CLINICAL STUDY

Long-term DHEA substitution in female adrenocortical failure, body composition, muscle function, and bone metabolism: a randomized trial

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Abstract

Context: Adrenal derived androgens are low in women with adrenal failure. The physiological consequences of substitution therapy are uncertain.

Objective: To investigate the effects of DHEA substitution in women with adrenal failure on body composition, fuel metabolism, and inflammatory markers.

Design, participants and intervention: In this study, ten female patients (median age 38.5 years, range 28–52) with adrenal failure were treated with DHEA 50 mg for 6 months in a double-blind, randomized, placebo-controlled, and crossover study. The participants underwent dual-energy X-ray absorptiometry (DXA) scan, computed tomography scan of abdominal fat, indirect calorimetry, bicycle ergometry, muscle and fat biopsies, and blood samples.

Results: Baseline androgens were normalized to fertile range during active treatment. Anthropometric data were unaffected, but lean body mass (LBM) slightly increased compared with placebo (delta LBM (kg) placebo versus DHEA: K0.48 G6.1 vs 1.6 G3.4, P<0.02) with no alterations in total or abdominal fat mass. PTH increased with DHEA, but no significant changes were observed in other bone markers or in bone mineral content. The mRNA levels of markers of tissue inflammation (adiponectin, interleukin 6 (IL6), IL10, monocyte chemoattractant protein 1, and tumor necrosis factor α) in fat and muscle tissue were unaffected by DHEA treatment, as was indirect calorimetry and maximal oxygen uptake. A high proportion of self-reported seborrheic side effects were recorded (60%).

Conclusion: In female adrenal failure, normalization of androgens with DHEA 50 mg for 6 months had no effects on muscle, fat, and bone tissue and on fuel metabolism in this small study. A small increase in LBM was observed. Treatment was associated with a high frequency of side effects.

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Introduction

The androgen receptor, being a member of the nuclear receptor superfamily, is responsible for mediating development of primary and secondary sex characteristics during fetal life, childhood, and puberty and for maintaining these features during adult life. The beneficial impact of endogenous testosterone as well as testosterone replacement in hypogonadal males on maintenance of bone (1, 2), muscle mass (2, 3), body fat distribution, and quality of life (4) is well documented. Cessation of androgen secretion in the adult female is observed in adrenal insufficiency where adrenal androgen precursor production is blunted or almost absent (5, 6). Substitution therapy with an oral dose of 50 mg of the adrenal androgen DHEA is followed by normalization of the spectrum of circulating androgens including testosterone (7–9). Questionnaires in controlled clinical trials have shown some (9–12) or no (13–15) effects on quality of life, and a high proportion of self-reported skin related side effects (9–11, 13, 14). Substantial physiological alterations upon androgen substitution with DHEA in female adrenocortical failure are still controversial and probably obscured by the associated hormone deficiencies (i.e. hypocortisolism with or without other aspects of hypopituitarism), and it remains to be determined whether DHEA has any effect on muscle and fat distribution.

Therefore, we evaluated the influence of DHEA substitution in female adrenal failure on muscle, fat, and bone tissue as well as on indicators of fuel metabolism.

We undertook biopsies on both fat and muscle, which were analyzed for expression of enzymes and proteins known to be involved in hormonal and inflammatory processes.
pathways, and determined muscle and fat distribution by dual-energy X-ray absorptiometry (DXA) scan and abdominal computed tomography (CT) scan. A daily dose of 50 mg DHEA was administered for 6 months in a crossover, randomized and placebo-controlled trial.

**Subjects and methods**

In this study, ten females with adrenocortical failure were included. Exclusion criteria were lactation and pregnancy, neoplastic, thromboembolic, and cardiovascular diseases and diabetes mellitus. Two participants discontinued the study because of seborrhoeic side effects and anxiety. The examined study group (Addison’s disease, n = 6; monotrope ACTH deficiency, n = 2) had a median age of 38.5 years (range 28–52). All were on stable hydrocortisone (20–40 mg/day) and fludrocortisone (0–0.2 mg/day) treatment. One of two postmenopausal patients was treated with vaginal 17β-estradiol (E2; vaginal capsules, E2 25 μg). Naturally menstruating patients used contraceptives (four intra uterine devices and two combined oral contraceptives). Other concomitant medication included thyroid hormones (one patient) and calcium and vitamin D (two patients). None of the participants were previously treated with DHEA or androgens. Studies were performed during the early follicular phase (days 5–10) of regular cycle or in the corresponding phase of a tablet cycle. The protocol was approved by the Aarhus County ethics scientific committee (no. 2001 0130). All participants gave informed oral and written consent. The clinical trial was registered at ClinicalTrials.gov (NCT00471900). Cardiovascular data from this study have previously been published (16).

**Study protocol**

The patients were treated for 6 months with a daily morning dose of DHEA (50 mg) or placebo in a double-blind, randomized, placebo-controlled, and crossover design study. Blinding and randomization was performed by the Hospital Pharmacy in blocks of 5. Everybody else was blinded to this procedure until the next exami-

**capsules in the European Pharmacopoeia. That means uniformity of capsule content, uniformity of capsule mass and disintegration of capsules. According to the analysis certificate the results are assay 101.5% (95–105%), mean weight variation 410.4 ± 3.6 mg (401–419 mg), and disintegration 3 min (< 15 min). Figures in parenthesis indicate the requirements of the law. Physical examination consisted of anthropometrics, muscle strength, ergometry, indirect calorimetry, and CT scan of abdominal fat distribution. Blood samples included routine biochemistry, bone markers, sex hormones, and regulatory hormones. This program was performed in similar sequence before and at the end of each treatment period. Muscle and fat biopsy and DEXA scan were done at the end of each study period. At baseline (t = 120–150 min), percutaneous muscle biop-

**Determination of adipokine mRNA levels**

In the fat tissue biopsies, mRNA expression of adiponectin, interleukin 6 (IL6), IL10, tumor necrosis factor α (TNFα), monocyte chemoattractant protein 1 (MCP1 or CCL2), and 11β-HSD (HSD11B1) were assessed. In accordance with tissue specificity only mRNA expression of IL6, TNFα, and MCP1 were assessed in the muscle tissue biopsies.

For mRNA determination the following oligonucleotide primer pairs were used: adiponectin, 5'-CATGACCAGGAAACCAGACT-3' and 5'-TGAATGCTGACCGGTAT-3'; IL6, 5'-AAATGCAGTTGCTGACGAAG-3' and 5'-AAC-AACAATCGAGGTGCCCATGC-3'; IL10, 5'-ATGGAGAGGT-TAGTGTCA-3' and 5'-CTCGCTTAA-TTGCATGTATGCT-3'; TNFα, 5'-CTGGTCACTGCTGACCA-3' and 5'-GATTCTTGGG-CTG-3'; MCP1, 5'-CAATCAATGCCCACTCAC-3' and 5'-GACTTTTGGGTTGAGTTG-3'; 11β-HSD, 5'-GACATAGACCTCTG-3' and 5'-GAGGGCAGAAAAAGGAGG-3'; β-actin, 5'-ACGGGGTGCACCACACTGTC-3' and 5'-CTGAGAGACACATTTTGG-3'. RNA was isolated from ~250 mg of adipose tissue using the Trizol Reagent (Invitrogen). RNA was quantified by measuring absorbance at 260 and 280 nm. The integrity of the RNA was examined by visual inspection of the two ribosomal RNAs, 18S and 28S, on an agarose gel. RNA was reversely transcribed with RT
and random hexamer primers at 23 °C for 10 min, 42 °C for 60 min, and 95 °C for 10 min according to the manufacturer’s instructions (GeneAmp RNA PCR kit, PerkinElmer Life and Analytical Sciences, Boston, MA, USA). Then 2 μl of each RT reaction was amplified in PCR mastermix containing the specific primers. Hot Star Taq DNA polymerase, and SYBR-Green PCR buffer. All samples were determined as duplicates. Real-time quantification of target gene (adiponectin, IL6, IL10, TNFa, MCP1, and 11β-HSD) relative to housekeeping gene (β-actin) was performed by a SYBR-Green real-time PCR assay and an iCycler PCR machine (Bio-Rad). In brief, samples were incubated in separate tubes for initial denaturation at 95 °C for 10 min, followed by 40 PCR amplification cycles. Each cycle consisted of 30 s at 95 °C, 30 s at 57 °C, and extension for 60 s at 74 °C. During final extension increasing fluorescence was measured in real time. Data were obtained as threshold cycle values (Ct, the cycle number at which fluorescence reached ten times the s.d. of the background fluorescence). Relative gene expression of target gene to β-actin was calculated as described in the User Bulletin No. 2, 1997 from PerkinElmer Life and Analytical Sciences (PerkinElmer Cetus, Norwalk, CT, USA).

**DXA and CT scans**

Bone mineral content (BMC) (g) and area-adjusted bone mineral density (aBMD) (g/cm²) were measured at the lumbar spine (L2–L4), the hip (femoral neck and trochanteric region), and the nondominant forearm (ultradistal and proximal part of distal third) by DXA on Hologic 1000/w or 2000/w osteodensitometers (Hologic, Inc., Waltham, MA, USA). Cross-calibration was ensured through the use of double measurements and a phantom. Precision for BMD was 1.5% for the lumbar spine, 2.1% for the femoral neck, and 1.9% for the ultradistal forearm. These quantities included crossover calibration, change in hardware, change in technicians, and long-term stability (<0.2%/year). The amounts of intra abdominal (visceral) and subcutaneous fat, as well as total abdominal area was determined by CT with a Somatom Plus-S scanner. The subjects were studied in the supine position. The area scanned comprised of a 10 mm cross-sectional slice at the umbilicus, using 120 kV and 330 mA. The same technician performed all the scans, which subsequently were analyzed blind by the same radiologist.

**Indirect calorimetry, muscle strength, and maximal oxygen uptake**

Indirect calorimetry (Deltatrac metabolic monitor; Datex, Helsinki, Finland) was performed for 30 min in basal state. The initial 5 min were used for acclimatization, and calculations of respiratory exchange ratio and resting energy expenditure (EE) were based on mean values of 25 measurements of 1 min each. Similarly, rates of protein, lipid and glucose oxidation were estimated after correction for urinary excretion of urea (17). Maximal oxygen consumption (VO2 max) test was performed on a bicycle ergometer by a standardized protocol. The initial workload was increased with 10 W every 30 s until exhaustion. Breath-by-breath gas exchange analysis was performed and VO2 max was determined as the highest O2 consumption achieved during exercise with a calorimeter (Jaeger Oxycon Delta, Erich Jaeger, Hoechberg, Germany), and VO2 max was calculated. The isometric strength of the right biceps brachialis and quadriceps muscles was assessed by means of a dynamometer (Good strength, Metitur Ltd, Jyväskylä, Finland), which electronically measures the isometric muscle functions in the upper and lower limbs. The strength was calculated as the mean of three voluntary maximum isometric contractions separated by 1 min intervals.

**Assays**

We measured DHEAS, α-4-androstendione, testosterone, dihydrotestosterone (DHT), and E2 by an in-house RIA after extraction and subsequent celite chromatography (18). We estimated free testosterone (fT) by a method described by Bartsch (19), based on measurement of sex hormone-binding globulin (SHBG), total testosterone, and DHT, using the law of mass action, the binding constant of testosterone and DHT to SHBG, and including a calculation of testosterone binding to albumin (assuming a constant association constant to albumin). In this system binding to cortisol-binding globulin is thought to be negligible. We analyzed SHBG by double-monoclonal immunofluorometric assay (AutoDelfia, Wallac, OY, Finland); intra- and inter-assay coefficient of variation (CV) was 7.5 and 5.2% respectively. Our inter- and intra-assay CV were as follows: SHBG, 7.5 and 5.2%; testosterone, 13.8 and 8.2%; fT, 6.4 and 4.7%; DHT, 11.0 and 9.1%; α-4-androstendione, 11.4 and 9.4%; DHEAS, 11.5 and 8.5%; E2, 10.5 and 7.4%. Plasma intact PTH was measured by a chemiluminescence assay using an automated instrument (Immulite, DPC, Los Angeles, CA, USA). Urine N-terminal cross-linking telopeptide of type I collagen (NTX) was measured by an immunometric assay using a Vitros ECI analyzer (Ortho Clinical Products, Amersham Pharmacia Biotech). This assay uses MAbs against human NTX (20). Plasma osteocalcin (total OC) was measured using the N-Mid-OC assay on an automated analyzer (Elecsys 2010 analyzer, Roche Diagnostics) with antibodies that determine both intact OC and the large N-Mid-terminal fragment. The CVtotal was 4–7% for the various automated assays. Plasma bone-specific alkaline phosphatase (bone ALP) was measured after lectin precipitation using a Hitachi 917 automated analyzer (Roche Diagnostics) (21). This assay was performed with a CVtotal of 8%. Plasma concentrations of procollagen I
Table 1  Serum values (median, range) of androgens and androgen precursor metabolites in female adrenocortical failure before and after 6 months treatment with 50 mg DHEA or placebo.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>DHEA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal range</td>
<td>Start</td>
<td>End</td>
</tr>
<tr>
<td></td>
<td>(fertile)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHEA (nmol/l)</td>
<td>3.8–15.9</td>
<td>1.74 (1.57–2.59)</td>
<td>2.25 (1.3–9.2)</td>
</tr>
<tr>
<td>DHEAS (nmol/l)</td>
<td>1200–9500</td>
<td>99 (99–240)</td>
<td>99 (99–210)</td>
</tr>
<tr>
<td>Androstenedione (nmol/l)</td>
<td>2.4–8.9</td>
<td>1.9 (0.27–3.91)</td>
<td>2.1 (0.21–3.75)</td>
</tr>
<tr>
<td>DHT (nmol/l)</td>
<td>0.25–1.2</td>
<td>0.31 (0.09–0.45)</td>
<td>0.27 (0.09–0.35)</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>0.55–1.8</td>
<td>0.55 (0.2–0.71)</td>
<td>0.52 (0.18–0.96)</td>
</tr>
<tr>
<td>Free testosterone (nmol/l)</td>
<td>0.006–0.034</td>
<td>0.01 (0–0.01)</td>
<td>0.01 (0–0.01)</td>
</tr>
<tr>
<td>E2 (pmol/l)</td>
<td>&lt;40–400</td>
<td>155 (39–540)</td>
<td>195 (39–1100)</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>41–170</td>
<td>88 (27–114)</td>
<td>96 (37–156)</td>
</tr>
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</table>

N-terminal propeptide (PINP) (22), procollagen III N-terminal propeptide (PIIINP) (23), and C-terminal cross-linking telopeptide of type I collagen (ICTP) (24) were determined by commercial RIA kits (Orion Diagnostica, Espoo, Finland). Intra- and inter-assay CV of 5 and 7% respectively, were observed. As indices of the IGF axis, serum IGF1 and IGF2 were measured by noncompetitive time-resolved immunofluorometric assays (TR-IFMA) (25), serum IGFBP2 was measured by an immunoradiometric assay (Diagnostics Systems Laboratories, Inc., Webster, TX, USA). Insulin was determined by a commercial ELISA (Dako, Glostrup, Denmark). Leptin was determined by a commercial RIA (Linco, St Louis, MO, USA). Cortisol was measured by an automated chemiluminescence system (Chiron Diagnostics, Fernwald, Germany). Free fatty acids (FFAs) were determined by a colorimetric method using a commercial kit (Wako Chemicals, Neuss, Germany). Total concentrations of thyroxine (T₄) and tri-iodothyronine (T₃) were measured in serum as described previously (26), whereas TSH was measured in a solid-phase, two-site chemiluminescent enzyme immunometric assay (Immulite; Diagnostic Products Corp., Los Angeles, CA, USA). We measured serum total adiponectin by a novel in-house TR-IFMA. Urea excretion in urine was determined by an indophenol method and serum urea by a commercial kit (COBAS INTEGRA; Roche).

**Safety parameters**

Standard blood count, liver enzymes, electrolytes, and renal parameters were measured four times during each treatment period and analyzed with routine methods in hospital central laboratory. There were no significant changes and no remarkable alterations.

**Statistical analysis**

All statistical calculations were carried out using SPSS for Windows version 13.0 (SPSS, Inc., Chicago, IL, USA). Data were examined by Student’s two-tailed unpaired t-test or the Mann–Whitney U test, where appropriate. All data were tested for period as well as carryover effects, which did not affect the level of significance. Analysis was done on delta values (end period value ‘minus’ start period value). P < 0.05 was considered statistically significant.

**Results**

Levels of DHEA, DHEAS, α-4-androstendione, testosterone, and FT rose significantly to medium normal fertile range during active treatment compared with baseline. No significant alterations were detected in E₂ and SHBG values (Table 1).

Anthropometric data (weight (kg) 71.3 ± 4.3; BMI (kg/m²) 25.7 ± 1.7; waist–hip ratio 0.81 ± 0.01) did not change significantly during the treatment period. Lean body mass (LBM) increased during active treatment (delta LBM (kg) placebo versus DHEA: −0.48 ± 6.1 vs 1.6 ± 3.4, P = 0.02). There was no change in total fat mass (delta TFM (kg), placebo versus DHEA: −1.2 ± 0.6 vs 0.6 ± 0.9, P = 0.1). We observed no change in abdominal fat distribution measured by CT scan in total abdominal area, subcutaneous fat area or intra-abdominal fat area (Fig. 1).

EE and estimated oxidation rates of glucose (P = 0.4), lipid (P = 0.6), and protein (P = 0.6), as well as the respiratory quotient did not change during the study (Fig. 2). No changes were observed in thyroid hormones.

![Figure 1](https://www.eje-online.org)
DHEA treatment and substituted cortisol levels were (Table 2). Insulin levels did not respond differently to IGF1, IGF2, IGFBP3, GHPB, FFAs, leptin or adiponectin 6 months treatment with 50 mg DHEA/placebo.

Indirect calorimetry in female adrenocortical failure before and after glucose (black), lipid (bright), and protein (gray) oxidation from Figure 2

Placebo DHEA

Start End Start End

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Placebo</th>
<th>DHEA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (nmol/l)</td>
<td>640±77</td>
<td>463±142</td>
<td>0.3</td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>97±45</td>
<td>81±16</td>
<td>0.7</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>17.0±2.2</td>
<td>13.5±2.1</td>
<td>0.2</td>
</tr>
<tr>
<td>T₃ (nmol/l)</td>
<td>1.7±0.1</td>
<td>1.5±0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>T₄ (nmol/l)</td>
<td>93±6</td>
<td>89±7</td>
<td>0.6</td>
</tr>
<tr>
<td>TSH (μU/ml)</td>
<td>2.0±0.6</td>
<td>2.3±0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>GHBP (nmol/l)</td>
<td>2.4±0.2</td>
<td>2.7±0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>IGF1 (μg/l)</td>
<td>212±26</td>
<td>201±17</td>
<td>0.5</td>
</tr>
<tr>
<td>IGF2 (μg/l)</td>
<td>796±50</td>
<td>800±46</td>
<td>0.1</td>
</tr>
<tr>
<td>IGFBP3 (μg/l)</td>
<td>4853±261</td>
<td>4986±320</td>
<td>0.7</td>
</tr>
<tr>
<td>FFA (nmol/l)</td>
<td>0.38±0.05</td>
<td>0.40±0.10</td>
<td>0.2</td>
</tr>
<tr>
<td>Adiponectin (mg/l)</td>
<td>14.9±2.3</td>
<td>14.0±2.4</td>
<td>0.9</td>
</tr>
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</table>

Table 2 Serum values (mean ± S.E.M.) of hormones, fat tissue markers and free fatty acids in female adrenocortical failure before and after 6 months treatment with 50 mg DHEA or placebo.

**Discussion**

In this randomized placebo-controlled trial, 6 months of DHEA substitution in women with adrenocortical insufficiency was associated with a complete biochemical normalization of circulating androgen levels. The only significant effect was a small gain in LBM of 1.6 kg. This occurred without concomitant changes in body weight or fat mass. All other examined variables were essentially unchanged including both subcutaneous and intra-abdominal fat mass determined by CT scan, and we found no alterations in fuel metabolism or in the expression of mRNA of a host of inflammatory markers.

DHEA is regarded an androgen precursor with no affinity for the androgen receptor but with in vitro effects on several membrane-associated receptors (27), including direct binding to estrogen receptors in the growth plate (28). The downstream conversion of DHEA to testosterone and DHT, as well as aromatization to estrogen, may take place inside target cells. A local degradation of the receptor-bound hormone would then
obscure a sex hormone action from serological detection, hence the term ‘intracrinology’ has been introduced (29). Effects of DHEA treatment in adrenocortical failure beyond 12 months have not been evaluated, and in agreement with our findings 1 year of DHEA treatment increased total LBM by 1.8%, with the increase being observed in females only (14). In the same study an increase in BMD at the femoral neck was observed only in DHEA treated patients. On the contrary, no significant alterations were observed on DXA scans of body composition and BMD in 39 male and female patients after 3 months (10) and in 38 female hypopituitary women after 6 months (11). Like in this study, no changes in circulating bone markers have been reported in either mixed female and male populations (10) or in female patients only (11, 13, 30). In this study, we also evaluated muscle function, determined as muscle strength, and found absolutely no change in this measure, and likewise we did not detect any change in maximal oxygen uptake, another measure which reflects the size of the muscle mass.

In spite of some evidence of minor LBM accumulation in response to DHEA substitution, we (31) and others (32) have not found any alterations in forearm and whole body amino acid turnover in short-term trials (1 and 2 weeks). In accordance with our previous short-term study on GH secretory patterns (8), we did not find any augmentation of GH derived growth factors or their binding proteins. Slightly stimulated IGF1 levels are reported in some (9, 14, 15) but not all studies (8, 12, 13, 33). In a 3 months study with DHEA or placebo treatment (50 mg) to a group of middle aged female Addison patients insulin sensitivity increased (33), while others found unchanged insulin sensitivity (11, 31). In this study, we did not find any evidence of altered fuel metabolism by indirect calorimetry or any changes in pertinent hormones and metabolites. As expected, the surrogate markers of adipose tissue mass, adiponectin and leptin, were unaffected by DHEA treatment. In line with these findings, mRNA expression of specific inflammatory markers in both fat tissue and skeletal muscle remained unchanged. We did find a slight increase in LBM, but without concomitant changes in any other parameters as mentioned above. However, LBM and other DXA-derived measures are determined with a precision of about 2%. The observed difference in LBM could not be replicated in relation to body weight (determined with a precision (or imprecision) of up to 3 kg (about 5%)), or supported by any other measures of body composition, anthropometrics, serum samples or fat and muscle samples, why we rather consider it a chance finding.

We detected a high proportion (60%) of self-reported side effects during active treatment. All reports related
to skin problems and probably reflect stimulation of the pilosebaceous unit. Our findings are consistent with the frequency reported in previous trials (9–14) and it may be concluded that the skin is the most DHEA sensitive organ. However, attempts to evaluate this phenomenon by sebutape (14) and body hair score (11) have failed. The design of the present pilot study, however, has limitations. Only eight patients completed the trial, which introduces a risk for a type 2 error. It is also possible that longer term duration of treatment would show (positive) changes in body composition, although we doubt this, due to the almost complete absence of positive effects after 6 months treatment. In addition, the expected effect size of the measured variables may also preclude definite conclusions. However, under similar conditions using small study samples, significant effects on body composition has been found. For instance, using the same methodology in our own laboratory, we observed profound changes in body composition in females with Turner syndrome (n = 12) treated with GH or placebo after only 2 months of treatment (34). In addition, a study of postmenopausal women treated with a weak androgen (nandrolone) ten females increased their muscle mass and decreased fat mass in comparison with ten females receiving placebo and ten females receiving an antiandrogen (spironolactone) (35). Thus, exclusion of a physiological effect of DHEA may not be possible based on the present data, but we may be able to conclude that we could not find any physiologically relevant effect of DHEA treatment in hypoadrenal women.

In conclusion, the present evaluation of DHEA treatment in female adrenocortical failure does not document convincing anabolic effects and does not contribute to a scientific justification for this treatment modality.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References
