Effects of dehydroepiandrosterone (DHEA) supplementation on hormonal, metabolic and behavioral status in patients with hypoadrenalism

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ABSTRACT. Oral DHEA administration to patients with hypoadrenalism, in addition to glucocorticoid and mineralocorticoid replacement, may improve both well-being and hormonal/metabolic parameters. Twenty patients (13 men, 7 women, 26-76 yr; 11 with Addison’s disease, 9 with central hypoadrenalism) were recruited in a placebo-controlled, randomized study. Hormone levels, carbohydrate and lipid parameters, bone metabolism, body composition and psychological parameters were evaluated at baseline and after treatment with DHEA 50 mg/day or placebo for 4 months. After 4 months of DHEA administration, serum DHEAS levels raised both in men (from 0.71 ± 0.18 to 8.28 ± 1.66 μmol/l, p < 0.005) and in women (from 0.25 ± 0.07 to 5.65 ± 1.93 μmol/l, p < 0.05). Only in hypoadrenal women an increase in testosterone (T; from 0.4 ± 0.1 to 1.45 ± 0.26 nmol/l, p < 0.05) and androstenedione (A; from 0.86 ± 0.34 to 2.05 ± 0.29 nmol/l, p < 0.05) levels was observed. In men no significant modifications in T and 17-hydroxyprogesterone (17-OHP) levels were found, whereas serum SHBG significantly decreased. As far as the metabolic parameters are concerned, only in patients with Addison’s disease a significant decrease in total cholesterol and in low-density lipoproteins after 4 months of DHEA administration was found. No changes in glucose metabolism and insulin sensitivity were observed. In basal conditions, mean serum osteocalcin (OC) was normal and significantly decreased after DHEA treatment. A significant reduction in body fat mass percentage (BF%) after DHEA administration was observed. As far as well-being is concerned, DHEA replacement did not cause any relevant variation of subjective health scales and sexuality in both sexes. Our study confirms that DHEA may be beneficial for female patients with hypoadrenalism, mainly in restoring androgen levels. Concerning the health status, more sensitive and specific instruments to measure the effects of DHEA treatment could be necessary.

INTRODUCTION

DHEA and its sulfate ester (DHEAS) are among the most abundant products of adrenal steroidogenesis in humans. In recent yr, many studies have shown a positive effect of DHEA administration on well-being in aging men and women (1-4). Moreover, it has been reported that DHEA is able to increase osteocalcin (OC) levels (2), to augment muscle strength (5) and to improve insulin sensitivity (6). Other important effects may be exerted on the regulation of the immune response, probably by an increase of interleukin-2 (7), and recently, the self-perceived mental health in patients with advanced HIV disease has been improved by DHEA replacement therapy (8). The association between DHEA and cardiovascular disease is still debated. A protective role of DHEA for atherosclerotic disease indicating its possible usefulness in aging has recently been suggested: in fact, it has been shown that DHEA regulates vascular function through the induction of endothelial nitric oxide (NO) synthesis, providing a rationale for some of its vascular effects (9).

Patients with primary and secondary adrenocortical failure have abnormally low levels of DHEA relative to age: they are usually treated either with gluco-
corticoid and mineralocorticoid supplementation or only with glucocorticoids, while the lack of adrenal androgens is not replaced. These patients may show mental fatigue and low stress tolerance, even when glucocorticoid and mineralocorticoid replacement is adequately given, suggesting a possible role of androgens on psychological well-being and behavior. In fact, DHEA exerts indirect endocrine effects after its conversion to androgens or estrogens and it also acts on neurotransmitter receptors in the brain (10). Taking these aspects in consideration, it has been suggested that androgen supplementation could be of benefit in patients with primary and secondary adrenocortical failure. Therefore, DHEA replacement therapy has been proposed as adjunctive therapy in hypoadrenalism and found to exert beneficial actions (4, 11-13).

The aim of this study was to carry out a double-blind, placebo-controlled study in order to assess the effects of DHEA supplementation on some hormonal, metabolic and psychological parameters in a group of patients with Addison’s disease or central hypoadrenalism.

MATERIALS AND METHODS
Study protocol
We studied 20 patients (13 men and 7 women, mean age 45±4.4 and 45.8±2.6 yr, respectively): 11 had primary adrenal insufficiency and 9 central hypoadrenalism, secondary to pituitary or hypothalamic tumors. Some clinical and hormonal characteristics of 9 patients with central hypoadrenalism before DHEA replacement are shown in Table 1. All patients with central hypoadrenalism also had thyroid and gonadal insufficiency and they were adequately treated. Eight out of these 9 subjects had GH deficiency but this defect was not treated. All subjects gave their informed consent to participate in the study.

The study was a double-blind, placebo-controlled, crossover design with a prearranged randomization schedule. Each patient received in a randomized order 50 mg of DHEA po for 4 months and placebo tablets for 4 months: the two treatment periods were separated by one month wash-out period.

All patients were evaluated before treatment, after 4 months of DHEA, after one month of wash-out and after 4 months of placebo.

In all instances the following hormones were measured: serum DHEAS, testosterone (T), androstenedione (A), 17-hydroxyprogesterone (17-OHP), SHBG, LH, FSH, 17α-estradiol (17β-E2), PRL, GH, IGF-1, TSH, free T4 (FT4), free T3 (FT3) levels. In addition, carbohydrate and lipid parameters (glucose, insulin, total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides) and some markers of bone metabolism [PTH, OC, urinary deoxypyridinoline (DPD), bone alkaline phosphatase (B-ALP)] were evaluated. Insulin resistance was determined using homeostasis model assessment (HOMA-IR) and Quantitative Insulin-Sensitivity Check Index (QUICKI) methods, according to Matthews et al. (14) and Katz et al. (15), respectively.

Assays
Radioimmunoassay methods were used on unextracted serum samples for serum DHEAS (Diagnostic System, Webster, USA), A (Diagnostic System, Webster, USA) and 17-OHP (Biosource, Nivelles, Belgium); serum T and SHBG levels were determined by fluororimmunoassay methods (Delfia, Wallac Oy, Turku, Finland). The lower limits of sensitivity were 0.04 μmol/l for DHEAS, 0.1 nmol/l for A, 0.06 nmol/l for 17-OHP, 0.4 nmol/l for T and 0.5 nmol/l for SHBG. In all methods, the intra- and interassay coefficients of variation were <6 and <10.5%, respectively. The Free Androgen Index (FAI) was calculated by using the formula: T (nmol/l) × 100/SHBG (nmol/l).

Serum LH, FSH, 17β-E2, PRL, GH, IGF-1, TSH, FT4, FT3, insulin levels, plasma PTH and OC concentrations and urinary DPD were measured using commercial assay kits. Other blood parameters were determined by established colorimetric or enzymatic assays.

Body composition was evaluated by whole body bioelectrical impedance analysis (BIA), using a portable impedance analyzer (Akern/RJL Systems, Detroit, MI). Body fat percentage (BF%) was calculated using Segal’s regression equation.

Psychological evaluation
Psychological evaluations were performed at each visit with validated questionnaires. The revised version of the 90-item Symptom Checklist-90 (SCL-90) is a multidimensional self-report inventory designed to reflect the psychological symptom patterns of community, medical and psychiatric respondents. Each of the 90 items is rated on a five-point scale of distress (0-4) ranging from “not at all” to “extremely.” The nine primary symptom dimensions are labeled as somatization, obsessive-compulsive traits, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety,