Dehydroepiandrosterone in Morbidly Obese Adolescents: Effects on Weight, Body Composition, Lipids, and Insulin Resistance

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The hormone dehydroepiandrosterone (DHEA) has been reported to have beneficial effects on obesity, diabetes mellitus, and serum lipids in animal studies, but results in human studies are less clear. We conducted a randomized double-blind placebo-controlled trial to determine the effects of DHEA treatment on obesity and related physiologic conditions in adolescents and young adults. In this 10-week study, 13 morbidly obese subjects received a placebo for 2 weeks. After this run-in period, patients were randomized, with seven subjects (mean age, 15.5 years; body mass index [BMI, derived by dividing body weight in kilograms by height in meters squared], 48.2 ± 9.7 [mean ± SD]) receiving DHEA 40 mg sublingually twice daily for 8 weeks and six subjects (mean age, 18.0 years; BMI, 52.9 ± 14) receiving placebo. Variables measured included body weight, body composition, resting metabolic rate (RMR), serum lipid levels, insulin sensitivity, and serum steroid levels. Treatment with DHEA resulted in a statistically significant increase in plasma DHEA and DHEA sulfate (DHEAS) concentrations ($P < .01$). Testosterone (T) levels were significantly increased in females who received DHEA. DHEA administration had no effect on body weight, sense of well-being, or any other measured variables. These findings suggest that DHEA 40 mg administered sublingually twice daily for 8 weeks has no positive effect on body weight, body composition, serum lipids, or insulin sensitivity in extremely obese adolescents and young adults.

DEHYDROEPIANDROSTERONE (DHEA) administration in animals has been reported to reduce body weight and body fat. This was demonstrated first in mice in 1977 by Yen et al[1] and confirmed later in several other animal studies.[2,3] The results of these studies indicate that DHEA affects a number of pathways of fat and carbohydrate metabolism, several of which are unique to the liver. Inhibition of hepatic glucose-6-phosphate dehydrogenase activity, alterations in the cycle of deacylation/reacylation and increased peroxisomal oxidation of fatty acids, and effects on hepatic mitochondrial respiration by DHEA have all been proposed as mechanisms of action of DHEA as an antiobesity agent.[2,3]

Evidence supporting the use of DHEA for the treatment of human obesity remains less clear. Studies in normal and obese men and postmenopausal women using pharmacologic doses of DHEA (1,600 mg/d orally) for 4 weeks show conflicting results.[4-7] In another study, DHEA 50 mg/d administered orally for 12 weeks in aging men and women improved their sense of well-being but had no effect on weight.[8] To our knowledge, there are no published reports in which DHEA has been administered to children or adolescents.

We report herein the results of administration of DHEA 40 mg sublingually twice daily for 8 weeks in a double-blind placebo-controlled trial. We examined the effects of DHEA on body weight, body composition, serum lipids, and insulin sensitivity in a population of adolescents and young adults with extreme or "morbid" obesity (body mass index [BMI], derived by dividing body weight in kilograms by height in meters squared, >30).

SUBJECTS AND METHODS

Subjects

Nineteen extremely obese subjects were recruited for the study. Six subjects withdrew from the study before its completion. These subjects did not differ in any way from those remaining in the study, and we report data only on subjects who completed the entire study.

Thirteen morbidly obese young people, three males and 10 females aged 13 to 26 years (mean age, 16.5), completed the study. BMI was 49 ± 11.8 (mean ± SD), with a range of 35 to 60.5. All subjects were in good health except for being obese, and all had completed puberty (Tanner stage V). They all reported having been obese since early childhood, and felt unable to comply with a weight-reducing diet regimen. Most of them had attempted weight reduction by diet alone years before the study, without success. None of them had been treated pharmacologically before, and none were on a weight-reducing regimen for at least 6 months before the study. Exclusion criteria were mental retardation, diabetes mellitus, treatment with any medication that could affect lipid levels, untreated hypothyroidism or hyperthyroidism, pregnancy, and concurrent participation in any other weight-reduction program or study. The protocol was approved by the Institutional Review Board, and written informed consent was obtained from all subjects and from parents of the minors.

Study Design

All subjects received placebo for the first 2 weeks as a single-blind run-in period. This was designed to exclude individuals who were unlikely to be compliant and to ensure stable body weight before randomization. The patients were then randomly assigned to two double-blind treatment groups: seven subjects (mean age, 15.5 years; BMI, 48.2 ± 9.7) received DHEA 40 mg sublingually twice daily for 8 weeks, and six subjects (mean age, 18.0 years; BMI, 52.9 ± 14) received placebo. Table 1 shows the characteristics of each study group. There was no stratification by any criteria for the randomization.

Eligible subjects were admitted to the Clinical Research Center

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Table 1. Demographic Characteristics of Each Study Group

	Placebo	DHEA
No.	6	7
Mean age, yr (range)	18 (13-26)	15.5 (13-19.5)
Sex (females/males)	4/2	6/1
Race (white/black/Hispanic)	3/2/0	1/3/3
Weight, kg (mean ± SD)	144 ± 55	130 ± 32
BMI (mean ± SD)	52.9 ± 14.1	48.2 ± 9.7

NOTE. There are no statistically significant differences in age, weight, or BMI between the two groups.

of The New York Hospital-Cornell Medical Center before and at completion of the trial for the following measurements and tests: concentrations of serum DHEA, DHEA sulfate (DHEAS), D4-androstenedione (D4), testosterone (T), total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and lipoprotein(a) [Lp(a)], and intravenous (IV) glucose tolerance (modified minimal model).[9] Total body fat and body composition were assessed by Lange skinfold calipers, dual-energy x-ray absorptiometry (DXA), and bioelectrical impedance analysis (BIA). Resting metabolic rate (RMR) was measured by indirect calorimetry. During the 10-week study period, subjects were followed weekly as outpatients. Weight-reducing diet instructions were not given to them; they were asked not to make any changes in diet or exercise and to keep a weekly food diary to ensure a constant diet during the trial. At each visit, subjects were weighed on the same scale and asked about any side effects or concurrent illnesses. A 1-week supply of pills was provided, and unused pills were counted. The bottles containing identical-appearing pills of active drug or placebo were provided by Pharmedic (Wheeling, IL). Plasma DHEA, DHEAS, D4 and T concentrations were measured at weeks 1, 3, 5, and 7.

Methods

DHEA and other steroid levels were measured by specific radioimmunoassays using modifications of previously described methods.[10] Sensitivities of the assays were 15 pg for DHEA and DHEAS, 5 pg for T, and 13 pg for D4. Intraassay coefficients of variation were less than 10% for DHEA, T, and D4 and less than 11% for DHEAS. Interassay coefficients of variation were less than 14% for DHEA, T, and D4 and less than 11% for DHEAS. Serum concentrations of TC and TG were measured by enzymatic methods after a 12-hour fast. HDL cholesterol level was measured enzymatically after precipitation of lipoproteins containing apolipoprotein B with dextran sulfate–magnesium chloride.[11] LDL cholesterol content was calculated by the Friedewald equation. Lp(a) (total mass) content was measured using the Incstar Lp(a) assay.[12] All measurements were made using the Roche COBAS FARA II clinical chemistry analyzer.

Insulin sensitivity was assessed by an IV glucose tolerance test using the modified minimal model.[9] After an overnight fast, a glucose bolus (300 mg/kg) was administered IV, followed 20 minutes later by a bolus of tolbutamide (500 mg IV). Blood for determination of glucose and insulin was obtained from a contralateral vein at 0, 2, 4, 8, 19, 22, 30, 40, 50, 70, 90, and 180 minutes. Insulin sensitivity (S_I) and insulin effectiveness (S_G) were calculated using the modified minimal model computer program. Glucose was analyzed in whole blood by the glucose oxidase method. Insulin level was measured by radioimmunoassay.[13]

Body composition was measured by DXA (software 3.2, total body scanner-DPX; Lunar Radiation, Madison, WI) and BIA (four-terminal impedance analyzer, model BIA-103; RJL Systems, Detroit, MI). Assessment of body fat by measuring skinfold thickness using the Lange calipers was attempted but was not possible in the majority of patients, since the grip of the calipers was not sufficiently large to encompass the various skinfolds. RMR was calculated by indirect calorimetry using a Deltatrac Metabolic Monitor after an overnight fast, with the subject lying supine for 30 minutes.

Analysis of Data

The results are expressed as the mean ± SD. The change in various measurements (weight, lipids, body fat, lean body mass, RMR, S_I, and S_G) from the run-in period to the end of study for the control group was compared with the change over the same period for the DHEA group using a paired t test. Analysis of changes in various steroids over time and between the two groups was performed using ANOVA. P less than .05 was considered significant for all analyses.

RESULTS

Body Weight, Body Composition, and RMR

No significant changes in body weight were seen during the initial single-blind placebo period. Body weight was not affected by 8 weeks of DHEA administration (0.15 ± 0.1 kg weight gain in the DHEA group v 1.86 ± 3.4 kg in the control group, NS). No significant changes in body fat (kilograms) and lean body mass (kilograms) by DXA and BIA for the two groups were detected at the end of the trial (Table 2). RMR increased by 5% in the DHEA group, versus no change in the placebo group (104 ± 161 kcal/24 h in the DHEA group v 8.33 ± 100 kcal/24 h in the control group). This difference did not reach statistical significance.

Serum Lipid Concentrations and Insulin Resistance

No significant changes in lipid levels were observed (Table 2). A noted trend was an increase in TC in the DHEA group (0.73 ± 0.18 v −0.07 ± 0.46 mmol/L in the control group). According to baseline measurements, all of these subjects showed extreme insulin resistance without evidence of diabetes. DHEA did not cause any significant change in insulin sensitivity (S_I) or glucose effectiveness (S_G), as calculated by the minimal model, between the study groups (Table 2).

DHEA and Other Androgens

Treatment with DHEA resulted in a statistically significant increase of DHEA ($P < .01$), DHEAS ($P < .001$), and D4 ($P < .001$) concentrations in treated subjects versus the placebo group. Serum concentrations for each measured steroid are shown in Table 3. The highest serum DHEA levels were seen in week 3 (118% increase from baseline). DHEAS increased in the DHEA-treated group from 5.4 ± 2.4 μmol/L at baseline to 21 ± 1.4 μmol/L in week 5 (288% increase). D4 concentrations were increased significantly in the DHEA group versus the placebo group ($P < .001$). This increase can be partly explained by higher D4 concentrations at baseline in the DHEA group ($P = .046$). However, the increase in D4 concentrations over time was significant in the DHEA group only ($P = .006$), demonstrating the positive effect of treatment on D4 levels. Serum T values were not significantly in-

Table 2. Change in Weight, Body Composition, RMR, Insulin Sensitivity, and Lipid Concentrations in Placebo and DHEA Groups

Parameter	Placebo			DHEA		
	Pre	Post	Pre − Post	Pre	Post	Pre − Post
Weight (kg)						
First 2 weeks of placebo	144 ± 55	144.2 ± 55	0.2 ± 1.1	130 ± 32	129 ± 32	−1 ± 1.1
DHEA *v* placebo	144.2 ± 55	146.06 ± 53	1.86 ± 3.4	129 ± 32	129.15 ± 29	0.15 ± 0.1
Fat by DXA (kg)	56.74 ± 10.3	58.63 ± 11.3	1.89 ± 1.49	50 ± 4.3	49.89 ± 5.3	−0.11 ± 1.15
Lean by DXA (kg)	56.64 ± 8.3	55.72 ± 5.4	−0.92 ± 4	56.68 ± 8.8	57.2 ± 8.6	0.5 ± 1.6
Fat by BIA (kg)	59.45 ± 9.9	59.8 ± 6	0.35 ± 4	51.5 ± 10	48.92 ± 12	−2.58 ± 2.8
Lean by BIA (kg)	63.24 ± 4.7	64.5 ± 5.6	1.26 ± 3	61.18 ± 8.4	64.25 ± 9	3 ± 2.85
RMR (kcal/24 h)	2,405 ± 695	2,396 ± 774	−8.33 ± 100	2,091 ± 322	2,195 ± 308	104 ± 161
S_I ($min^{-1} \cdot uU^{-1} \cdot mL^{-1}$)	1.33 ± 0.88	0.92 ± 0.72	−0.4 ± 0.7	1.2 ± 1.2	1.79 ± 1.13	0.58 ± 0.7
S_G (min^{-1})	0.023 ± 0.004	0.034 ± 0.008	0.018 ± 0.016	0.028 ± 0.09	0.026 ± 0.08	0.002 ± 0.014
TC (mmol/L)	5.45 ± 2.33	5.38 ± 2.37	−0.07 ± 0.46	4.09 ± 0.75	4.82 ± 2.45	0.73 ± 0.18
LDL (mmol/L)	3.87 ± 2.31	3.81 ± 2.33	−0.06 ± 0.41	2.53 ± 0.8	3.22 ± 2.09	0.69 ± 1.73
HDL (mmol/L)	1.04 ± 0.24	0.94 ± 0.20	−0.10 ± 0.19	0.91 ± 0.26	0.77 ± 0.13	−0.15 ± 0.28
Cholesterol/HDL ratio	5.33 ± 1.95	5.80 ± 2.30	0.50 ± 0.80	4.80 ± 1.40	5.90 ± 2.60	1.20 ± 1.79
VLDL (mmol/L)	0.54 ± 0.22	0.63 ± 0.10	0.09 ± 0.17	0.64 ± 0.19	0.60 ± 0.17	−0.04 ± 0.08
TG (g/L)	1.04 ± 0.41	1.22 ± 0.22	0.17 ± 0.31	1.25 ± 0.38	1.16 ± 0.33	−0.09 ± 0.17
Lp(a) (mg/dL)	43.6 ± 49	40.6 ± 47	−3 ± 7.8	36 ± 47	30.8 ± 38	−5.2 ± 12

NOTE. Results are the mean ± SD. All results are statistically nonsignificant.
Abbreviations: Pre, pretreatment; Post, posttreatment.

creased during DHEA administration. However, when female subjects were analyzed separately, a significant increase in T concentrations was found in the DHEA-treated group ($P = .01$; Table 3).

The relationship between serum DHEA concentration at baseline and BMI was also studied. An inverse correlation between serum DHEA level and BMI in morbidly obese premenopausal women has been previously demonstrated.[14] Contrary to that results, we found no correlation between BMI and DHEA concentrations ($R^2 = .001$, $P = .9$; Fig 1), and no gender influence on these results was seen ($R^2 = .03$ and $P = .8$ when female subjects were analyzed separately).

Other Measures

No side effects were reported during the study. Hirsutism in female subjects did not develop or progress. No changes in appetite, activity, or sense of well-being were reported, and menstruation patterns remained unchanged.

DISCUSSION

DHEA has been proposed as a treatment for a wide variety of conditions, including obesity, diabetes, aging, cancer, and cardiovascular disease. It is thought to have beneficial effects on immune responses and nervous system pathophysiology.[15] However, despite multiple research efforts, the biological roles of DHEA and its metabolite, DHEAS, have not yet been clearly delineated.

DHEA levels are influenced by age, with a progressive decline to very low levels in the elderly, and by genetics and physiological status.[16,17] In obese subjects, both normal and low DHEA levels have been reported, and production and clearance rates of the hormone have both been shown to be

Table 3. Serum Concentrations (mean ± SD) of DHEA, DHEAS, D4, and T During DHEA Administration

Parameter	Pretreatment	Week 1	Week 3	Week 5	Week 7	Posttreatment	*P**
DHEA (nmol/L)							
DHEA	16.8 ± 7.8	21.5 ± 11.2	36.7 ± 19.2	23.4 ± 4.2	21.6 ± 10.8	18.4 ± 6.9	<.01
Placebo	12.8 ± 8.1	13.5 ± 7.6	13.3 ± 8.8	13.6 ± 6.6	15.1 ± 11.2	9.0 ± 2.1	
DHEAS (μmol/L)							
DHEA	5.4 ± 2.4	14.7 ± 12.7	17.2 ± 6.2	21.0 ± 1.4	17.1 ± 7.9	12.3 ± 4.5	<.001
Placebo	5.3 ± 3.3	7.5 ± 4.3	6.0 ± 2.3	5.8 ± 2.9	5.7 ± 2.5	5.3 ± 1.8	
D4 (nmol/L)†							
DHEA	5.0 ± 2.1	7.9 ± 6.7	6.9 ± 3.1	7.9 ± 2.7	6.2 ± 2.6	5.9 ± 2.2	<.001
Placebo	2.8 ± 0.9	2.8 ± 1.0	3.2 ± 1.1	2.8 ± 1.5	3.4 ± 1.8	2.7 ± 1.3	
T (nmol/L), all subjects							
DHEA	2.8 ± 2.6	4.8 ± 4.7	4.9 ± 4.9	4.1 ± 4.7	3.5 ± 3.0	3.0 ± 3.1	.6
Placebo	2.7 ± 2.5	2.8 ± 3.4	3.0 ± 3.3	3.5 ± 4.4	3.7 ± 5.2	3.0 ± 3.5	
T (nmol/L), female subjects							
DHEA	1.9 ± 0.9	2.4 ± 1.0	2.3 ± 0.7	2.0 ± 0.9	2.3 ± 0.6	1.8 ± 0.5	.01
Placebo	1.3 ± 0.4	1.1 ± 0.8	1.4 ± 1.0	1.2 ± 0.7	1.4 ± 0.9	1.2 ± 0.7	

*Effect of DHEA treatment on various steroid levels between DHEA and placebo groups as analyzed by ANOVA.
†Baseline steroids between DHEA and placebo groups were not different, except for D4 ($P = .04$).

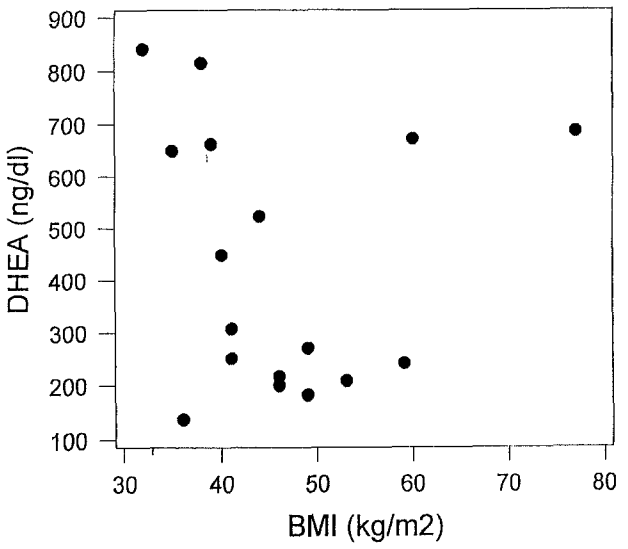

Fig 1. Lack of correlation between BMI and serum DHEA concentrations (multiply units in ng/dL by 0.03472 to obtain nmol/L).

increased.[18] In morbidly obese women (mean BMI, 41.8), a linear inverse correlation was found between BMI and DHEA levels.[14] Similar correlations were not seen in our study population, suggesting that other factors may influence metabolism of the hormone in subjects with a very high BMI.

The potential usefulness of DHEA as an antiobesity agent is indicated by previous trials of DHEA administration in animals. Numerous studies in rodents indicate that DHEA alters several enzymes involved in lipid and carbohydrate metabolism and induces futile cycling, resulting in decreased energy stored as fat.[2,3] DHEA also has been shown to have antiglucocorticoid actions caused by direct modulation of the hepatic glucocorticoid receptor, and it has been proposed that its antiobesity effect may represent chronic antiglucocorticoid activity.[19,20] The results of DHEA administration in human obesity are disappointing and conflicting. The current study failed to show any beneficial effects of sublingual DHEA administration on weight, body composition, lipids, and insulin resistance in morbidly obese young people. A 5% reduction in body weight and fat, a 10% change in RMR, and a 15% change in TC could have been detected by this trial with 90% certainty given the sample size, indicating that treatment with DHEA does not result in clinically significant changes to justify its use as an antiobesity medication. The effects of treatment on S_I and LDL cholesterol remain uncertain, given the large variability over the study period and the small sample size. Since insulin resistance in men is associated with obesity and body composition, it becomes very unlikely that DHEA administration at the present dose would have a beneficial effect on S_I.

Perhaps the effects of DHEA in pharmacological doses in rodents are different from those in humans. In contrast to humans, rodent adrenal glands lack the enzyme, 17-hydroxylase/17,20-lyase, and thus do not normally produce DHEA.[21] Moreover, not all animal strains respond to DHEA in the same fashion, suggesting that additional genetic factors influence these responses. Possibly, various human populations will respond differently to treatment with DHEA. We tried to address the above issue by studying the effects of DHEA in a population of morbidly obese young subjects with a history of severe obesity since early childhood. Although there are not yet genetic markers for human obesity, our study population represents one in which genetic factors would be expected to play a significant role.

Other possible explanations for our negative findings include the small sample size, the short trial period, and/or the modest increase in DHEA levels. Compared with previous reports, the increases in DHEA and DHEAS levels were less pronounced,[4-7] most likely due to the much smaller dose of DHEA used (80 mg/d in the current study *v* 1,600 mg/d in earlier studies). Serum DHEA levels increased to a maximum of 118% after 3 weeks, but then showed a decline. This finding is unlikely to be due to noncompliance, since medications were dispensed weekly and drugs were strictly accounted for during each follow-up visit. A similar decline in DHEA levels after 2 weeks was previously reported.[6] This finding merits further confirmation, since it suggests that compensatory changes in synthesis or metabolic clearance occur when serum DHEA levels increase. The current study used a route of administration of DHEA—sublingual instead of oral—different from that of previous studies in an attempt to overcome the first passage through the liver, which could lead to rapid metabolism of the hormone. A trial with a higher dosage of DHEA in a similar population would carry the risk of virilization associated with a greater increase in T concentrations in female subjects, but might be considered in males.

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