Abnormal growth hormone secretion : clinical aspects

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Chapter 5

Effects of DHEA, superimposed on growth hormone substitution, on quality of life and IGF-I in patients with secondary adrenal insufficiency: a randomised, placebo controlled, crossover trial

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Abstract

To assess whether DHEA substitution, superimposed on growth hormone (GH) substitution, improves quality of life of patients with secondary adrenal failure, we studied the effects of DHEA (50 mg/day, 16 weeks) *versus* placebo (16 weeks) in GH and ACTH deficient postmenopausal women (n=16, age 61 ± 2 yrs) and men (n=15, age 52 ± 3 yrs), in a double-blind, placebo controlled, cross-over study. All patients were on stable hormone replacement therapy, including a fixed dose of human recombinant GH during the study. The female patients did not receive estrogen substitution. The men received testosterone substitution.

At baseline, multiple parameters of quality of life were impaired compared to age- and sex-matched controls, especially in female patients. These parameters were not improved by DHEA treatment. DHEA improved only slightly 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, DHEA affected IGFBP-3 levels.

We conclude, that DHEA, superimposed on GH substitution, does not improve quality of life substantially in patients with secondary adrenal insufficiency, irrespective of gender. In addition, DHEA increases IGF-I levels in estrogen depleted females, but not in testosterone treated males, with secondary adrenal insufficiency.

Introduction

Growth hormone (GH) deficiency 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 as an inactive precursor of sex steroids. However, deficiency of dehydroepiandrostenedione (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 are reported on other parameters like 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 focussed on the effects of DHEA in female patients with secondary adrenal failure and 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/day, 16 weeks) *versus* placebo (16 weeks) in GH and ACTH deficient postmenopausal women (n=16) and GH and ACTH deficient men (n=15), in a double-blind, placebo controlled, cross-over study. All patients were on stable hormone replacement therapy, including a fixed dose of recombinant human GH (rhGH) during the study. As 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 on stable testosterone replacement.

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

Patients and methods

Patients

Patients with pituitary diseases and both ACTH and GH deficiency were recruited from the Outpatients Clinic of the Department Endocrinology and Metabolism from the Leiden University Medical Center. Recruitment of patients took place between October 2001 and April 2002. The Leiden University Medical Center is a large tertiary referral centre for pituitary disorders. Inclusion criteria were GH deficiency, proven by insufficient stimulation of GH secretion (GH < 7 mU/L) during insulin-induced hypoglycemia (minimal glucose concentration after insulin administration 2.2 mmol/L) with stable replacement therapy with rhGH for at least 3 months prior to the start of the study, and ACTH deficiency, proven by insufficient cortisol secretion (cortisol < 0.55 umol/L) during insulin-induced hypoglycemia, with stable hydrocortisone replacement therapy for at least 3 months prior to 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 ADH were allowed, as long as stable substitution with thyroxin and ADH were realized for at least 3 months prior to the study. Thyroxin was dosed to obtain plasma FT4 values in the upper 50 % range of the normal reference values. The dose of thyroxin was stable for at least 3 months prior to starting the study. For all male participants, stable testosterone replacement by transdermal testosterone application (50 mg/day) 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

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 [&]	Design [#]	DHEA dose	Effect of DHEA on IGF-I
Arlt *et al* (11)	24	F	14 Primary 10 Secondary (combined analysis)	ER or ED	Double blind RCT, Cross over design DHEA *vs.* placebo Treatment for 4 m Wash-out 4 w Single center	50 mg	Increased only in primary, but not in secondary adrenal failure
Hunt *et al* (12)	39	24 F 15 M	Primary	F: ER or ED M; Testosterone replete	Double blind RCT, Cross over design DHEA *vs.* placebo Treatment for 3 m Wash-out 4 w Single center	50 mg	No effect
Johannsson *et al* (13)	38	F	Secondary	ER or ED Fixed rhGH substitution in 37 pts	Double blind RCT Parallel control group DHEA *vs.* placebo Treatment for 6 m Multicenter	20 (age > 45 yr) or 30 mg (age < 45 yr)	No effect
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 9m Multicenter	25 mg	No effect
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 m Wash out 8 w Single center	50 mg	F; increase M: no change

[&] ER: estrogen replete (including estrogen replacement therapy (with or without progestagen)), ED: Estroge
or secondary hypogonadism.

[#] duration of trial: w=weeks, m= months, RCT: randomised controlled trial;

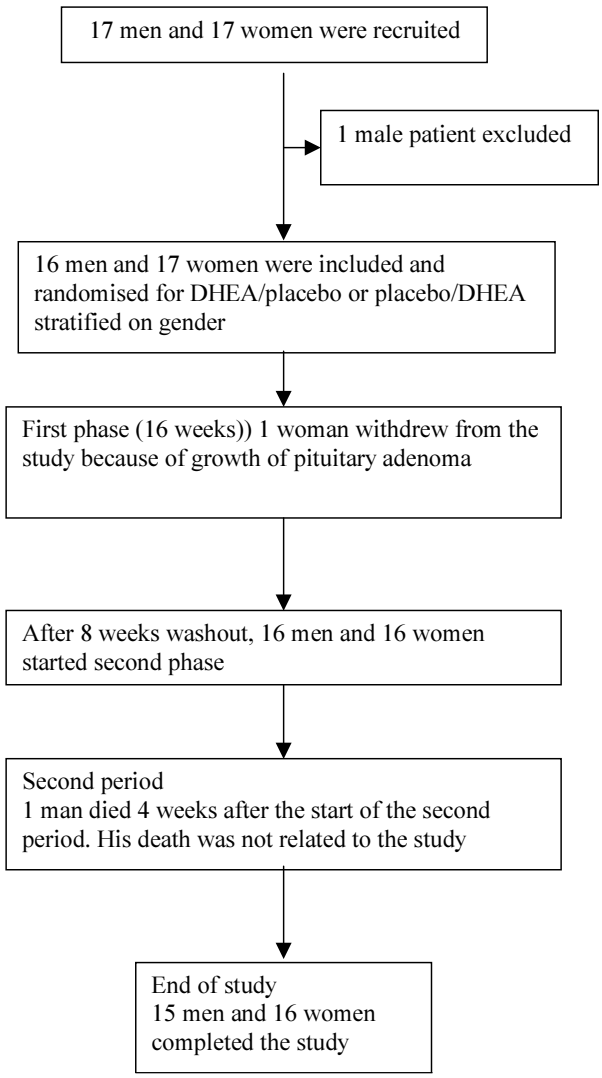
¶ +: improvement in 1 or more items, =: no effect; Symptom checklist-90: the 90-item Checklist 90 (revised
Multidimensional Mood Questionnaire, VAS: Visual analogue scale, GHQ-30: General Health Questionna
Hospital anxiety and depression scale. MFI-20 : Multidimensional Fatigue Inventory-20, QOL-AGHDA: C
in adults.

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 randomised placebo controlled, double blind crossover

Figure 1 Study Flow-Chart.



study with two treatment periods of 16 weeks separated by an 8-week wash-out period. A block randomisation 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 of Dehydroepiandrosterone (Vito Fit Corp., Helmond, The Netherlands) or placebo capsules (containing cellulose). Purity and quantity of DHEA were verified by HPLC analysis at the Department of Pharmacy of Leiden University Medical Center. 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 de-blinded after all study data were authorized and introduced in a database, that was closed before deblinding.
The Medical Ethic Committee of The Leiden University Medical Center approved the study protocol, and all patients gave written informed consent.

Measurements
All visits took place at the outpatient clinic between 8.00 and 10.00 a.m.

Quality of life questionnaires
Quality of life investigation was performed with 5 validated questionnaires at baseline and at the end of each treatment period. The questionnaires are described in detail below. Questionnaires were filled-out in a quiet room in the morning. The baseline measurements were compared with an age- and sex-matched control group: for each participant in the DHEA study, 2 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 the LUMC (Table 4). The socioeconomic status (level of education, profession, marital state, living area) of controls and participants was comparable.

Short Form-36
The Short Form (SF)-36 comprises 36 items, which record general well being during the previous 30 days (22). The items are formulated as statements or questions and were scored as numbers. Eight parameters

are 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, whereas 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 growth hormone deficiency in Adults
The quality of life assessment of GH deficiency in adults (QOL-AGHDA) 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
The Multidimensional Fatigue Inventory-20 (MFI–20) records fatigue using 20 statements (25). Five parameters are calculated of the statements (general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue), with a maximum score of 20 per parameter: A high score indicates a higher level of fatigue or impairment (26).

Hospital Anxiety and Depression Scale
The hospital anxiety and depression scale (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 ³ 6 on the depression scale or ³ 7 on the anxiety scale, is considered abnormal (28;29).

Eleven Questions on Sexual Function
The Eleven Questions on Sexual Function (ESF) questionnaire is developed by the National Institute for Social Sexual Research (Rutgers Nisso Group, Utrecht, The Netherlands), with the Department of Sexuology of the LUMC. It measures sexual experience during the previous 30 days using 11 questions. For all patients, 3 parameters are

calculated out of 8 questions: Sexual fantasies, libido and general sexual satisfaction. For patients with partners, 3 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 indicating a higher degree of satisfaction**.**

Endocrine parameters

All blood samples were taken between 08.00 and 10.00 A.M., before regular medication and study drugs were taken, with the exception of cortisol replacement therapy.

Study parameters were serum measurements of IGF-I, IGF-BP3, DHEA, DHEA-S, testosterone, estradiol, estrone, SHBG, serum lipids, HBA1C, and insulin. These measurements were performed at baseline and at the end of each study period. All blood samples were stored immediately at –80^{o}C until measurement. Other study parameters were anthropomorphic measurements (weight, BMI, waist-hip ratio).

Safety parameters

A general health questionnaire was done before the study. Laboratory safety parameters were serum levels of sodium, potassium, ALAT, ASAT, ãGT, AF and creatinin. Weight, heart rate and blood-pressure were recorded at every visit.

Laboratory Assays

All analyses of each subject were analyzed in the same run. Total serum IGF-I concentration was measured by ILMA after dissociation and blocking of the IGF-binding proteins with IGF-II (Nichols Advantage, Nichols Institute Diagnostics, San Clemente, CA, USA). Detection limit was 0.12 ng/ml (0.9 nmol/L). The intra-assay coefficient of variation (CV) was 4.4-5.2% and the inter-assay CV was 5.7-7.4%. Plasma IGF-BP3 concentration was measured by RIA (Nichols Institute Diagnostics, San Clemente, CA, USA). The inter-assay CV was below 6.8 % at the concentrations measured in the present study. The limit of detection was 0.0625 mg/L (2.8 nmol/l). Normal values range form 46 to 122

nmol/l in subjects aged 30-50 years, and 49-112 nmol/l for subjects between 50-70 years. GH concentrations were measured with a sensitive time-resolved fluoro-immunoassay (Wallac, Turku, Finland), specific for the 22-kDa GH. The standard was recombinant human GH (Genotropin, KabiVitrium, Uppsala, Sweden), which was calibrated against the WHO First International Reference Preparation 80/505. To convert mU/L to µg/L, 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/L. The intra-assay CV ranged from 1.6 to 8.4 % in the assay range between 0.26-47 mU/L, with corresponding inter-assay CV of 2.0–9.9 %. DHEA was measured by RIA after extraction (DHEA-kit, DPC, Bad-Nauheim, Germany). The detection limit was 0.012 ug/L (0.04 nmol/L), the intra-assay CV was 5.2-10.8 %, and the inter-assay CV 5.9-11.7 %. DHEA-sulphate (DHEAS) was measured by ILMA (Immulite DPC, Los Angeles, Ca USA). The detection limit was 148 ug/L (0.4 ìmol/L), the intra-assay CV 7.0-9.5 %, the inter-asay variation 8-15 %. Androstenedione was measured by RIA (SL, Sinsheim, Germany), with a detection limit 0.02 ng/ml (0.07 nmol/L), an intra-assay CV of 2.7-6.3 %, and an inter-assay CV of 9.3-11.7 %. Total testosterone was measured by RIA (DPC, Los Angeles, Ca USA) with a detection limit of 0.08 ng/ml (0.2 nmol/l), and an intra- and interassay CV of 10-19 %. Estrone was measured using RIA (DSL, Veghel, The Netherlands), with a detection limit of 1,1 pg/ml (40 pmol/L), an intra-assay CV of 4.4-9.4%, and an inter-assay CV of 5-17 %. SHBG was measured with ILMA (Immulite, DPC, Bad-Nauheim, Germany) with a detection limit of 0.34 mg/L (4.0 nmol/L), an intra-assay CV of 4.1-7.7 % and an inter-assay CV of 4-20 %. Estradiol was determined with the Elecsys E170 (Roche Diagnostic Systems, Basle, Switzerland), detection limit 1,36 pg/ml (5 pmol/l), with an intra assay CV of 1.6-2.0 % and an inter-assay CV of 1.6-2.7 %. HBA1C was measured with the BioRad Variant method (BioRad Laboratories, Veenendaal, the Netherlands) with a detection limit of 3,6%, an intra-assay CV of 1% and an inter-assay CV of 1-2%. Serum insulin was measured by IRMA (BioSource, Etten-Leur, The Netherlands) with a detection limit of 0.1 mU/L (0.6 pmol/L), an intra-assay CV of 2.1-4.5% and an inter-assay CV of 3.1-4.3%.

A Hitachi 747 autoanalyzer (Roche Diagnostics, Mannheim, Germany) was used to quantify serum concentrations of total-cholesterol and triglycerides with enzymatic tests (all from Roche Diagnostics). High density lipoprotein (HDL) cholesterol was measured with a homogenous enzymatic assay (Hitachi 911, Roche Diagnostics). LDL-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 of Arlt et al (11). In this study, a pooled standard deviation of changes in IGF-I of 11% was found. It was calculated that with 2 groups of 15 patients, a rise in IGF-I of 12% could be detected with 80% power and alpha of 0.05. When no carry-over effect would be present, a minimal IGF-I rise of even 8% could be detected.

Data were analysed on a per protocol base. Treatment effects were analysed using univariate analysis of variance (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 carry-over and time effects. The tests for carry-over and time effects followed the procedures described by Hills and Armitage (30). Carry-over and time effects were also tested. If no time or carry over effects were detected, data from both study periods were combined. Categorical data were analysed with the Chi-square test. Data are presented as mean ± SEM. SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL) was used for analysing and a p value of 0.05 was considered to be significant.

Table 2. Baseline characteristics of 31 patients who were treated with 50 mg/day DHEA during 16 weeks or placebo in a randomised cross-over design with 8-weeks 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 m –17 years)
Dose of GH therapy (mg/day)	
Men	0.41 ± 0.03
Women	0.45 ± 0.04
Cause of pituitary deficiency	
Non-functional 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-Thyroxin	30
Cortisol	31
Estrogen/testosterone	0/15(only men)

Results

Clinical characteristics

Thirty-four patients were recruited, 17 women, and 17 men (Figure 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 non-endocrine pituitary adenoma, documented by MRI 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 death cause could not be verified as no autopsy was performed. Data from these 2 patients were not included in the analyses of the data (see Figure 1). Thirty-one patients (16 women, 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 did not receive estrogen replacement therapy. All men used transdermal testosterone replacement therapy. All patients had GH deficiency that had been treated for a mean period of 5.2 ± 0.6 years. 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. Women scored significantly worse than age and sex-matched controls in 7 out of 15 tested parameters, whereas men scored worse in 3 out 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). Both in men and women, social functioning (SF-36) and activity level (MFI-20) were worse than in controls.

Quality of life: Effects of DHEA versus placebo

The effects of DHEA on the outcome of the quality of life questionnaires in female and male patients are given separately in Table 4. There were

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

	Women			**Men**		
	Controls	*Patients*	*P value vs. Controls*	*Controls*	*Patients*	*P value Vs. Controls*
Number	32	16		30	15	
Age (years)	61.2 ± 1.3	61.1 ± 1.7	P=0.940	53.1 ± 2.5	52.1 ± 3.3	0.800
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 expressed as mean ± SEM
HADS: Hospital anxiety and depression scale
SF-36: Short Form (SF)-36
MFI-20 : Multidimensional Fatigue Inventory-20

Table 4. Quality of life parameters in 31 patients with substituted ACTH and GH deficiencies after 16 weeks treatment with 50 mg/day DHEA or placebo

	Women			**Men**		
	Placebo	*DHEA*	*P value vs. placebo*	*Placebo*	*DHEA*	*P value vs. placebo*
Questionnaire						
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	N=10			N=9		
Problems erection/lubrication	1.60 ± 2.60	2.47 ± 0.36	0.085	1.78 ± 0.28	1.67 ± 0.29	0.347
Problems 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 mean ± SEM

QOL-AGHDA: QOL-assessment of GH deficiency in adults
HADS: Hospital anxiety and depression scale
SF-36: Short Form (SF)-36
MFI-20: Multidimensional Fatigue Inventory-20
ESF: Eleven Questions on Sexual Functioning

no carry-over 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.

IGF-I and IGF-BP3 concentrations: effects of DHEA versus placebo
DHEA treatment significantly increased serum IGF-1 levels by ~18 % in female patients, compared to placebo treatment ($p<0.001$, Table 5 and Figure 2). In contrast, in male patients, there was no significant effect of DHEA, compared to placebo, on IGF-I levels (Table 5, Figure 2). DHEA did not influence IGF–BP3 levels in female or in male patients.

Other plasma concentrations: effects of DHEA versus 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 of women reached baseline levels of men.

Other parameters: effects of DHEA versus 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 both groups. There were no differences observed between DHEA *versus* placebo treatment in systolic or diastolic blood pressures, pulse rate or in safety laboratory parameters.

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

	Women			**Men**		
Hormones	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
IGF-BP3 (mg/L)	2.04±0.08	2.24±0.16	0.116	3.03±0.13	3.04±0.1	0.449
DHEA (nmol/L)	1.0±0.5	8.5±0.8	<0.001	0.5±0.1	5.6±0.5	<0.001
DHEA-S (ng/mL)	8.1±1.1	208.6±27.9	<0.001	10.0±2.0	269.7±30.8	<0.001
Androstenedione (nmol/L)	0.3±0.1	1.7±0.2	<0.001	1.2±0.2	1.9±0.2	0.011
Estradiol (pmol/L)	17.4±4.2	32±2.2	0.006	49.1±8.5	46.8±6.3	0.814
Estrone (pmol/L)	22.0±4.2	94.5±9.4	<0.001	55.5±8.1	108.7±11.8	<0.001
Testosterone (nmol/L)	0.2±0.0	0.7±0.1	0.008	14.3±2.9	12.5±1.5	0.526
SHBG (nmol/L)	60.6±6.6	60.7±8.0	0.990	40.0±5.5	35.7±3.8	0.204

Data expressed as mean ± SEM.
Conversion factors (SI to metric): DHEA 0.288 (ug/L), Androstenedione 0.286 (ng/ml), Estradiol 0.272 (pg/ml), Estrone 0.027 (pg/ml), Testosterone 0.288 (ng/ml), SHBG 0.086 (mg/L).

Discussion

The present study was performed to study if 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 improvements occurred only in parameters, that were not different from age- and sex matched controls at baseline.

At present 4 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 of Lovas *et al.* found no significant effects by DHEA on these parameters (31). However, that study was criticized, because of being underpowered (32). They used a parallel group design, which requires a much larger number of patients, compared to the crossover design of the other 3 studies. In addition, Lovas *et al.* used a low dose of DHEA, compared to the other studies and compared to our study.

With respect to the effects of DHEA in secondary adrenal failure, our study can only be compared with the study of Johannsson *et al.* (13). Although 3 other studies also contained patients with secondary adrenal failure, their analyses did not include, or did not permit, separate evaluation of patients with primary *versus* 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.*, we observed only subtle 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

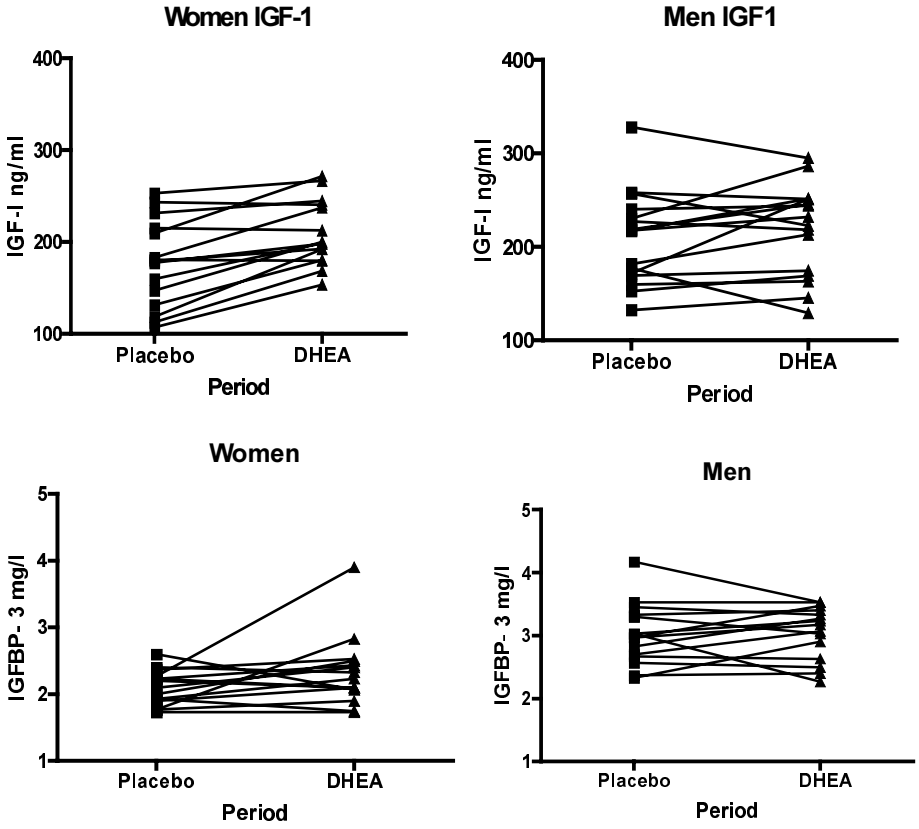
parameters. It can be proposed that the study is underpowered to detect significant changes in quality of life. However, the absolute changes in quality of life scores that were abnormal at baseline were hardly influenced by DHEA. The most severely affected parameter, role limitations due to physical 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 of Arlt *et al.* indicated that treatment with 50 mg of DHEA increased IGF-I slightly only in patients with primary adrenal failure, but not in patients with secondary adrenal failure. These authors suggested, that this differential effect of DHEA on IGF-I in primary *versus* secondary adrenal failure may be due to a GH mediated effect (11;33). In the present study we controlled for an effect of GH, by including only patients with GH deficiency on a fixed dose of rhGH during the whole 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, independently 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

Figure 2 Serum levels of IGF-I and IGF-BP3 in 31 patients at the end of 16-weeks therapy with 50 mg/day DHEA or placebo.



in our study effects of DHEA were found on IGF-I in estrogen deplete women, whereas this effect was not found in the study of 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 to a positive effect of DHEA in other studies. In healthy subjects, and in patients primary and secondary adrenal failure, positive effects of DHEA are 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, but not in testosterone treated males, with secondary adrenal insufficiency.

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