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Original Paper

Dehydroepiandrosterone in the treatment of erectile dysfunction in patients with different organic etiologies

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Abstract. In 1994 the Massachusetts Male Aging Study described an inverse correlation of the serum levels of dehydroepiandrosterone sulfate (DHEAS) and the incidence of erectile dysfunction (ED). The positive results of a pilot study in the treatment in patients with no organic etiology prompted a detailed investigation on the efficacy of DHEA therapy for ED in patients with different organic etiologies, in a prospective study. The inclusion criteria included ED, a normal physical condition, normal serum levels of testosterone, prolactin and PSA and a serum DHEAS level <1.5 µmol/l. The study patients comprised 27 patients (group 1) with hypertension, 24 patients (group 2) with diabetes mellitus, six patients with neurological disorders (group 3) and 28 patients (group 4) with no organic etiology were treated with 50 mg DHEA p.o. for 6 months. We assessed efficacy by using the responses to question 3 (frequency of penetration) and question 4 (maintenance of erections after penetration) of the 15-question International Index of Erectile Function (IIEF). DHEA treatment was associated with statistically significantly higher mean scores compared to baseline values for question 3 and question 4 of the IIEF in groups 1 and 4 after a period of 24 weeks. The differences between the mean scores of groups 2 and 3 and the baseline values were not statistically significant. Our results suggest that oral DHEA-treatment may be of benefit to patients with ED who have hypertension or to patients with ED without organic etiology. There was no impact of DHEA therapy on patients with diabetes mellitus or with neurological disorders.

Keywords. Dehydroepiandrosterone - Erectile dysfunction - Organic etiology

Introduction

Dehydroepiandrosterone (DHEA) and its sulfated metabolite DHEA-S, often called weak androgens, are endogenous hormones secreted by the adrenal cortex in response to adrenocorticotropin (ACTH) [*17*]. Despite the identification of DHEA and DHEA-S more than 50 years ago, their physiological role remains to be precisely defined. Interest in these hormones is considerable. A medline search of articles published from 1963 to 2000 identified 1789 publications in English that had DHEA and or DHEA-S as a focus, with 43% (777) published during the 8 years from 1993 to 2000.

Unlike ACTH and cortisol in humans, plasma concentrations of DHEA and DHEA-S are age and gender dependent. DHEA concentrations decline from birth until 5 years of age, then rise rapidly from age 9 in boys [*23*]. until concentrations reach their peak between the ages of 20 and 30 [*2,* 23]. There follows a progressive decline to about 10% of maximum levels during advanced age [*9*]. Although the average serum level of DHEA-S in men 25 to 34 years of age is around 6.44±2.29 µg/ml, it falls to 1.15±0.52 µg/ml in men 75-84 years old [*10*]. DHEA and DHEA-S metabolism includes the formation of active androgenic and estrogenic steroids, which, in turn, are metabolized. Active sex hormone substances from DHEA metabolism affect many cells types that have androgen or estrogen receptors, for example adipose tissue, skin, prostate, brain, breast, muscle, and liver.

In 1994, Feldman et al. [*7*] demonstrated the prevalence of erectile dysfunction (ED) and its physiological and psychosocial correlates in a general population using results from the Massachusetts Male Aging Study (MMAS). Of the 17 hormones measured in MMAS subjects, only the adrenal androgen DHEA-S showed a strong inverse correlation to ED. The positive results of a pilot study [*19*] in the treatment of ED in patients with no organic etiology prompted a detailed investigation on the efficacy of DHEA therapy for ED in patients with different organic etiologies in an open, prospective study.

Materials and methods

Subjects

Between January 1998 and September 1998, 87 men with a mean age of 62.7 years (range 35 to 69) were recruited after attending our ED clinic. The inclusion criteria included ED for more than 6 months, a normal physical condition, serum levels of testosterone, prolactine and PSA in the normal range and a serum DHEAS level below 1.5 µmol/l. Exclusion criteria included ischemic heart disease, hyperlipidemia and a history of radical prostatectomy. Twenty-seven patients (group 1) with hypertension, 24 patients (group 2) with non-insulin dependent diabetes mellitus, six patients (group 3) with neurological disorders and 28 patients (group 4) with no organic etiology for ED were treated with 50 mg DHEA p.o. for 6 months. All patients from group 1 had normotensive blood pressure values during treatment. The age difference between these four groups was not statistically significant. All participants were non-smokers. No participant had taken hormone replacement therapy previously nor used any treatment for ED. All participants were carefully screened to assess medical factors known or suspected to alter endocrine function. Medical illness was excluded by history, physical and neurological examination, blood chemistry profiles (including renal and hepatic panels), digital rectal examination, urinalysis, and complete blood count.

Blood was drawn for the determination of DHEAS, T and PSA, as well as liver function, renal function, electrolytes and complete blood count was made at the beginning of the study (baseline data) and at 12-weeks and 24-weeks. Treatment efficacy was evaluated by using the responses to question 3 (frequency of penetration) and question 4 (maintenance of erections after penetration) of the

International Index of Erectile Function (IIEF) [*21*], a validated, multidimensional, self-administered 15-item questionaire used for the clinical assessment of ED and treatment outcomes in clinical studies. The responses to these two questions were rated on a scale of 1 (almost never or never) to 5 (almost always or always). A score of 0 indicated no attempt at sexual intercourse.

Assays

Non-fasting blood samples were taken by venipuncture from the antecubital space. After coagulation, the samples were centrifuged. Serum was stored at -20°C for the determination of DHEAS, T and PRL and at -70° for the determination of PSA until further processing. Assays employed were as follows (inter-and intra-assay coefficients respectively)): DHEAS Radioimmunoassay (10.6%/7.4%) (Immunotech Int.), Enzymun Prolactin (5.2%/3.2%) (Boehringer Mannheim), Testosterone RIA Coat-A-Count (12.9%/5.1%) (Diagnostics Products), and PSA Tandem Monoclonal Radioimmunoassay (5.7%/5.1%) (Hybritech).

Statistical analysis

The effects of DHEA treatment on the IIEF and hormone levels were determined using a computer software package (SPSS 6.0 for Windows, Microsoft). Subsequent paired comparison of differences between the groups were done using the Mann-Whitney U test with significance set at $P<0.05$.

Results

All 27 patients from group 1 and all 28 patients from group 4 completed the 24-week study period. The drop-out rate was 7% in group 2 after a mean time of 10.3 weeks (range 7 to 15 weeks) and 50% in group 3 after a mean time of 6.3 weeks (range 3 to 8 weeks) due to insufficient response to therapy. No adverse experience was noticed. The serum levels of DHEAS of all patients who were still participating at this time, were above 2 µmol/l after 12 weeks of treatment.

DHEA treatment was associated with statistically significantly higher mean scores to question 3 and question 4 of the IIEF in group 1 and 4 after 24 weeks, compared to baseline values. The differences in the mean scores of group 2 and 3 between the baseline data and the end of the study period were not statistically significant. The results are presented in Figs. 1 and 2.

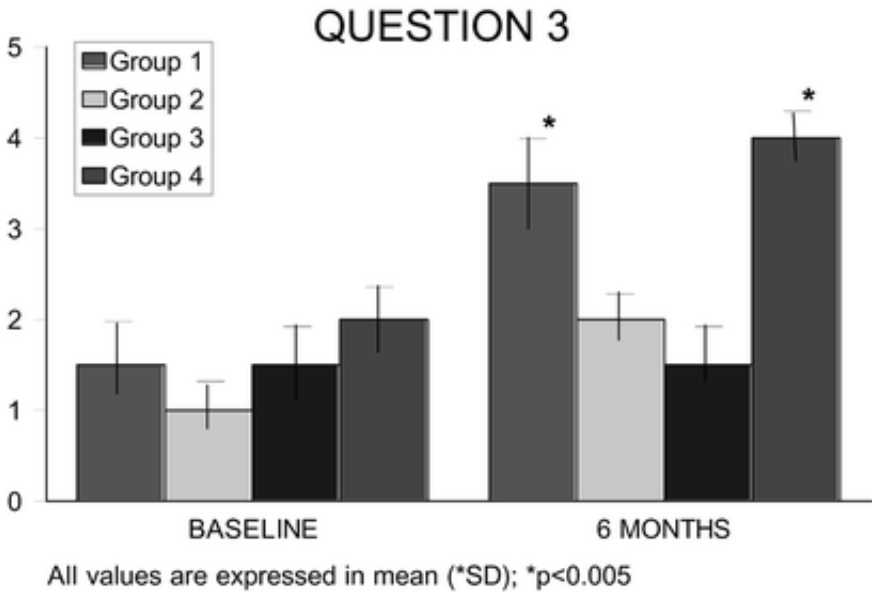

Fig. 1. Mean scores for question 3 of the IIEF (frequency of penetration) at baseline and after 6 months of DHEA treatment

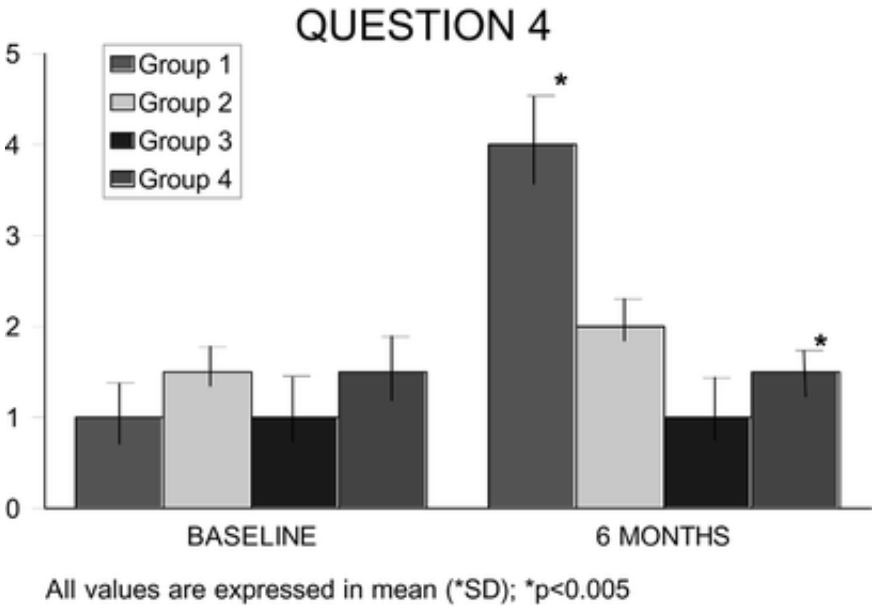

Fig. 2. Mean scores for question 4 of the IIEF (maintenance of erections after penetrations) at baseline and after 6 months of DHEA treatment

Discussion

Until 1998, the available treatment options for ED included vacuum-constriction devices [*22*], implantation of penile prostheses [*4*], intracavernosal injections of vasoactive agents [*15*], and transurethral delivery of aprostadil [*18*]. Sildenafil then became [*8*] the first drug to be approved for oral treatment of ED by the United States Food and Drug Administration. Testosterone is the only hormone which has been used in the treatment of ED in larger series. The response to testosterone therapy has not been effective in restoring or improving sexual function except in patients with primary or secondary testicular failure [*11*].

DHEA is a C19 steroid also known as 5-androsten-3 β -ol-17-one. Hydrosteroid sulfatases convert

DHEA to DHEA-S, which is the most abundant circulating steroid in humans. The specific cytosolic enzyme responsible has been commonly referred to as dehydroepiandrosterone sulfotransferase because of its high affinity for catalyzing this reaction. The adrenal cortex is the primary source of circulating concentrations of DHEA and DHEA-S but it is estimated that 5% of DHEA-S and 10% to 25% of DHEA are secreted by the testes [*24*]. Once in circulation, DHEA-S can be metabolized back to DHEA by sulfohydrolases in peripheral and adrenal tissues [*12*]. DHEA and DHEA-S are also classified among the group of steroids known as neurosteroids, so named because they can be synthesized de novo in the central nervous system [*16*]. Concentrations of DHEA and DHEA-S are considerably higher in the brain than in other organs [*3*]. In common with other neurosteroids, DHEA and DHEA-S act directly on two major receptors: the γ -aminobutyric acid

(GABA)-benzodiazepine-receptor-complex, to which GABA, the major inhibitory neurotransmitter, binds [*5*], and the *N*-methyl-D-aspartase receptor, a major receptor for excitatory amino acids [*6*]. DHEA and DHEA-S metabolism includes the formation of active androgenic and estrogenic steroids which, in turn, are metabolized. Labrie et al. demonstrated that DHEA itself has a three- to tenfold predominance in androgenic as opposed to estrogenic activity, as determined by measuring the

reversal of the effects of gonadectomy in rats [*13*]. A year later Labrie et al. showed that DHEA and DHEA-S serve as the precursor to approximately 50% of androgens in adult men [*14*]. In contrast to these papers Arlt et al. [*1*] revealed a significant increase in circulating estrogens in elderly men after oral administration of 50 mg DHEA. Serum testosterone and dihydrotestosterone remained unchanged. Reiter et al. [*19*] demonstrated that oral administration of DHEA may be beneficial in the treatment of ED. Furthermore, it was possible to show that the mean serum levels of DHEAS in patients with ED are lower than the levels in an age-matched control group until 60 years of age [*20*].

Our results reveal an increase in the frequency of penetration and the maintainance of an erection after penetration in group 1 and group 4 after DHEA treatment. The positive results of group 4 confirm previous published data [*19*]. Due to the fact that the real mode of action of DHEA on cavernous tissue is unclear, the reasons for success or failure of DHEA treatment in patients with ED cannot currently be explained. Although this study lacks a control group and our patient database is too small to do relevant statistical analysis, we believe that our data support a previously presented, biologically obvious trend [*19*]. Further studies on the molecular pathways of DHEA treatment on cavernous tissue are now mandatory and should be awaited before starting larger clinical trials.

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