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## DEHYDROEPIANDROSTERONE REPLACEMENT IN WOMEN WITH ADRENAL INSUFFICIENCY

WIEBKE ARLT, M.D., FRANK CALLIES, M.D., JAN CHRISTOPH VAN VLIJMEN, INES KOEHLER, MARTIN REINCKE, M.D., MARTIN BIDLINGMAIER, M.D., DORIS HUEBLER, M.D., MICHAEL OETTEL, PH.D., MICHAEL ERNST, M.S., HEINRICH MARIA SCHULTE, M.D., AND BRUNO ALLOLIO, M.D.

### ABSTRACT

**Background** The physiologic role of dehydroepiandrosterone in humans is still unclear. Adrenal insufficiency leads to a deficiency of dehydroepiandrosterone; we therefore investigated the effects of dehydroepiandrosterone replacement in patients with adrenal insufficiency.

**Methods** In a double-blind study, 24 women with adrenal insufficiency received in random order 50 mg of dehydroepiandrosterone orally each morning for four months and placebo daily for four months, with a one-month washout period. We measured serum steroid hormones, insulin-like growth factor I, lipids, and sex hormone-binding globulin, and we evaluated well-being and sexuality with the use of validated psychological questionnaires and visual-analogue scales, respectively. The women were assessed before treatment, after one and four months of treatment with dehydroepiandrosterone, after one and four months of placebo, and one month after the end of the second treatment period.

**Results** Treatment with dehydroepiandrosterone raised the initially low serum concentrations of dehydroepiandrosterone, dehydroepiandrosterone sulfate, androstenedione, and testosterone into the normal range; serum concentrations of sex hormone-binding globulin, total cholesterol, and high-density lipoprotein cholesterol decreased significantly. Dehydroepiandrosterone significantly improved overall well-being as well as scores for depression and anxiety. For the global severity index, the mean ( $\pm$ SD) change from base line was  $-0.18 \pm 0.29$  after four months of dehydroepiandrosterone therapy, as compared with  $0.03 \pm 0.29$  after four months of placebo ( $P=0.02$ ). As compared with placebo, dehydroepiandrosterone significantly increased the frequency of sexual thoughts ( $P=0.006$ ), sexual interest ( $P=0.002$ ), and satisfaction with both mental and physical aspects of sexuality ( $P=0.009$  and  $P=0.02$ , respectively).

**Conclusions** Dehydroepiandrosterone improves well-being and sexuality in women with adrenal insufficiency. (N Engl J Med 1999;341:1013-20.)

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**H**UMANS and some other primates are unique in having adrenal glands that secrete large amounts of dehydroepiandrosterone and its sulfate ester.<sup>1</sup> In normal subjects there is an age-related decline in dehydroepiandrosterone secretion,<sup>2-4</sup> but whether this represents a harmful hormone deficiency or a beneficial age-related hormonal adaptation is not known. Administration of dehydroepiandrosterone to normal elderly men and women has been reported to increase bone density, muscle strength, the sense of well-being, and serum concentrations of insulin-like growth factor I (IGF-I).<sup>5-11</sup> However, well-being was not assessed with the use of validated questionnaires, and most studies were open label, so that a placebo effect could not be ruled out.

We hypothesized that the biologic role of dehydroepiandrosterone might best be evaluated in patients with adrenal insufficiency who had premature cessation of dehydroepiandrosterone secretion. In previous studies, we and others have found that a dose of 50 mg of dehydroepiandrosterone given orally once daily is appropriate for women with adrenal insufficiency.<sup>12,13</sup> Therefore, we used validated questionnaires to investigate the effect of this dose of dehydroepiandrosterone on well-being and sexuality in a group of women with adrenal insufficiency.

### METHODS

#### Patients

We studied 24 women who had had adrenal insufficiency for a mean ( $\pm$ SD) of  $9 \pm 2$  years (range, 2 to 37) and whose mean age was  $42 \pm 9$  years (range, 23 to 59). Fourteen of the women had

From the Department of Endocrinology, Medical University Hospital, Wuerzburg (W.A., F.C., J.C.V., I.K., M.R., B.A.); Medical University Hospital Innenstadt, Munich (M.B.); Jenapharm, Jena (D.H., M.O., M.E.); and the Institute for Hormone and Fertility Research, Hamburg (H.M.S.) — all in Germany. Address reprint requests to Dr. Arlt at the Department of Endocrinology, Medical University Hospital, Josef-Schneider Str. 2, 97080 Wuerzburg, Germany, or at w.arlt@medizin.uni-wuerzburg.de.

primary adrenal insufficiency (mean age,  $47 \pm 8$  years): 11 from autoimmune adrenalitis and 3 as a result of bilateral adrenalectomy. The other 10 had secondary adrenal insufficiency (mean age,  $36 \pm 7$  years): 6 as a result of pituitary surgery, 3 from Sheehan's syndrome, and 1 from autoimmune hypophysitis. The mean body-mass index (the weight in kilograms divided by the square of the height in meters) was  $23.4 \pm 4.0$  (range, 17.8 to 31.4). All 24 women had been taking a constant dose of glucocorticoid, and 14 had been taking a constant dose of mineralocorticoid for at least three months. Seven women were postmenopausal, 3 had primary hypogonadism, and 7 had secondary hypogonadism; 13 of these 17 women were receiving hormone-replacement therapy with estrogen-progestin. The women were otherwise healthy. The results of physical examinations and routine laboratory tests at the time of enrollment were normal, except that four women had slight elevations in serum aminotransferase concentrations. The study protocol was approved by the Ethics Committee of the University of Wuerzburg, and all the women gave written informed consent.

### Treatment

The study had a double-blind, placebo-controlled, crossover design with a prearranged randomization schedule. Each woman received in random order 50 mg of dehydroepiandrosterone (Jenapharm, Jena, Germany) orally each morning for four months and placebo for four months. The two treatment periods were separated by a one-month washout period.

### Evaluation

The women were assessed before treatment, after one and four months of dehydroepiandrosterone, after one and four months of placebo, and one month after the end of the second treatment period. The women reported to the ambulatory unit between 9 and 11 a.m. after an overnight fast and having taken their regular morning replacement medications but not the dehydroepiandrosterone or placebo capsule. They underwent a physical examination, and blood samples were obtained. The women were then given a standard breakfast along with the dehydroepiandrosterone or placebo capsule, and the psychological evaluations were performed.

### Measurements

At each visit blood counts and tests of hepatic and renal function were performed, and serum total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, Lp(a) lipoprotein, steroids, and other hormones were measured. Serum hormones were measured by established radioimmunoassays with kits obtained from Diagnostic Systems Laboratories (Sinsheim, Germany) in the case of dehydroepiandrosterone, androstenediol glucuronide, and estrone; Diagnostic Products Corporation (Bad Nauheim, Germany) in the case of dehydroepiandrosterone sulfate, androstenedione, testosterone, and dihydrotestosterone; BioChem ImmunoSystems (Freiburg, Germany) in the case of  $17\beta$ -estradiol; and Biomerieux (Marcy-l'Étoile, France) in the case of sex hormone-binding globulin and IGF-I. Serum IGF-binding protein 3 was measured by an enzyme-linked immunoassay (Diagnostic Systems Laboratories), but the secondary antibody was labeled with biotin; after the addition of streptavidin-europium, fluorescence was measured with a fluorometer (model 1232, Delfia, Wallac, Turku, Finland).

Psychological evaluations were performed at each visit with five validated questionnaires. The revised version of the 90-item Symptom Checklist measures nine psychological dimensions as well as provides a global index of severity.<sup>14,15</sup> The women were asked to respond to statements indicating their state of mind during the preceding seven days, including the day of testing, with one of five answers, ranging from "I completely disagree" or "Not at all" (a score of 0) to "I completely agree" or "Extremely" (a score of 4). The scores for each subscale are summed and divided by the number of items. The global severity index is the sum of all scores divided by the total number of items. Higher scores (maximal, 4.00) indicate poorer well-being.

The Multidimensional Mood Questionnaire consists of 24 items defined according to the degree of unpleasantness (pleasant to unpleasant), sleepiness (awake to sleepy), and restlessness (calm to restless).<sup>16</sup> The women rated the items on a five-step scale ranging from 1 (not at all) to 5 (very much); the subscale scores are the sums of the respective item ratings. Higher scores indicate increased well-being.

The von Zerssen Symptom List consists of two similar questionnaires with 24 items each. Each item is rated on a four-point scale from 0 to 3. The global score (raw value) is calculated from the mean of the two scores. The maximal global score is 72; higher scores indicate poorer well-being.<sup>17</sup> The short form of the Gieszen Complaint List consists of 24 items pertaining to the severity of exhaustion, gastric symptoms, limb pain, and heart symptoms, rated on a five-point scale from 0 to 4. The sum of the four subscale scores yields the global score of discomfort.<sup>18</sup> The higher the score, the greater the impairment of well-being.

The German Version of the Hospital Anxiety and Depression Scale consists of 14 items pertaining to anxiety and depression. Each item is rated on a four-point scale from 0 to 3. The maximal score for each subscale (the subscale for anxiety and the subscale for depression) is 21, with higher scores indicating more severe anxiety or depression.<sup>19,20</sup>

Sexual functioning was measured by four visual-analogue scales that assessed the frequency of sexual thoughts, sexual interest, and satisfaction with the mental and physical aspects of sexual experience. The 100-mm scale used included the words "not at all" or "never" at the 0-mm mark and "very" or "always" at the 100-mm mark. The women placed a mark at the point that best corresponded with their feelings during the preceding seven days. The distance in millimeters from the beginning of the line to the mark was measured and used for statistical analysis.

### Statistical Analysis

The serum measurements and the scores from the questionnaires were compared by analysis of variance for data from two-period, repeated-measurements, crossover designs, as described by Wallenstein and Fisher.<sup>21</sup>

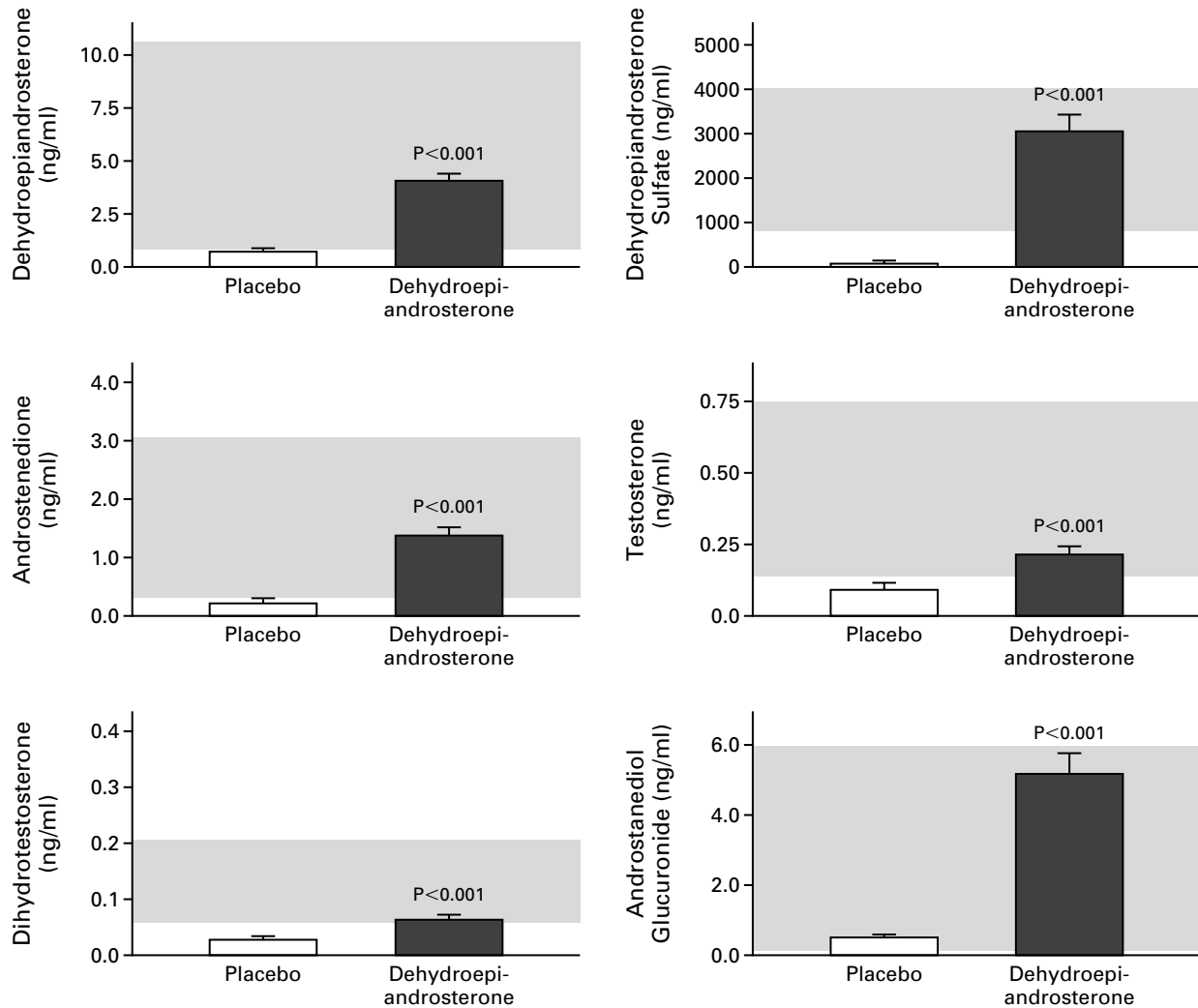
## RESULTS

### Serum Steroid Hormone and Sex Hormone-Binding Globulin Concentrations

At base line, all the women had low serum dehydroepiandrosterone, dehydroepiandrosterone sulfate, and active androgen concentrations. During treatment with dehydroepiandrosterone, serum dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione concentrations increased to the normal range; serum testosterone and dihydrotestosterone concentrations increased to the low-normal range; and serum androstenediol glucuronide concentrations increased to the upper level of the normal range (Fig. 1). Serum estrone and  $17\beta$ -estradiol concentrations did not change significantly during dehydroepiandrosterone treatment. Serum sex hormone-binding globulin concentrations were significantly lower after four months of dehydroepiandrosterone treatment than after four months of placebo ( $1.7 \pm 0.2$  vs.  $2.1 \pm 0.2 \mu\text{g}$  per deciliter [ $59 \pm 8$  vs.  $72 \pm 8$  nmol per liter],  $P = 0.01$ ).

### Serum IGF-I and IGF-Binding Protein 3 Concentrations

Serum IGF-I concentrations increased significantly during treatment with dehydroepiandrosterone: the



**Figure 1.** Mean (+SE) Serum Concentrations of Dehydroepiandrosterone, Dehydroepiandrosterone Sulfate, Androstenedione, Testosterone, Dihydrotestosterone, and Androstenediol Glucuronide after Four Months of Treatment with Dehydroepiandrosterone or Placebo. The stippled areas represent the normal ranges for women, according to the manufacturers of the radioimmunoassay kits. To convert the values for dehydroepiandrosterone to nanomoles per liter, multiply by 3.47; to convert the values for dehydroepiandrosterone sulfate to micromoles per liter, multiply by 0.0027; to convert the values for androstenedione to nanomoles per liter, multiply by 3.49; to convert the values for testosterone to nanomoles per liter, multiply by 3.47; to convert the values for dihydrotestosterone to nanomoles per liter, multiply by 3.47; to convert the values for androstenediol glucuronide to nanomoles per liter, multiply by 2.13.

mean value was  $149 \pm 82$  ng per milliliter ( $19.5 \pm 10.7$  nmol per liter) at base line and  $166 \pm 94$  ng per milliliter ( $21.8 \pm 12.3$  nmol per liter) after four months of treatment ( $P=0.02$ ). Serum IGF-I values increased only in the women with primary adrenal insufficiency ( $P=0.01$  for the comparison with base-line values). The value at four months was similar to that in the placebo group ( $150 \pm 73$  ng per milliliter [ $19.7 \pm 9.6$  nmol per liter],  $P=0.14$ ). Treatment with dehydroepiandrosterone did not affect serum concentrations of IGF-binding protein 3 or the molar ratio of IGF-I to IGF-binding protein 3 in serum.

**Serum Lipid Concentrations**

During treatment with dehydroepiandrosterone, serum total and high-density lipoprotein cholesterol concentrations decreased significantly, as compared with the absolute change from base line in the placebo group, but serum low-density lipoprotein cholesterol, Lp(a) lipoprotein, and triglyceride concentrations did not change significantly (Table 1).

**Well-Being**

Treatment with dehydroepiandrosterone, but not with placebo, resulted in a significant decrease in the

**TABLE 1. SERUM LIPID CONCENTRATIONS BEFORE AND DURING TREATMENT WITH DEHYDROEPIANDROSTERONE OR PLACEBO.\***

VARIABLE	BASE LINE	4 Mo
	milligrams/deciliter	
Total cholesterol		
Placebo	220±40	221±56
DHEA	232±43	210±36†
LDL cholesterol		
Placebo	133±37	125±49
DHEA	135±45	124±32
HDL cholesterol		
Placebo	65±21	70±15
DHEA	74±19	64±19‡
Triglycerides		
Placebo	116±36	131±62
DHEA	114±40	112±40
Lp(a) lipoprotein		
Placebo	29.3±40.6	30.4±41.3
DHEA	22.6±27.8	28.6±30.9

\*Plus-minus values are means ±SD. DHEA denotes dehydroepiandrosterone, LDL low-density lipoprotein, and HDL high-density lipoprotein. To convert the values for cholesterol to millimoles per liter, multiply by 0.026. To convert the values for triglycerides to millimoles per liter, multiply by 0.11. Statistical analysis was carried out by analysis of variance.

†P=0.02 for the comparison with the absolute change from base line in the placebo group. P=0.008 for the comparison with the value at four months in the placebo group.

‡P=0.009 for the comparison with the absolute change from base line in the placebo group. P=0.19 for the comparison with the value at four months in the placebo group.

scores on the revised version of the 90-item Symptom Checklist for depression, anxiety, obsessive-compulsive traits, and hostility, as well as for the global severity index (Table 2). For the global severity index, the mean absolute change from base line was  $-0.18 \pm 0.29$  after four months of dehydroepiandrosterone therapy, as compared with  $0.03 \pm 0.29$  after four months of placebo (P=0.02). The corresponding changes were  $-0.33 \pm 0.43$  and  $0.10 \pm 0.59$  (P=0.02) for the depression score and  $-0.23 \pm 0.59$  and  $0.03 \pm 0.60$  (P=0.01) for the anxiety score. Scores on all three subscales of the Multidimensional Mood Questionnaire also significantly improved after treatment with dehydroepiandrosterone (Table 3).

As compared with placebo, dehydroepiandrosterone treatment also improved the scores on the Hospital Anxiety and Depression Scale for anxiety (P=0.04) and depression (P=0.01) as well as scores on the short form of the Giessen Complaint List subscale for the tendency toward exhaustion (P=0.03). The raw scores for the von Zerssen Symptom List decreased significantly from the base-line value after four months of dehydroepiandrosterone treatment

(P=0.001), but the scores were similar at the end of the dehydroepiandrosterone and placebo periods.

There were no significant differences between women treated with dehydroepiandrosterone and those given placebo in scores on any of the well-being questionnaires after one month of treatment. The base-line scores and changes after four months of dehydroepiandrosterone treatment did not differ significantly between the women with primary and secondary adrenal insufficiency, and the order of treatment had no influence on the changes.

### Sexuality

Treatment with dehydroepiandrosterone resulted in significant increases in the scores of all four visual-analogue scales for sexuality (Table 4). The frequency of sexual thoughts or fantasies and the degree of sexual interest increased significantly after one month of dehydroepiandrosterone treatment, but sexual satisfaction increased only after four months. There was a significant carryover effect of dehydroepiandrosterone treatment with respect to sexual interest (P=0.05).

### Side Effects

Five women reported androgenic side effects (greasy skin, acne, and increased growth of body hair) during treatment with dehydroepiandrosterone. In one woman the dose of dehydroepiandrosterone was reduced to 50 mg every other day because of hair loss, after which the hair loss ceased. By the end of the study, 19 of the 24 women had reported at least some skin-related androgenic effects, most of which were transient and mild. Four women had slightly elevated serum aminotransferase concentrations at base line, which persisted throughout the study. In three other women, serum aminotransferase concentrations were slightly elevated after one month of dehydroepiandrosterone treatment but returned to normal after four months.

## DISCUSSION

We found that dehydroepiandrosterone-replacement therapy resulted in a significant improvement in well-being and sexuality in women with adrenal insufficiency. An increase in the perception of well-being during treatment with dehydroepiandrosterone has previously been reported in normal men and women, but structured psychometric evaluations were not done.<sup>5,9,10</sup> In our study, the greatest improvements during dehydroepiandrosterone treatment occurred in the levels of depression and anxiety and their physical correlates (e.g., a tendency toward exhaustion), a finding that supports previous studies suggesting a neurosteroidal action of dehydroepiandrosterone.<sup>22</sup>

In rodents dehydroepiandrosterone has an anxiolytic effect<sup>23,24</sup> and increases hypothalamic serotonin levels.<sup>25</sup> In vitro dehydroepiandrosterone can act as

**TABLE 2.** SCORES ON THE REVISED VERSION OF THE 90-ITEM SYMPTOM CHECKLIST BEFORE, DURING, AND AFTER TREATMENT WITH DEHYDROEPIANDROSTERONE OR PLACEBO.\*

VARIABLE	BASE LINE	1 Mo	4 Mo	FINAL EXAMINATION	NORMAL RANGE FOR WOMEN†
Somatization				0.71±0.65	0.41±0.31
Placebo	0.61±0.45	0.53±0.43	0.64±0.55		
DHEA	0.70±0.51	0.57±0.53	0.56±0.43		
Obsessive-compulsive traits				0.79±0.79	0.51±0.39
Placebo	0.68±0.42	0.67±0.49	0.67±0.64		
DHEA	0.77±0.70	0.59±0.61	0.52±0.46‡		
Interpersonal sensitivity				0.48±0.53	0.47±0.41
Placebo	0.48±0.42	0.39±0.38	0.38±0.44		
DHEA	0.47±0.42	0.33±0.48	0.34±0.40		
Depression				0.76±0.77	0.49±0.42
Placebo	0.61±0.46	0.54±0.47	0.66±0.74		
DHEA	0.74±0.59	0.52±0.54	0.41±0.37§		
Anxiety				0.53±0.63	0.35±0.35
Placebo	0.48±0.44	0.44±0.46	0.45±0.54		
DHEA	0.58±0.52	0.40±0.54	0.35±0.34¶		
Hostility				0.45±0.52	0.38±0.36
Placebo	0.39±0.42	0.35±0.29	0.45±0.61		
DHEA	0.47±0.54	0.32±0.35	0.30±0.34		
Phobic anxiety				0.28±0.37	0.17±0.26
Placebo	0.26±0.39	0.19±0.36	0.23±0.48		
DHEA	0.24±0.36	0.19±0.41	0.17±0.28		
Paranoid ideation				0.39±0.54	0.38±0.38
Placebo	0.42±0.54	0.32±0.37	0.26±0.36		
DHEA	0.44±0.49	0.26±0.42	0.28±0.31		
Psychotic tendencies				0.26±0.32	0.21±0.26
Placebo	0.20±0.26	0.19±0.23	0.18±0.27		
DHEA	0.21±0.24	0.17±0.26	0.15±0.23		
Global severity index				0.56±0.54	0.39±0.26
Placebo	0.49±0.35	0.43±0.33	0.48±0.46		
DHEA	0.55±0.40	0.40±0.42	0.37±0.31**		

\*Plus-minus values are means ±SD. Scores can range from 0.00 to 4.00; higher scores indicate poorer well-being.<sup>14,15</sup> DHEA denotes dehydroepiandrosterone.

†A total of 505 women were evaluated.<sup>15</sup>

‡P=0.08 for the comparison with the absolute change from base line in the placebo group. P=0.03 for the comparison with the value at four months in the placebo group.

§P=0.02 for the comparison with the absolute change from base line in the placebo group. P=0.05 for the comparison with the value at four months in the placebo group.

¶P=0.01 for the comparison with the absolute change from base line in the placebo group. P=0.09 for the comparison with the value at four months in the placebo group.

||P=0.03 for the comparison with the absolute change from base line in the placebo group. P=0.13 for the comparison with the value at four months in the placebo group.

\*\*P=0.02 for the comparison with the absolute change from base line in the placebo group. P=0.07 for the comparison with the value at four months in the placebo group.

an antagonist of the  $\gamma$ -aminobutyric acid<sub>A</sub> receptor<sup>26</sup> and as an agonist of the *N*-methyl-D-aspartate receptor.<sup>27</sup> An antidepressant effect of dehydroepiandrosterone was also suggested by an open-label study in six patients with major depression.<sup>28</sup> Thus, the brain seems to be a physiologic target of dehydroepiandrosterone action.

In our study significant improvement in well-being occurred after four months of dehydroepiandrosterone treatment, but not after one month. This delay in the action of dehydroepiandrosterone may explain why some recent studies found no psychological effects in normal subjects who were treated with dehydroepiandrosterone for two weeks.<sup>29-31</sup>

We found a significant improvement in sexuality, as assessed by visual-analogue scales, in association with an increase in serum androgen but not estrogen concentrations. Although serum androgens are commonly linked to libido in women, the few clinical studies that have been conducted were not blinded, randomized, or placebo-controlled.<sup>32</sup>

Dehydroepiandrosterone is the precursor of androgens in women.<sup>13,33</sup> In keeping with the findings of previous single-dose pharmacokinetic studies,<sup>12,13</sup> we found that women with adrenal insufficiency had a pronounced deficiency of active androgens and that a single daily dose of 50 mg of dehydroepiandrosterone overcame this deficiency, which is usually

**TABLE 3.** SCORES ON THE MULTIDIMENSIONAL MOOD QUESTIONNAIRE BEFORE, DURING, AND AFTER TREATMENT WITH DEHYDROEPIANDROSTERONE OR PLACEBO.\*

SUBSCALE	BASE LINE	1 Mo	4 Mo	FINAL EXAMINATION
Degree of unpleasantness (unpleasant–pleasant)				32±7
Placebo	31±7	33±6	29±9	
DHEA	32±6	34±6	34±6†	
Degree of alertness (sleepy–awake)				29±8
Placebo	29±8	30±6	28±8	
DHEA	29±7	31±7	31±6‡	
Degree of restlessness (restless–calm)				32±7
Placebo	30±8	32±6	30±7	
DHEA	30±6	32±7	33±6§	

\*Plus–minus values are means ±SD. The lowest possible score is 8 (unpleasant, sleepy, and restless), and the maximal score is 40 (pleasant, awake, and calm). DHEA denotes dehydroepiandrosterone.

†P=0.03 for the comparison with the absolute change from base line in the placebo group. P=0.008 for the comparison with the value at four months in the placebo group.

‡P=0.08 for the comparison with the absolute change from base line in the placebo group. P=0.03 for the comparison with the value at four months in the placebo group.

§P=0.05 for the comparison with the absolute change from base line in the placebo group. P=0.01 for the comparison with the value at four months in the placebo group.

**TABLE 4.** SCORES ON VISUAL-ANALOGUE SCALES OF SEXUAL ACTIVITY BEFORE, DURING, AND AFTER TREATMENT WITH DEHYDROEPIANDROSTERONE OR PLACEBO.\*

VARIABLE	BASE LINE	1 Mo	4 Mo	FINAL EXAMINATION
Frequency of sexual thoughts or fantasies				31±20
Placebo	40±21	34±23	27±19	
DHEA	29±14†	44±23‡	42±23§	
Degree of sexual interest				35±22
Placebo	33±24	35±19	27±20	
DHEA	31±15	48±23¶	45±22	
Level of mental satisfaction with sex				46±30
Placebo	41±26	44±31	36±30	
DHEA	34±25	46±28	55±25**	
Level of physical satisfaction with sex				42±27
Placebo	44±26	43±31	34±29	
DHEA	32±20†	49±27	51±26††	

\*Plus–minus values are means ±SD. The total length of the scale was 100 mm; lower values indicate a lower frequency, degree of interest, or level of satisfaction. DHEA denotes dehydroepiandrosterone.

†P=0.04 for the comparison with the placebo group at base line.

‡P=0.007 for the comparison with the absolute change from base line in the placebo group. P=0.07 for the comparison with the value at one month in the placebo group.

§P<0.001 for the comparison with the absolute change from base line in the placebo group. P=0.006 for the comparison with the value at four months in the placebo group.

¶P=0.03 for the comparison with the absolute change from base line in the placebo group. P=0.06 for the comparison with the value at one month in the placebo group.

||P=0.01 for the comparison with the absolute change from base line in the placebo group. P=0.002 for the comparison with the value at four months in the placebo group.

\*\*P=0.002 for the comparison with the absolute change from base line in the placebo group. P=0.009 for the comparison with the value at four months in the placebo group.

††P=0.001 for the comparison with the absolute change from base line in the placebo group. P=0.02 for the comparison with the value at four months in the placebo group.

neglected.<sup>34</sup> Accordingly, the significant decrease in serum sex hormone-binding globulin and high-density lipoprotein cholesterol concentrations in our dehydroepiandrosterone-treated patients was probably due to an androgenic effect. However, since dehydroepiandrosterone sulfate can be converted to androgens in peripheral target cells,<sup>35</sup> the androgenic potential of dehydroepiandrosterone may be more correctly reflected by concentrations of androgen metabolites such as androstenediol glucuronide,<sup>36</sup> which increased to the upper-normal range during treatment with dehydroepiandrosterone.

It has been suggested that the beneficial effects of dehydroepiandrosterone on well-being result from an increase in serum IGF-I concentrations.<sup>5,8,10,11</sup> In our patients, serum IGF-I concentrations increased only in the women with primary adrenal insufficiency, suggesting that the effect of dehydroepiandrosterone on IGF-I production is dependent on growth hormone. Since the increases in well-being did not differ significantly between those with primary adrenal insufficiency and those with secondary adrenal insufficiency, changes in the serum IGF-I concentrations seem to be of minor importance with respect to the beneficial effects of dehydroepiandrosterone on mood.

The side effects of dehydroepiandrosterone during the four months of treatment were few and transient. Some women were pleased by the androgenic skin effects, because they had previously had dry skin and loss of axillary and pubic hair. However, in one woman a reduction in the dose was required because of androgenic side effects. Therefore, for some women a lower dose of dehydroepiandrosterone (25 to 30 mg daily) may be more suitable for long-term treatment. Larger trials with a longer duration of treatment will be needed to evaluate the safety of long-term treatment with dehydroepiandrosterone. Because dehydroepiandrosterone is rapidly converted into potent sex hormones, treatment might be contraindicated in women with hormone-dependent diseases, such as breast cancer. Thus, it should only be taken under medical supervision.

In conclusion, we found that replacing dehydroepiandrosterone in women with adrenal insufficiency improved well-being and sexuality as a result of a direct effect of dehydroepiandrosterone on the nervous system, an increase in peripheral androgen synthesis, or both. Our findings suggest that dehydroepiandrosterone should become part of the hormone-replacement regimen in women with adrenal insufficiency. Whether it has similar beneficial effects in men with adrenal insufficiency is not known but should be evaluated.

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## REFERENCES

- Cutler GB, Glenn M, Bush M, Hodgen GD, Graham CE, Loriaux DL. Adrenarche: a survey of rodents, domestic animals, and primates. *Endocrinology* 1978;103:2112-8.
- Orentreich N, Brind JL, Rizer RL, Vogelman JH. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *J Clin Endocrinol Metab* 1984;59:551-5.
- Belanger A, Candas B, Dupont A, et al. Changes in serum concentrations of conjugated and unconjugated steroids in 40- to 80-year-old men. *J Clin Endocrinol Metab* 1994;79:1086-90.
- Baulieu EE. Dehydroepiandrosterone (DHEA): a fountain of youth? *J Clin Endocrinol Metab* 1996;81:3147-51.
- Morales AJ, Nolan JJ, Nelson JC, Yen SSC. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *J Clin Endocrinol Metab* 1994;78:1360-7. [Erratum, *J Clin Endocrinol Metab* 1995;80:2799.]
- Casson PR, Andersen RN, Herrod HG, et al. Oral dehydroepiandrosterone in physiologic doses modulates immune function in postmenopausal women. *Am J Obstet Gynecol* 1993;169:1536-9.
- Casson PR, Faquin LC, Stentz FB, et al. Replacement of dehydroepiandrosterone enhances T-lymphocyte insulin binding in postmenopausal women. *Fertil Steril* 1995;63:1027-31.
- Yen SSC, Morales AJ, Khorram O. Replacement of DHEA in aging men and women: potential remedial effects. *Ann N Y Acad Sci* 1995;774:128-42.
- Labrie F, Diamond P, Cusan L, Gomez JL, Belanger A, Candas B. Effect of 12-month dehydroepiandrosterone replacement therapy on bone, vagina, and endometrium in postmenopausal women. *J Clin Endocrinol Metab* 1997;82:3498-505.
- Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SSC. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. *Clin Endocrinol (Oxf)* 1998;49:421-32.
- Casson PR, Santoro N, Elkind-Hirsch K, et al. Postmenopausal dehydroepiandrosterone administration increases free insulin-like growth factor-I and decreases high-density lipoprotein: a six-month trial. *Fertil Steril* 1998;70:107-10.
- Young J, Couzinet B, Nahoul K, et al. Panhypopituitarism as a model to study the metabolism of dehydroepiandrosterone (DHEA) in humans. *J Clin Endocrinol Metab* 1997;82:2578-85.
- Arlt W, Justl HG, Callies F, et al. Oral dehydroepiandrosterone for adrenal androgen replacement: pharmacokinetics and peripheral conversion to androgens and estrogens in young healthy females after dexamethasone suppression. *J Clin Endocrinol Metab* 1998;83:1928-34.
- Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale — preliminary report. *Psychopharmacol Bull* 1973;9:13-28.
- Franke HG. Eine weitere Ueberprüfung der Symptom-Check-Liste (SCL-90-R) als Forschungsinstrument. *Diagnostica* 1992;38:160-7.
- Steyer R, Schwenkmezger P, Notz P, Eid M. Theoretical analysis of a multidimensional mood questionnaire (MDBF). *Diagnostica* 1994;40:320-8.
- Zerssen D, Koeller DM. Die Beschwerden-Liste (Manual). Klinische Selbstbeurteilungsskalen aus dem Muenchner Psychiatrischen Informationssystem (PSYCHIS). Weinheim, Germany: Beltz-Verlag, 1976.
- Brähler E, Scheer JW. Skalierung psychosomatischer Beschwerdenkomplexe mit dem Giessener Beschwerdebogen (GGB). *Psychother Med Psychol (Stuttg)* 1979;29:14-27.
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361-70.
- Herrmann C, Buss U. Vorstellung und Validierung einer deutschen Version der "Hospital Anxiety and Depression Scale" (HAD-Skala): ein Fragebogen zur Erfassung des psychischen Befindens bei Patienten mit körperlichen Beschwerden. *Diagnostica* 1994;40:143-54.
- Wallenstein S, Fisher AC. The analysis of the two-period repeated measurements crossover design with application to clinical trials. *Biometrics* 1977;33:261-9.
- Corpechot C, Robel P, Axelson M, Sjoval J, Baulieu EE. Characterization and measurement of dehydroepiandrosterone sulfate in rat brain. *Proc Natl Acad Sci U S A* 1981;78:4704-7.
- Melchior CL, Ritzmann RF. Dehydroepiandrosterone is an anxiolytic in mice on the plus maze. *Pharmacol Biochem Behav* 1994;47:437-41.
- Prasad A, Imamura M, Prasad C. Dehydroepiandrosterone decreases behavioral despair in high- but not low-anxiety rats. *Physiol Behav* 1997;62:1053-7.
- Abadie JM, Wright B, Correa G, Browne ES, Porter JR, Svec F. Effect of dehydroepiandrosterone on neurotransmitter levels and appetite regulation of the obese Zucker rat: the Obesity Research Program. *Diabetes* 1993;42:662-9.

26. Majewska MD, Demigoren S, Spivak CE, London ED. The neurosteroid dehydroepiandrosterone sulfate is an allosteric antagonist of the GABA<sub>A</sub> receptor. *Brain Res* 1990;526:143-6.
27. Compagnone NA, Mellon SH. Dehydroepiandrosterone: a potential signalling molecule for neocortical organization during development. *Proc Natl Acad Sci U S A* 1998;95:4678-83.
28. Wolkowitz OM, Reus VI, Roberts E, et al. Dehydroepiandrosterone (DHEA) treatment of depression. *Biol Psychiatry* 1997;41:311-8.
29. Wolf OT, Neumann O, Hellhammer DH, et al. Effects of a two-week physiological dehydroepiandrosterone substitution on cognitive performance and well-being in healthy elderly women and men. *J Clin Endocrinol Metab* 1997;82:2363-7.
30. Wolf OT, Naumann E, Hellhammer DH, Kirschbaum C. Effects of dehydroepiandrosterone replacement in elderly men on event-related potentials, memory, and well-being. *J Gerontol A Biol Sci Med Sci* 1998;53:M385-M390.
31. Kudielka BM, Hellhammer J, Hellhammer DH, et al. Sex differences in endocrine and psychological responses to psychosocial stress in healthy elderly subjects and the impact of a two-week dehydroepiandrosterone treatment. *J Clin Endocrinol Metab* 1998;83:1756-61.
32. Casson PR, Carson SA. Androgen replacement therapy in women: myths and realities. *Int J Fertil Menopausal Stud* 1996;41:412-22.
33. Abraham GE. Ovarian and adrenal contribution to peripheral androgens during the menstrual cycle. *J Clin Endocrinol Metab* 1974;39:340-6.
34. Oelkers W. Adrenal insufficiency. *N Engl J Med* 1996;335:1206-12.
35. Martel C, Melner MH, Gagne D, Simard J, Labrie F. Widespread tissue distribution of steroid sulfatase, 3 beta-hydroxysteroid dehydrogenase/delta 5-delta 4 isomerase (3 beta-HSD), 17 beta-HSD 5 alpha-reductase and aromatase activities in the rhesus monkey. *Mol Cell Endocrinol* 1994;104:103-11.
36. Labrie F, Belanger A, Cusan L, Candas B. Physiological changes in dehydroepiandrosterone are not reflected by serum levels of active androgens and estrogens but of their metabolites: intracrinology. *J Clin Endocrinol Metab* 1997;82:2403-9.

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