superimposed on replacement with rhGH, has effects on quality of life in patients with pituitary diseases resulting in GH and ACTH deficiencies. At baseline, we found that multiple quality of life parameters were worse in patients than in controls. This observation was more pronounced in women than in men. DHEA treatment showed subtle improvements in a limited number of quality of life parameters in men and women. However, these improve-

TABLE 3. Quality of life parameters in 31 patients with substituted ACTH and GH deficiencies obtained at baseline and in 62 age- and sex-matched controls

	Women			Men		
	Controls	Patients	*P*	Controls	Patients	*P* value
No.	32	16		30	15	
Age (yr)	55.4 ± 1.3	61.5 ± 1.7	0.480	56.7 ± 1.9	52.6 ± 3.5	0.628
Questionnaire						
HADS						
Anxiety	4.66 ± 0.62	5.53 ± 0.88	0.424	3.07 ± 0.50	4.88 ± 0.84	0.075
Depression	3.11 ± 0.44	3.76 ± 0.82	0.489	3.60 ± 0.56	4.50 ± 1.05	0.457
Total	7.77 ± 0.96	9.29 ± 1.47	0.392	6.67 ± 0.92	9.38 ± 1.55	0.145
SF-36						
Physical functioning	86.6 ± 2.6	70.9 ± 7.3	0.017	85.2 ± 3.9	87.9 ± 2.5	0.567
Social functioning	93.0 ± 2.6	76.5 ± 6.1	0.003	93.3 ± 2.6	80.5 ± 5.5	0.020
Role limitations due to physical problems	93.4 ± 3.4	66.2 ± 9.3	0.002	86.7 ± 5.8	68.8 ± 9.5	0.121
Role limitations due to emotional problems	93.1 ± 3.4	72.6 ± 10.4	0.022	92.2 ± 4.1	81.3 ± 7.4	0.209
Bodily pain	86.6 ± 3.2	77.6 ± 6.1	0.201	85.5 ± 3.2	91.2 ± 3.4	0.232
General health perception	71.5 ± 2.9	60.0 ± 6.1	0.062	74.0 ± 3.1	58.8 ± 3.8	0.003
Change in health	55.4 ± 2.5	52.9 ± 4.2	0.766	56.7 ± 3.4	53.1 ± 3.1	0.446
MFI-20						
General fatigue	7.71 ± 0.60	11.35 ± 1.37	0.005	7.72 ± 0.54	9.38 ± 1.22	0.163
Physical fatigue	7.43 ± 0.62	10.12 ± 1.37	0.043	7.83 ± 0.65	9.13 ± 1.09	0.283
Reduced activity	7.17 ± 0.58	9.47 ± 0.91	0.042	6.86 ± 0.50	9.19 ± 0.98	0.023
Reduced motivation	7.17 ± 0.59	8.18 ± 0.98	0.386	7.24 ± 0.60	9.50 ± 1.10	0.083
Mental fatigue	8.43 ± 0.77	9.41 ± 1.29	0.517	7.10 ± 0.69	9.31 ± 1.32	0.151

Data are expressed as the mean ± SEM.

TABLE 4. Quality of life parameters in 31 patients with substituted ACTH and GH deficiencies after 16-wk treatment with 50 mg/d DHEA or placebo

Questionnaire	Women			Men		
	Placebo	DHEA	*P*	Placebo	DHEA	*P* value
HADS						
Anxiety	5.06 ± 0.99	4.69 ± 1.00	0.478	3.00 ± 0.70	3.33 ± 0.76	0.625
Depression	4.00 ± 0.82	2.38 ± 0.52	0.022	4.47 ± 0.99	3.73 ± 0.96	0.661
Total	9.06 ± 1.53	7.06 ± 1.34	0.078	7.47 ± 1.40	7.07 ± 1.62	0.653
SF-36						
Physical functioning	68.1 ± 7.9	71.9 ± 8.1	0.221	93.3 ± 1.6	92.9 ± 1.8	0.792
Social functioning	76.6 ± 7.2	82.8 ± 7.2	0.119	82.5 ± 4.7	85.8 ± 4.0	0.217
Role limitations due to physical problems	60.9 ± 11.2	68.8 ± 10.3	0.370	93.3 ± 3.8	93.3 ± 3.0	1.000
Role limitations due to emotional problems	60.4 ± 11.5	68.8 ± 10.3	0.523	80.0 ± 7.8	82.2 ± 7.9	0.719
Bodily pain	72.6 ± 6.7	70.0 ± 6.9	0.661	95.1 ± 2.5	95.1 ± 2.9	1.000
General health perception	67.8 ± 5.5	63.8 ± 5.7	0.254	61.3 ± 4.9	63.3 ± 4.2	0.645
Change in health	57.8 ± 5.0	67.2 ± 4.4	0.009	56.3 ± 3.6	65.0 ± 4.5	0.034
MFI-20						
General fatigue	11.1 ± 1.28	10.56 ± 1.24	0.620	9.53 ± 1.23	8.60 ± 1.03	0.178
Physical fatigue	9.88 ± 1.24	10.19 ± 1.37	0.789	9.00 ± 1.01	7.93 ± 0.92	0.064
Reduced activity	10.19 ± 1.11	9.00 ± 1.08	0.284	9.07 ± 0.96	8.60 ± 0.85	0.388
Reduced motivation	8.25 ± 0.83	7.25 ± 0.72	0.198	8.87 ± 1.09	8.80 ± 1.01	0.923
Mental fatigue	9.13 ± 1.35	8.44 ± 1.17	0.491	8.07 ± 1.16	8.20 ± 1.32	0.862
QOL-AGHDA						
Total	7.31 ± 1.46	6.50 ± 1.47	0.422	6.33 ± 1.61	6.60 ± 1.61	0.653
ESF						
All patients						
Fantasies	2.20 ± 0.43	2.13 ± 0.45	0.843	3.57 ± 0.48	3.57 ± 0.52	1.000
Libido	2.27 ± 0.33	2.20 ± 0.37	0.774	3.14 ± 0.28	3.36 ± 0.40	0.533
Satisfaction	3.07 ± 0.25	3.20 ± 0.22	0.582	2.92 ± 0.34	2.71 ± 0.29	0.426
Patients with partners (10 women, 9 men)						
Problems with erection/lubrication	1.60 ± 2.60	2.47 ± 0.36	0.085	1.78 ± 0.28	1.67 ± 0.29	0.347
Problems with orgasm	1.70 ± 0.27	2.10 ± 0.31	0.210	1.50 ± 0.28	1.39 ± 0.33	0.347
Pain	1.30 ± 0.21	1.40 ± 0.16	0.591	1.00 ± 0.00	1.11 ± 0.11	0.336

Data expressed as the mean ± SEM. ESF, Eleven Questions on Sexual Functioning; QOL-AGHDA, Quality of Life Assessment of GHD in Adults.

ments occurred only in parameters that were not different from those in age- and sex-matched controls at baseline.

At present, four randomized trials have been published on the effect of DHEA substitution on quality of life parameters in patients with primary and/or secondary adrenal insufficiency. These studies are summarized in Table 1. Three studies documented beneficial effects on parameters of quality of life (11–13). In contrast, the study by Lovas *et al.* (31) found no significant effect of DHEA on these parameters. However, that study was criticized, because of it was severely underpowered (32). The researchers used a parallel group design, which requires a much larger number of patients, compared with the crossover design of the other three studies. In addition, Lovas *et al.* (31) used a low dose of DHEA, compared with the other studies and with our study.

With respect to the effects of DHEA in secondary adrenal failure, our study can only be compared with that by Johannsson *et al.* (13). Although three other studies also contained patients with secondary adrenal failure, their analyses did not include or did not permit separate evaluation of patients with primary *vs.* secondary adrenal failure (11, 12, 31). In contrast with the beneficial effects of DHEA on quality of life predominantly assessed by the partners of the patients reported by Johannsson *et al.* (13), we observed only subtle

TABLE 5. Endocrine parameters of 31 patients with substituted ACTH and GH deficiencies at the end of 16-wk therapy with 50 mg/d DHEA or placebo

Hormones	Females			Males		
	Placebo	DHEA	*P* value *vs.* placebo	Placebo	DHEA	*P* value *vs.* placebo
IGF-I (ng/ml)	169 ± 13.8	200 ± 12.8	<0.001	209 ± 12.4	218 ± 12.3	0.107
IGFBP-3 (mg/liter)	2.04 ± 0.08	2.24 ± 0.16	0.116	3.03 ± 0.13	3.04 ± 0.1	0.449
DHEA (nmol/liter)	1.0 ± 0.5	8.5 ± 0.8	<0.001	0.5 ± 0.1	5.6 ± 0.5	<0.001
DHEAS (ng/ml)	8.1 ± 1.1	208.6 ± 27.9	<0.001	10.0 ± 2.0	269.7 ± 30.8	<0.001
Androstenedione (nmol/liter)	0.3 ± 0.1	1.7 ± 0.2	<0.001	1.2 ± 0.2	1.9 ± 0.2	0.011
Estradiol (pmol/liter)	17.4 ± 4.2	32 ± 2.2	0.006	49.1 ± 8.5	46.8 ± 6.3	0.814
Estrone (pmol/liter)	22.0 ± 4.2	94.5 ± 9.4	<0.001	55.5 ± 8.1	108.7 ± 11.8	<0.001
Testosterone (nmol/liter)	0.2 ± 0.0	0.7 ± 0.1	0.008	14.3 ± 2.9	12.5 ± 1.5	0.526
SHBG (nmol/liter)	60.6 ± 6.6	60.7 ± 8.0	0.990	40.0 ± 5.5	35.7 ± 3.8	0.204

Data are expressed as the mean ± SEM. Conversion factors (Systeme International to metric): DHEA, 0.288 (μg/liter); androstenedione, 0.286 (ng/ml); estradiol, 0.272 (pg/ml); estrone, 0.027 (pg/ml); testosterone, 0.288 (ng/ml); SHBG, 0.086 (mg/liter).

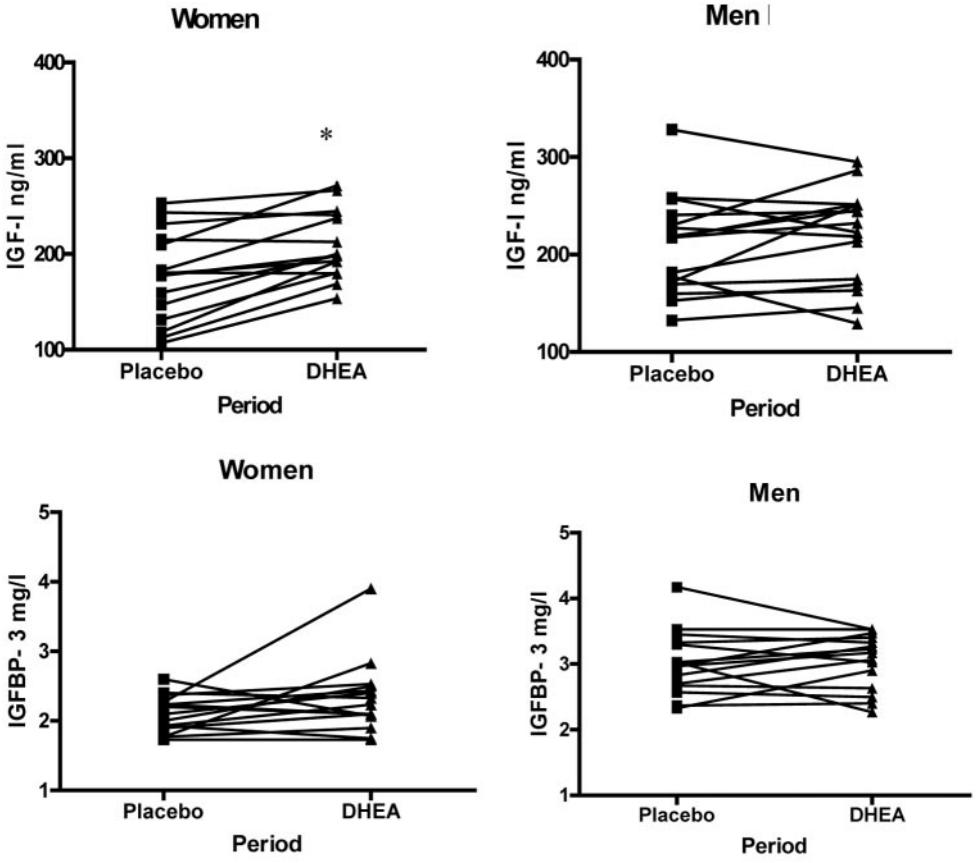

FIG. 2. Serum levels of IGF-I and IGFBP-3 in 31 patients at the end of 16-wk therapy with 50 mg/d DHEA or placebo.

beneficial effects of DHEA on quality of life reported by the patients themselves.

In the present study we confirmed the impaired quality of life in female and male patients with pituitary diseases despite conventional hormonal substitution therapy. DHEA substitution had only limited effects on these parameters. It can be proposed that the study is underpowered to detect significant changes in quality of life. However, the absolute changes in quality of life scores that were abnormal at baseline were hardly influenced by DHEA. The most severely affected parameter, role limitations due to physical problems (SF-36), changed only from 66.2 (baseline) to 68.8 (DHEA), whereas the control value was 93.4. Therefore, our data argue against a major effect of DHEA on quality of life parameters in such patients.

It is presently unclear by which mechanisms DHEA improves quality of life. The mechanism of action of DHEA is attributed to the conversion of DHEA into estrogens and androgens. Although this is also reflected in the changes in plasma concentrations of the respective hormones in the present study, these hormonal changes were not accompanied by apparent major changes in quality of life.

Another mechanism could be that DHEA increases quality of life by increasing IGF-I levels. Remarkably, in the presence of fixed GH availability, DHEA increased IGF-I levels in estrogen-depleted females, but not in testosterone-treated males, with secondary adrenal insufficiency. However, the increase in IGF-I was again not accompanied by an important improvement in quality of life in women.

The study by Arlt *et al.* (11, 33) indicated that treatment with 50 mg DHEA increased IGF-I slightly only in patients with primary adrenal failure, but not in patients with secondary adrenal failure. These researchers suggested that this differential effect of DHEA on IGF-I in primary *vs.* secondary adrenal failure may be due to a GH-mediated effect. In the present study we controlled for an effect of GH by including only patients with GHD taking a fixed dose of rhGH during the entire study. Therefore, an effect of DHEA cannot be caused by any changes in GH availability. In accordance, other studies did not find any effect of DHEA substitution in healthy volunteers on GH secretion (15, 21). These observations point to an effect of DHEA, independent of GH, on IGF-I production and/or clearance. Remarkably, this effect of DHEA was only present in estrogen-depleted women. In a study by Span *et al.* (34), it was demonstrated that estrogen replacement blunts the IGF-I response to rhGH in women. This could explain why in our study, effects of DHEA were found on IGF-I in estrogen-deplete women, whereas this effect was not found in the study by Johannsson *et al.* (13). We did not find an effect of DHEA on IGF-I in testosterone-substituted men. It is known that testosterone in healthy subjects and GHD patients enhances IGF-I levels (35–37), which may preclude an additional effect of DHEA. Apparently, the effect of DHEA on IGF-I levels is sex- and/or sex hormone dependent.

The absence of relevant effects of DHEA on quality of life points to a fundamental problem in the concept of conventional hormonal substitution. Hormonal substitution therapy has been extremely successful in the treatment of the major syndromes of endocrine insufficiency, with respect to reduction of morbidity and mortality. However, in general, many patients treated for endocrine insufficiencies still suffer from more or less vague complaints and a decreased quality of life. It is likely that these complaints are at least in part caused by intrinsic imperfections of hormone replacement strategies in mimicking normal hormone secretion (38). Accordingly, the patients with pituitary diseases evaluated in the present study showed decreased quality of life for several parameters, compared with age- and sex-matched controls, despite optimal endocrine replacement therapy according to current standards. The fact that DHEA superimposed on conventional endocrine therapy causes only subtle improvements points to our limited understanding of the mechanisms by which quality of life in these patients is affected.

DHEA did not affect sexual satisfaction in our study, in contrast with a positive effect of DHEA in other studies. In healthy subjects and in patients with primary and secondary adrenal failure, positive effects of DHEA were described on sexual function (11, 13, 15, 16, 31). However, these studies were carried out in younger patients. In our study, the women were postmenopausal, almost half of the patients had no partner, and the men were substituted with testosterone replacement. We cannot exclude the possibility that these factors may have obscured a potential positive effect of DHEA on sexual function.

In conclusion, DHEA substitution, superimposed on replacement with rhGH, has only subtle aspects of quality of life in patients with pituitary diseases with GH and ACTH deficiencies. Remarkably, DHEA increases IGF-I levels only in estrogen-depleted females, not in testosterone-treated males, with secondary adrenal insufficiency.

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