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A Randomized, Double-Blind, Placebo-Controlled Study of 3-Acetyl-7-Oxo-Dehydroepiandrosterone in Healthy Overweight Adults

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ABSTRACT

Objective: **The purpose of this study was to determine the effects of 3-acetyl-7-oxo-dehydroepiandrosterone (7-oxo-DHEA) in healthy overweight adults.**

Methods: **In a double-blind, placebo-controlled protocol, 30 adults (28 women and 2 men; mean age, 44.5 ± 11.5 years) with a mean body mass index of 31.9 ± 6.2 kg/m^2 were randomly divided into 2 groups of 15: Group 1 received 7-oxo-DHEA 100 mg twice daily and Group 2 received placebo for 8 weeks. All subjects participated in an exercise training program 3 times per week. Each exercise session consisted of 60 minutes of cross-training (aerobic and anaerobic exercise) under the supervision of an exercise physiologist. In addition, each subject was instructed to follow a diet of ~1800 kcal/d (20 kcal/[kg · d]) by a registered dietitian. Subjects received biweekly dietary counseling to encourage compliance. Study participants underwent serum multiple-assay chemistry testing, as well as body composition, blood pressure, and dietary analysis at baseline, week 4, and week 8.**

Results: **Of the 30 subjects who entered the study, 23 completed the 8-week protocol. Seven subjects dropped out for personal reasons unrelated to the study. Group 1 lost a significant amount of body weight compared with Group 2 (−2.88 kg vs −0.97 kg; $P = 0.01$) over the 8 weeks. Group 1 also achieved a significant reduction in body fat compared with Group 2 (−1.8% vs −0.57%; $P = 0.02$). The rate of change in body fat per 4-week interval in Group 1 was 3.1 times that in Group 2 (−0.88% vs −0.28%; $P < 0.01$). Group 1 also experienced a significant increase in triiodothyronine (T3) levels compared with Group 2 over the 8-week study period (+17.88 ng/dL vs 2.75 ng/dL; $P = 0.04$). There were no significant changes in levels of thyroid-stimulating hormone (TSH) or thyroxine (T4) in either group. In addition, no significant changes were observed in vital signs, blood sugar, testosterone and estradiol levels, liver and renal function, or overall caloric intake during the study. No subjective adverse effects were reported throughout the study.**

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Conclusions: **The results of the study suggest that 7-oxo-DHEA combined with moderate exercise and a reduced-calorie diet significantly reduces body weight and body fat compared with exercise and a reduced-calorie diet alone. In addition, 7-oxo-DHEA significantly elevated T3 levels but did not affect TSH or T4 levels, indicating that it does not adversely affect thyroid function in the short term.**

Key words: **dehydroepiandrosterone, 7-oxo-DHEA, weight loss, body fat, thyroid function. (*Curr Ther Res Clin Exp.* 2000;61: 435–442)**

INTRODUCTION

The adrenal steroid dehydroepiandrosterone (DHEA) in supplemental doses has been shown in murine studies to increase thermogenesis and prevent obesity.[1,2] Previous research with DHEA has indicated that it can foster futile cycling, increase the rate of mitochondrial oxidation, and increase the activity of mitochondrial dehydrogenases in the liver. 3-Acetyl-7-oxo-dehydroepiandrosterone* (7-oxo-DHEA) is a natural metabolite of DHEA. 7-Oxo-DHEA differs from DHEA in that it has no androgenic activity, nor is it converted into estrogens.[3] Both thyroid hormone (thyroxine) and 7-oxo-DHEA induce the formation of liver mitochondrial glycerol-3-phosphate dehydrogenase (G3PD) and malic enzyme, suggesting that these agents increase thermogenesis through a similar mechanism.

Bobyleva et al[1] demonstrated that feeding rats 7-oxo-DHEA resulted in increases in liver catalase activity (+67%), rate of mitochondrial substrate oxidation, and fatty acyl-CoA oxidase activity (+128%). In addition, 7-oxo-DHEA has been shown to increase cytosolic G3PD activity, distinguishing it from thyroid hormone.[1] In 1997, Bobyleva et al[4] evaluated the effects of 7-oxo-DHEA on mitochondrial membrane potential and thermogenesis and found that when treated with respiratory inhibitors (eg, succinate and G3PD), liver mitochondria from rats treated with 7-oxo-DHEA or thyroid hormones showed a more rapid decline in membrane potential than did normal mitochondria. A lower membrane potential indicates greater thermogenesis. Noting that the pharmacokinetic profile of 7-oxo-DHEA is similar to that of thyroid hormone, these investigators studied the effects of 7-oxo-DHEA in both the euthyroid and hypothyroid rat. 7-Oxo-DHEA had no effect on mitochondrial respiration in the euthyroid rat, but did restore mitochondrial function in the hypothyroid rat.[4]

Given the thyroid hormone-like activity of 7-oxo-DHEA, and the fact that it restores the ATP/ADP carrier under thyroidectomy conditions, the next step in this investigation was to examine the effects of 7-oxo-DHEA in a human model. The purpose of this study was to evaluate the effects of

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7-oxo-DHEA in healthy overweight (body mass index >27 kg/m^2) adults. In addition, we examined the effects of 7-oxo-DHEA on thyroid function, sex hormones, and other physiological parameters.

SUBJECTS AND METHODS

In a double-blinded, placebo-controlled protocol, 30 subjects (28 women and 2 men; mean age, 44.5 ± 11.5 years) were randomly assigned to the experimental group or the placebo group. Healthy, physically active adults with a body mass index >27 kg/m^2 were eligible to participate in the study. Exclusion criteria included a history of heart disease, hypertension, diabetes mellitus (type 1 or 2), psychiatric disorders, use of any antidepressant medication, pregnancy, lactation, thyroid disease, cancer, allergy to any of the ingredients used in the test product, current or recent use of an anorectic medication (eg, phentermine, sibutramine, orlistat), and a reduced-calorie diet. Subjects were also excluded if they had no history of exercise or physical activity. All procedures were approved by the institutional review board, and written informed consent was obtained from all patients in a manner consistent with the Helsinki Declaration.

Dietary Supplements

Subjects in Group 1 received 2 capsules daily (200 mg/d) of 7-oxo-DHEA, and those in Group 2 received a matching maltodextrin placebo capsule. All capsules were identical in weight, color, size, and shape. To monitor compliance with the medication regimen, all unused capsules were returned at each scheduled laboratory visit.

Body Weight, Body Composition, and Blood Testing

Each subject was evaluated at baseline, week 4, and week 8. All appointments were with the same technician at approximately the same time of day and under the same conditions. Total body weight was measured using a balanced medical scale (Detecto Scale, Webb City, Missouri). Subjects were weighed while wearing only essential clothing after a 4-hour fast and voiding of the bladder. Body composition was determined using a skinfold caliper (Lange Caliper, Cambridge, Maryland) at the chest, midaxilla, triceps, abdomen, thigh, and subscapular and suprailiac areas. A trained exercise physiologist measured body composition under the same testing conditions at each laboratory visit. Percentage body fat was calculated using the Jackson-Pollack equation (7-site) for determining body density and the Siri equation for determining body fat.[5,6] In addition, all subjects had blood drawn from their antecubital vein for serum multiple-assay chemistry analysis (SMAC-20, Quest Diagnostics, Wallingford,

Connecticut). Each subject also underwent multiple blood pressure testing, pulse monitoring, plethysmography to determine hydration status, and Profile of Mood States testing (Educational and Industrial Testing Service, San Diego, California) at baseline, week 4, and week 8.

A pharmacokinetic subgroup of 6 female subjects was tested to determine the effect, if any, of 7-oxo-DHEA on testosterone and estradiol levels. Blood testing was conducted by an independent third party and both the researchers and subjects remained blinded to the additional testing.

Nutrition

Each subject was placed on a ~1800 kcal/d (20 kcal/[kg · d]) diet. The macronutrient composition of the diet was 50% to 55% carbohydrates, 30% fat, and 15% to 20% protein. The diet was also consistent with the National Cholesterol Education Program Step One Diet guidelines (NCEP-1).[7] All study participants received counseling every 2 weeks from a registered dietitian on how to follow the study diet. In addition, at each laboratory visit (baseline, week 4, and week 8), each subject met with the dietitian to review food choices and dietary compliance. Multiple dietary recalls were collected and analyzed via the Nutritionist IV program (First DataBank, Hearst Corporation, San Bruno, California).

Exercise

All subjects participated in a circuit training exercise program 3 days per week under the guidance of an exercise physiologist. At each session, subjects exercised for 60 minutes at ~70% of age-predicted heart rate maximum (Karvonen formula) and ~70% of predicted 1 repetition maximum (1RM). The exercise program consisted of step aerobics and weight training.

Baseline analyses were carried out using the Wilcoxon and Fisher exact test. Mean changes from baseline were tested within each group using the signed rank test; mean changes from baseline across study groups were analyzed using the Wilcoxon test. $P \leq 0.05$ was considered statistically significant.

RESULTS

Of the 30 subjects who entered the study, 23 completed the 8-week protocol—13 in Group 1 and 10 in Group 2. Seven subjects dropped out for personal reasons unrelated to the study (work-related duty, car accident, family illness, relocation, and inability to comply with study protocol while traveling). No significant differences were found at baseline between groups with respect to age, body mass index, body weight, body fat, blood

pressure, hydration status, or thyroid hormone levels (Table I). All subjects completed the prescribed number of exercise sessions and took the prescribed number of pills (100% compliance). There were no objective complaints of adverse events in either group, and no adverse effects were detectable in the blood chemistry analyses.

Table I. Baseline characteristics (mean ± SD) of the experimental and placebo groups.*

	7-Oxo-DHEA (n = 13)	Placebo (n = 10)
Age (y)	43.7 ± 7.8	45.3 ± 15.3
Body mass index (kg/m^2)	32.1 ± 5.4	31.7 ± 7.0
Body weight (kg)	87.34 ± 17.4	95.91 ± 33.5
Body fat (%)	28.22 ± 4.02	28.57 ± 4.73
Systolic blood pressure (mm Hg)	112.4 ± 10.6	120.8 ± 12.5
Diastolic blood pressure (mm Hg)	73.87 ± 7.35	74.53 ± 7.83
TBW (%)	50.00 ± 5.34	50.37 ± 7.64
T3 (ng/dL)	117.9 ± 18.2	129.2 ± 33.4
TSH (MIU/mL)	1.76 ± 0.83	1.72 ± 0.95
T4 (μg/dL)	8.55 ± 1.93	8.41 ± 1.88

TBW = total body water; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; T4 = thyroxine.
* No significant differences between groups were observed at baseline.

Compared with subjects in Group 2, subjects in Group 1 lost a significant amount of weight at both weeks 4 (−1.71 kg vs −0.01 kg; $P < 0.01$) and 8 (−2.88 kg vs −0.97 kg; $P = 0.01$) (Table II). The rate of weight loss was also greater in Group 1 at both time points ($P < 0.01$).

At week 4 there were no significant changes between the groups in mean percentage body fat. At week 8, subjects in Group 1 lost a significant amount of body fat compared with those in Group 2 (−1.80% vs −0.57%; $P = 0.02$).

Group 1 experienced a mean 17.88 ng/dL increase in triiodothyronine (T3) over the 8-week period compared with a 2.75 ng/dL increase in Group 2. The change versus baseline for Group 1 and the difference between groups was significant ($P = 0.04$). At all measurement points, T3 levels remained within the normal range (75–220 ng/dL). There were no significant changes in levels of thyroxine (T4) or thyroid-stimulating hormone (TSH).

In the subgroup of 6 subjects who were tested for the effect of 7-oxo-DHEA on sex hormones, there were no significant changes in either testosterone or estradiol levels at weeks 4 and 8.

No significant changes from baseline were observed in systolic or diastolic blood pressure, hydration status, caloric intake, measures of fatigue and vigor from the Profile of Mood States, serum glucose levels, total cholesterol levels, renal and liver function, or hematological profiles within and across groups at weeks 4 and 8.

Table II. Physical and physiological findings (mean ± SD) at week 8 versus baseline.

	7-Oxo-DHEA (n = 13)			Placebo (n = 10)		
	Baseline	Week 8	Mean Change	Baseline	Week 8	Mean Change
Body weight (kg)	87.34 ± 17.4 (range: 63.6–168)	83.63 ± 18.4 (range: 58.1–168)	-2.88*	95.91 ± 33.5 (range: 66.8–112.0)	88.95 ± 29.6 (range: 65.5–105)	-0.97
Body fat (%)	28.22 ± 4.02	25.95 ± 4.86	-1.80†	28.57 ± 4.73	28.06 ± 4.45	-0.57
Systolic blood pressure (mm Hg)	112.4 ± 10.6	116.9 ± 12.3	5.4	120.8 ± 12.5	117.8 ± 11.3	-0.6
Diastolic blood pressure (mm Hg)	73.87 ± 7.35	73.4 ± 5.1	0.5	74.53 ± 7.83	73.4 ± 7.8	-1.4
T3 (ng/dL)	117.9 ± 18.2 (range: 91–163)	130.1 ± 17.3 (range: 98–206)	17.88‡	129.2 ± 33.4 (range: 91–170)	141.0 ± 27.3 (range: 119–170)	2.75
TSH (MIU/mL)	1.76 ± 0.83	1.61 ± 0.67	0.3	1.72 ± 0.95	1.58 ± 1.34	-0.23
T4 (μg/dL)	8.55 ± 1.93	8.41 ± 2.08	-0.34	8.41 ± 1.88	8.78 ± 2.77	0.22
Testosterone§ (ng/dL)	34.17 ± 14.2 (range: 14–48)	40.50 ± 16.3 (range: 10–73)	9.5			
Estradiol§ (pg/mL)	80.50 ± 27.1 (range: 62–124)	61.50 ± 46 (range: 27–113)	-46.5			

T3 = triiodothyronine; TSH = thyroid-stimulating hormone; T4 = thyroxine.
* Significant difference versus placebo ($P = 0.01$).
† Significant difference versus placebo ($P = 0.02$).
‡ Significant difference versus placebo ($P = 0.04$).
§ Measurements were made in a subgroup of 6 female subjects.

DISCUSSION

In the present study, administration of 7-oxo-DHEA 200 mg/d combined with moderate amounts of exercise and a reduced-calorie diet of 1800 kcal/d for 8 weeks resulted in significant changes in body composition. The group receiving the 7-oxo-DHEA supplements experienced a statistically significant 4.4% weight reduction over the course of the study. Eighty-six randomized clinical trials evaluating the effectiveness of diets on weight loss show a strong and consistent weight loss of 8% to 10% in studies that lasted 3 to 12 months.[8,9] Indeed, a loss of 8% to 10% of initial body weight for an overweight person reduces his or her risk for heart disease, diabetes, cancer, and other overweight- and obesity-related disease.[8] The duration of the current study was 8 weeks. Given that the rate of weight loss per 4-week interval was significant, we postulate that if the study had been longer in duration, a greater mean weight loss would have been observed. The results of the study support the recommendation of the American Dietetic Association that weight loss programs should focus on improving health through small weight losses that are achievable and maintainable.[9] The rate of weight loss in the placebo group was <0.5 kg per week versus 1.4 kg per week in the 7-oxo-DHEA group. We postulate that this difference is due to the efficacy of 7-oxo-DHEA and not lack of compliance with the diet or exercise portions of the study in the placebo group. The nonsignificant weight change observed in the placebo group may have been greater if a more severe caloric restriction or more rigorous exercise had

been prescribed. The reduction in body fat observed in the group treated with 7-oxo-DHEA is consistent with the thermogenic profile of this agent. In a previous study, 7-oxo-DHEA induced an increase in fatty acyl-CoA oxidase activity.[4] Fatty acyl-CoA oxidase, or acyl-CoA synthetase, is the major enzyme responsible for the first step in the oxidation of fatty acids. The loss of body fat in the group treated with 7-oxo-DHEA suggests that fat stores were the major fuel source for energy in the subjects who ingested the supplement. Because we did not measure the respiratory quotient, the loss in body fat can be attributed only partially to an increase in the oxidation of fat.

7-Oxo-DHEA, like thyroid hormone, increases mitochondrial respiration, which may contribute to its thermogenic effect.[4] In this study, the group receiving 7-oxo-DHEA had a significant increase (+17.88 ng/dL; 9.4%) in levels of T3, whereas the mean changes in the group receiving placebo (+2.75 ng/dL) were within the normal daily variance of T3. The increase in T3 is also indicative of the thermogenic effect of 7-oxo-DHEA and supports the theory that 7-oxo-DHEA promotes the burning of fat for energy by enhancing fat oxidation.

Despite the elevations in T3 levels, there were no significant changes in TSH or T4 levels, suggesting that 7-oxo-DHEA does not induce untoward downregulation of or negative feedback on thyroid function. The effect of long-term administration of 7-oxo-DHEA on thyroid function remains to be determined.

CONCLUSIONS

The results of the study suggest that 7-oxo-DHEA is a well-tolerated and effective weight loss aid. 7-Oxo-DHEA 200 mg/d in combination with exercise and reduced caloric intake is more effective in reducing body weight and body fat over 8 weeks than exercise and a reduced-calorie diet alone in overweight adults.

Acknowledgment

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