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Metabolic and Hormonal Effects of Oral DHEA in Premenopausal Women with HIV infection

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Abstract

Context—Patients with HIV infection, both men and women, sometimes use dehydroepiandrosterone (DHEA) because of its reputation as a “youth hormone” which can improve mood and energy level. DHEA can be obtained without a prescription. However, endocrine effects of DHEA in HIV- infected individuals are poorly understood. We recently reported the endocrine effects of DHEA in HIV-infected men. We now present the results of a randomized placebo controlled double-blind study of endocrine effects of DHEA in HIV-infected women.

Objective—our aim was to explore the effects of DHEA on the hypothalamic-pituitary-adrenal (HPA) axis, sex steroids, circulating insulin, adiponectin, IGF-I, IGFBP-1 and IGFBP-3 in HIV infected premenopausal females.

Subjects and Methods—We conducted an 8-week randomized placebo controlled pilot trial of DHEA in HIV positive men and women with non-major depression. Increasing doses (100–400mg/day) of oral DHEA were administered. One hundred forty-five patients (122 men and 23 women) were randomized to receive either DHEA or placebo. 133 patients, including all 23 women, completed the trial. Of these women, 15 agreed to participate in the endocrine sub-study, conducted at the Weill Cornell GCRC. Of these, nine women were randomized to receive oral DHEA and six to placebo. Low (1mcg) dose ACTH, CRF and GnRH stimulation tests were performed in each subject before and after 8 weeks of treatment with DHEA or placebo. DHEA,

DHT, total testosterone, free testosterone, sex hormone binding globulin, estrone, estradiol, cortisol, insulin, IGF-1, IGFBP-1, IGFBP-3 and adiponectin in plasma or serum were measured before and after 8 weeks of treatment with DHEA or placebo. Wilcoxon Signed Rank and the Mann Whitney tests were used to analyze the data.

Results—There was a significant increase in mean DHEA-S concentration (ELISA assay) (from 95+/-88 ng/ml before the study to 1138+/-849 ng/ml at week 8 of treatment, $p<0.008$) in the DHEA group, but not in the placebo group. There was a significant increase in the mean total testosterone concentration (0.21+/-0.1 vs. 0.76+/-0.6 ng/ml, $p<0.008$) and dihydrotestosterone (DHT) concentration (142.9+/-67 vs. 907.2+/-523 ng/ml, $p<0.004$) in the DHEA group but not in the placebo group. In addition, there was a significant increase in the estrone concentration in the DHEA group (144.3+/-83 vs 309.6+/-142 pg/ml, $p<0.03$) but not in the placebo group. There was a significant increase in the mean plasma concentrations of DHEA-S ($p<0.032$), DHEA ($p<0.0006$), total testosterone ($p<0.01$) and dihydrotestosterone ($p<0.005$) in the DHEA group when compared to the placebo group. There was no change in the cortisol concentration, fasting serum insulin, sex hormone binding globulin, free testosterone, estradiol, adiponectin, IGF-1, IGFBP-1 or IGFBP-3 concentrations, or ACTH, CRF or GnRH test results from week 1 to week 8 in either the DHEA or placebo groups.

Conclusion—We conclude that oral DHEA administration results in a significant increase in circulating DHEA-S, testosterone, DHT and, possibly, estrone levels in premenopausal women with HIV infection. These changes are not accompanied by significant changes in the overall function of pituitary or adrenal axes or in insulin/IGF indices. Long-term studies with larger numbers of patients are needed to confirm these data and to determine their clinical significance.

Keywords

Endocrine effects; DHEA; HIV-infected premenopausal women

Since 1981, when HIV/AIDS was first identified, women have been representing increasing proportion among HIV infected individuals. In the United States, the annual number of estimated AIDS cases increased 15% among women and only 1% among men from 1999 to 2003 ⁽¹⁾. HIV infection remains prevalent among women worldwide. Women account for nearly half of the 40 million people living with HIV (age 15 to 49) ⁽¹⁾. AIDS was the leading cause of death for black women in the age group of 25–34 years in 2001 ⁽²⁾.

DHEA is a naturally occurring adrenal hormone, a precursor to peripheral androgen and estrogen synthesis. It is one of the most abundant steroid hormones in the body. Circulating concentrations of DHEA decline with age ⁽³⁾ and are reduced in numerous disease states, including HIV infection and depressed mood ⁽⁴⁾. Some cross-sectional and longitudinal studies in individuals with HIV infection have suggested that reduced plasma DHEA and DHEA-S levels are associated with disease progression ⁽⁵⁾. Compared to uninfected controls, HIV positive patients have significantly lower mean plasma DHEA levels, which correlate with CD4 count ⁽⁶⁾. Moreover, in a sample of HIV positive men ⁽⁷⁾, initiation of antiretroviral therapy led to increase in serum DHEA-S level with improvement in CD4 cell count. In HIV-infected patients, DHEA replacement therapy could potentially lead to an improvement in the immune status, sense of well-being and increase in energy level ⁽⁸⁾. However, endocrine effects of DHEA in HIV infected women are poorly understood.

The aim of the present randomized placebo controlled pilot trial was to explore the effects of DHEA on the hypothalamic-pituitary-adrenal (HPA) axis, sex steroids, circulating insulin, adiponectin, IGF-I, IGFBP-1 and IGFBP-3 in HIV infected premenopausal females.

Subjects and Methods

We conducted an 8 week randomized, double-blind, placebo-controlled trial to assess primarily the effects of increasing doses (100–400mg/day) of oral DHEA on the mood ⁽⁹⁾. As a secondary goal we assessed the effects of oral DHEA on the hypothalamic-pituitary-adrenal axis (HPA), hypothalamic-pituitary-gonadal axis, insulin, adiponectin, IGF-1, IGFBP-1 and IGFBP-3 in 15 HIV infected premenopausal women (9 in the DHEA-treated group and 6 in the placebo group) (Table 1).

Eligible patients were HIV positive, ranged in age from 18 to 70 years, and had a DSM-IV diagnosis of dysthymia or subsyndromal depression of at least 3 months' duration. We excluded individuals with an unstable medical condition, initiation of steroids within the past 3 months, current major depressive disorder, and current substance use disorder. Study enrollment took place between December 2000 and May 2004.

Micronized DHEA in 100-mg tablets and matching placebo were provided by Belmar Pharmacy (Lakewood, Colo.). Subjects were randomized to receive either oral DHEA (9 subjects) or placebo (6 subjects). The initial dose of DHEA or placebo was 100 mg/d, on the basis of the prior experience ⁽⁹⁾. The dose was increased to 200 mg/day after 1 week and to 300 mg/day after 2 weeks in the absence of clinical improvement and dose-limiting side effects. After 4 weeks, an additional dose increase to 400 mg/day was permitted in the absence of clinical improvement and dose-limiting side effects.

The study protocol was approved by the Institutional Review Boards at New York State Psychiatric Institute, Weill Medical College of Cornell University and Beth Israel Medical Center, and all patients gave written consent after the risks and benefits of study participation were explained. FDA authorization was obtained for use of DHEA as an investigational drug.

At baseline and at the end of week 8, morning blood samples were drawn for the following measures: DHEA, DHT, total testosterone, free testosterone, sex hormone binding globulin, estrone, estradiol, cortisol, insulin, IGF-1, IGFBP-1, IGFBP-3 and adiponectin. At baseline and at the end of week 8, each patient underwent 3 stimulation tests. One hundred micrograms of synthetic luteinizing hormone-releasing hormone (LHRH) was injected intravenously, and serum concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured at 0, 30 and 60 minutes. One microgram of corticotropin (ACTH) analog was administered intravenously, and serum cortisol concentrations were determined at 0, 30 and 60 minutes. Corticotropin releasing factor (CRF) analog was injected intravenously; a serum cortisol and plasma ACTH levels were measured at 0, 30 and 60 minutes. Wilcoxon-Signed Rank and the Mann Witney tests were used to analyze the data. All results were considered significant if $p < 0.05$.

Results

There was a significant increase in the mean plasma concentrations of DHEA-S ($p < 0.008$), DHEA ($p < 0.004$), total testosterone ($p < 0.008$), dihydrotestosterone ($p < 0.004$) and estrone ($p < 0.003$) within the DHEA group but not in the placebo group from week 1 to week 8, as outlined in Table 2.

There was a significant increase in the mean plasma concentrations of DHEA-S ($p < 0.032$), DHEA ($p < 0.0006$), total testosterone ($p < 0.01$) and dihydrotestosterone ($p < 0.005$) in the DHEA group when compared with the placebo group, as demonstrated in figures 1–4. There was an increase in the mean plasma concentration of estrone in DHEA group, but not in the placebo group (DHEA group: from 144.3 ± 83.0 pg/ml to 309.6 ± 142.0 pg/ml, $p <$

0.003; placebo group: from 143.2 $\pm$ 125.0 pg/ml to 254.0 $\pm$ 213.0 pg/ml $p<0.063$). However, estrone change over time between the two groups was not statistically significant ($p < 0.594$).

There was no change in baseline cortisol concentration, fasting serum insulin, sex hormone binding globulin, free testosterone, estradiol, adiponectin, IGF-1, IGFBP-1 or IGFBP-3 concentrations from week 1 to week 8 in either the DHEA or placebo group, as detailed in Table 3.

There was no significant difference between the ACTH, CRF or GnRH stimulation test results from week 1 to week 8 between the DHEA and placebo groups (Fig. 6 – 10)

Discussion

In the United States, DHEA is widely available as an over-the-counter dietary supplement. Its effects on a wide variety of conditions, such as aging, diabetes, obesity, immune dysfunction, arthritis and depression, as well as its long-term safety, remain uncertain. Among HIV-infected individuals, DHEA is used to increase energy and muscle mass, to improve depressive symptoms, and even to improve the overall outcome of HIV infection (5, 8, 9, 10).

We recently reported the endocrine effects of DHEA in HIV-infected men. Oral DHEA supplementation in HIV-infected men results in significant increase in circulating levels of DHEA and DHEAS, free testosterone, DHT, androstenedione and estrone. DHEA therapy did not alter the overall function of the gonadal or hypothalamic-pituitary-adrenal axis and had no effect on the circulating levels of major lipids, insulin, adiponectin, and growth hormone, IGF-1, IGFBP-1 and IGFBP-3 (11).

This study reports a secondary analysis of the endocrine effects of oral DHEA in a group of premenopausal HIV-infected women with mild depression. The primary outcome of the study (the effect on depression) was reported separately and revealed that DHEA was superior in the intent-to-treat analysis, where the response rate was 56% for the DHEA group versus 31% for the placebo group (9).

In this endocrine study, we observed a significant increase in mean DHEA-S, total testosterone and DHT concentrations without a change in the circulating concentration of sex hormone binding globulin.

Individuals with HIV infection develop insulin resistance both independently and in association with the HIV-related lipodystrophy (12). Intake of DHEA has been reported to be associated with improved insulin sensitivity in some studies (13, 14). We observed that there was no change in the circulating concentrations of fasting serum insulin, adiponectin, IGF-1, IGFBP-1 and IGFBP-3.

HIV-infected individuals are at higher risk for the development of adrenal insufficiency (15). DHEA is a precursor of cortisol, and the HPA axis hypothetically could be suppressed if a high pharmacologic dose of DHEA is used. We examined the HPA axis in our patients by using low-dose (1 μ g) corticotropin stimulation test and CRH stimulation test. Our data demonstrated that there were no change in low dose ACTH stimulation test and CRH stimulation test results from week 1 to week 8 in either the DHEA or placebo group.

There is a possibility that DHEA may also suppress the HPG axis because of the conversion of DHEA to testosterone and then to estradiol through aromatization of testosterone. The GnRH stimulation test did not show the suppression of gonadal axis in our patients.

However, HIV-infected women did have an increased level of total testosterone with unchanged SHBG level in DHEA treated group. These results differ from our previous studies in HIV infected men, in whom we observed a significant increase in the circulating levels of free testosterone and DHT, accompanied by a decline in the circulating SHBG concentration in the DHEA-treated group ⁽¹¹⁾. The differences between the female patients and male patients receiving DHEA are not fully understood, but may have to do with the differences in endogenous correlations of sex steroids between men and women and the effects of endogenous sex steroids in SHBG levels.

We assessed estradiol and estrone levels because of the potential effect of DHEA on estrogen level and the association between the risk of breast cancer and persistently elevated serum estrogens ⁽¹⁶⁾. We observed that there was a significant increase in the mean plasma concentration of estrone in the DHEA group, but not the placebo group. However, the differences in the plasma estrone concentrations over time between two groups were not statistically significant. Similarly, there was no significant change in estradiol level between the two groups.

In conclusion, in a sample of HIV positive women, DHEA administration increased the circulating levels of DHEA, DHEA-S, DHT and total testosterone. DHEA administration might also increase the circulating level of estrone. DHEA administration did not have any effect on the circulating levels of cortisol, fasting serum insulin, sex hormone binding globulin, free testosterone, estradiol, adiponectin, IGF-1, IGFBP-1 or IGFBP-3. DHEA administration was not accompanied by significant changes in the results of ACTH-, CRF- or GnRH stimulation tests. Long-term studies with larger groups of patients are needed to confirm these data and to determine their clinical significance.

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Fig 1. DHEA-S change over time in DHEA treated group (●) and placebo group (○) ($p < 0.032$ for comparison between the groups);

Fig 2. DHEA change over time in DHEA treated group (●) and placebo group (○) ($p < 0.0006$ for comparison between the groups);

Fig 3. Total testosterone change over time in DHEA treated group (●) and placebo group (○) ($p < 0.01$ for comparison between the groups);

Fig 4. DHT change over time in DHEA treated group (●) and placebo group (○) ($p < 0.005$ for comparison between the groups);

Fig 5. Estrone change over time in the DHEA treated group (●) and placebo group (○) ($p=0.594$ for comparison between the groups).

Fig 6.
Serum cortisol concentrations during 1µg corticotropin stimulation test;

Fig 7.
Plasma corticotropin concentrations during CRH stimulation test;

Fig 8.
Serum cortisol concentrations during CRH stimulation test;

Fig 9.
Serum LH concentrations during GnRH stimulation test;

Fig 10.
Serum FSH concentrations during GnRH stimulation test.

Table 1

Baseline characteristics

	DHEA group	Placebo group
Number of subjects	9	6
Race	Hispanic: 3 African/American: 4 White: 2	Hispanic: 1 African/American: 5 White: 0
AIDS diagnosis	5	4
Mean Age (years)	41.33+/-10.37	44.33+/-7.09

Table 2

Parameters that changed in the DHEA-treated group, but not in the placebo group

Parameter	DHEA Group		Placebo Group		P value between two groups
	Week 1	Week 8	Week 1	Week 8	
DHEA-S (ng/ml)	95.3 +/- 88.0	1138.0 +/- 849.0	104.8 +/- 77.0	129.0 +/- 84	<0.032
DHEA (ng/ml)	2.7 +/- 1.7	63.3 +/- 75.9	6.5 +/- 3.6	6.5 +/- 8.0	< 0.0006
Total testosterone (ng/ml)	0.2 +/- 0.1	0.7 +/- 0.6	0.2 +/- 0.1	0.24 +/- 0.15	< 0.01
DHT (ng/ml)	142.9 +/- 67.0	907.2 +/- 523.0	159.0 +/- 67.0	199.6 +/- 88.0	<0.0625
Androstenedione (ng/ml)	0.87 +/- 0.53	3.94 +/- 2.86	1.24 +/- 0.80	2.83 +/- 1.93	0.51861
Estrone (pg/ml)	144.3 +/- 83.0	309.6 +/- 142.0	143.2 +/- 125.0	254 +/- 213.0	0.59380

Table 3

Parameters that did not change with DHEA treatment

	DHEA Group	
Parameter	Week 1	Week 8
Cortisol (μg/dl)	13.8+/-5.4	10.3+/-7.7
Fasting serum insulin (μIU/ml)	42.7+/-32.8	40.1+/-25.3
Sex hormone binding globulin	98.9+/-52.4	77.0+/-77.3
Free testosterone (ng/ml)	0.8+/-0.4	2.9+/-2.7
Estradiol (pg/ml)	175.7+/-197.3	94.5+/-49.7
Adiponectin (ng/ml)	13.0+/-6.3	12.9+/-7.0
IGF-1 (ng/ml)	174.8+/-55.1	195.4+/-101.4
IGFBP-1 (ng/ml)	28.5+/-33.7	25.6+/-21.7
IGFBP-3 (ng/ml)	2190.0+/-1413.0	2476.0+/-1552.0
	Placebo Group	
Parameter	Week 1	Week 8
Cortisol (μg/dl)	7.6+/-1.5	8.9+/-3.7
Fasting serum insulin (μIU/ml)	20.1+/-21.0	38.1+/-39.2
Sex hormone binding globulin	104.6+/-37.2	71.1+/-18.6
Free testosterone (ng/ml)	0.7+/-0.2	0.8+/-0.5
Estradiol (pg/ml)	110.1+/-58.2	178.2+/-156.1
Adiponectin (ng/ml)	7.0+/-7.3	6.4+/-4.3
IGF-1 (ng/ml)	81.5+/-48.8	134.7+/-21.2
IGFBP-1 (ng/ml)	20.2+/-20.1	15.6+/-10.3
IGFBP-3(ng/ml)	1578.0+/-592.2	1783.0+/-1002.0