The Effect of Dehydroepiandrosterone Combined with a Low-Fat Diet in Spontaneously Obese Dogs: A Clinical Trial

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Abstract

KURZMAN, ILENE D, DAVID L PANCIERA, JAMES B MILLER, E GREGORY MacEWEN. The effect of dehydroepiandrosterone combined with a low-fat diet in spontaneously obese dogs: A clinical trial. *Obes Res.* 1997;6:20–28.

Dehydroepiandrosterone (DHEA) has been shown to have antiobesity activity in rodents and spontaneously obese dogs. This study evaluated the effect of DHEA or placebo combined with a low-fat/high-fiber diet in spontaneously obese dogs in a clinical trial. Spontaneously obese, euthyroid dogs, referred to the University of Wisconsin School of Veterinary Medicine for treatment of their obesity, were evaluated for percent overweight, rate of weight loss, serum cholesterol, plasma lipoprotein and serum biochemistry profiles, complete blood count, and endocrine profiles (T4, T3, cortisol, insulin, and DHEA-sulfate). DHEA-treated dogs had a significantly increased rate of actual and percent excess weight loss compared with placebo-treated dogs. Serum cholesterol decreased in both treatment groups; however, DHEA-treated dogs had a significantly greater reduction than placebo-treated dogs. DHEA-treated dogs had a significant 32% reduction in total plasma cholesterol, which was due to a 27% reduction in the lipoprotein fraction containing the high-density lipoprotein (HDL) and a 50% reduction in the lipoprotein fraction containing the low-density lipoprotein (LDL). Placebo-treated dogs did not have a significant reduction in total plasma cholesterol or in the fraction containing LDL; however, they did have a significant 11% reduction in the fraction containing HDL. Significant decreases in serum T4 and T3 observed in dogs receiving DHEA were not noted in dogs receiving placebo. DHEA in combination with caloric restriction results in a faster rate of weight loss than does caloric restriction alone. In addition, DHEA has hypocholesterolemic activity, particularly affecting the lipoprotein fraction containing the LDL cholesterol.

Key words: anti-obesity, cholesterol, lipoproteins

Introduction

Dehydroepiandrosterone (DHEA) is a 17-ketosteroid of adrenal and gonadal origin and, in its sulfated form (DHEAS), is the most abundant steroid circulating in human plasma (11). In humans, concentrations of DHEAS undergo the most marked age-related decline of any steroid, peaking at around 20 years of age, progressively declining with age, and becoming constant at 50 years to 80 years of age (27,35,49). DHEA is the main precursor of placental estrogen and may be converted to active androgens and estrogen in peripheral tissue, although its biological role remains unclear (11,37). Early studies in obese mice and more recent studies in obese rats stimulated interest in the use of DHEA as an antiobesity agent (2,7–10,29,49,50). In a previous study, we showed that 13 (68%) of 19 spontaneously obese, euthyroid dogs treated with DHEA for 3 months lost 3% of their total bodyweight per month, without a reduction in food intake. Normal-weight dogs receiving DHEA did not lose weight (18). In addition, obese and normal-weight dogs had a significant reduction in serum cholesterol while on DHEA.

The exact pathogenesis of obesity is unknown; however, most studies suggest a delicate balance between energy intake and energy output. As in humans, most attempts to treat obesity in the dog involve a reduction in caloric intake (20). The purpose of the study reported here was to evaluate treatment with DHEA combined with a reduction in caloric intake and to compare the findings to dogs treated

Submitted for publication June 19, 1996.
Accepted for publication July 10, 1997.
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with caloric restriction and a placebo. We hypothesized that DHEA in combination with caloric restriction would have an additive effect, resulting in an increased rate of weight loss observed in treated dogs.

Methods and Procedures

Animals

Dogs entered into this study were from the population of privately owned patients of the University of Wisconsin Veterinary Medical Teaching Hospital (VMTH). The study protocol was approved by the University of Wisconsin Animal Care and Use Committee. To be eligible for the study, a dog had to be at least 15% overweight and in good health as determined by the pretreatment evaluation. The diagnosis of obesity for each dog was determined by gross observation (palpation) and comparison to ideal bodyweights for particular breed and stature (20). Ideal bodyweights for mixed breeds were independently estimated by three investigators (I.D.K., D.L.P., and J.B.M.) Information regarding a dog's previous bodyweight, which was estimated by its owner or veterinarian to be an optimal weight for that dog, was taken into consideration by the investigators when determining a dog's ideal bodyweight. Dogs that had abnormal thyroid or adrenal function were excluded from the study. Before entry, a signed study consent form was obtained from each dog's owner.

Pretreatment Evaluation

Preliminary evaluation of each dog included the following: a complete physical examination, bodyweight, subjective assessment of degree of adiposity, dietary recall history and at-home diet diary, complete blood count, serum biochemistry profile, thyroid and adrenal function tests (to rule out hypothyroidism and hyperadrenocorticism), and assessment of concentrations of serum cholesterol, insulin, and DHEAS (an immediate metabolite of DHEA), and plasma lipoproteins. All blood samples were collected after a 12-hour to 18-hour fast.

Treatment Assignment

Dogs were initially randomized to receive DHEA or placebo. Randomization was done by the pharmacist of the VMTH so that the dogs' owners and the investigators were blinded as to the treatment assignment. After 4 months to 6 months of treatment, if it was determined that the dog was not losing weight, the dog was crossed over to the other treatment group.

Treatment

At the time of entry, all dogs were placed on Hill's Prescription Diet r/d (kindly provided for this study by Hill's Pet Products, Topeka, KS), which is a reduced-fat, reduced-energy, and increased-fiber diet. Compared with Hill's Maintenance Diet, r/d has 55% less fat, 39% fewer kilocalories, and 670% more fiber. Hill's r/d contains 7% fat (61 kcal/100 g), 22% fiber (0 kcal/100 g), 25% protein (88 kcal/100g), and 39% carbohydrate (135 kcal/100 g). In comparison, Hill's Maintenance Diet contains 15.4% fat (134 kcal/100 g), 1.6% fiber (0 kcal/100 g), 25% protein (88 kcal/100 g), and 53.3% carbohydrate (187 kcal/100 g). For all dogs in the study, the r/d was prescribed at 60% of the kilocalories per day needed to maintain the dogs' estimated ideal bodyweight (as recommended for weight loss (20). Dogs were fed twice daily. To monitor for food compliance and quantity eaten, the owners were instructed to keep a food diary at home and return the completed form at each recheck visit. DHEA (Diosynth, Inc., Chicago, IL) was administered orally in capsules at a dose of 60 mg/kg per day (divided and given twice daily). The placebo consisted of capsules filled with lactose, prepared to look identical to the DHEA capsules and prescribed similarly at 60 mg/kg per day (divided and given twice daily). Treatment was discontinued when a dog reached its ideal bodyweight (20). To encourage compliance, only a 2-month supply of DHEA or placebo was dispensed at each recheck visit.

Treatment Evaluations

Monthly evaluations included a complete physical examination, bodyweight, and assessment of serum concentrations of DHEAS, cholesterol, and insulin, and a diary of the home diet. Every 4 months to 6 months, evaluations also included a serum biochemistry profile, thyroid and adrenal function tests, and a plasma lipoprotein profile. The final treatment evaluation for each dog was performed when the dog reached its ideal bodyweight (as defined above) or when the dog's weight had not changed for more than 2 consecutive months.

Assays

Complete blood counts and serum biochemistry profiles were done by the Clinical Pathology Laboratory of the VMTH. The thyroid function test was performed using 5 U of dermathycin, injected intravenously, and 0-hour and 4-hour serum samples were collected for assessment of thyroxine (T4) and triiodothyronine (T3) concentrations. Adrenal function was assessed by measuring serum cortisol concentration before and at 1 hour and 2 hours postadministration of 2.2 U/kg bodyweight of adrenocorticotropic hormone, injected intramuscularly. All endocrine assays were performed in the Radionuclide Laboratory of the School of Veterinary Medicine. Baseline and stimulated total T4, total T3, cortisol, and insulin concentrations were determined with commercially available solid-phase radioimmunoassay (RIA) kits (Coat-A-Count Total T4, Total T3, Cortisol, and Insulin; Diagnostic Products, Los Angeles, CA). Serum DHEAS concentration was determined with a commercially available RIA kit (ICN Biomedicals, Inc., Costa Mesa, CA) with the following modifications. After incubation of each

assay tube with the second antibody included in the kit (precipitating, goat anti-rabbit immunoglobulin G [IgG]), suspended complexes in each tube were incubated with 100 μL of a 10% solution of a second precipitating antibody (Goat Anti-Rabbit IgG; Sigma Chemical Company, St. Louis, MO) and 50 μL of a 4% solution of normal rabbit serum and then incubated for 10 minutes at 25°C. Each sample was then precipitated with 2 mL of a 3.3% PEG precipitating solution (PEG 8000; Sigma Chemical Company) and centrifuged at 1900*g* at 10°C. The tubes were then decanted and counted with a gamma counter. Cholesterol was determined with an enzymatic, colorimetric assay (Kit 352, Sigma Chemical Company).

Plasma lipoproteins were fractionated by ultracentrifugation. From previous studies in our laboratory (18; I.D. K., unpublished data), we have observed a minimal amount of cholesterol in fractions containing very low-density and intermediate-density lipoproteins (a total of approximately 3.5 mg/dL). For this study, we isolated the very low-density and intermediate-density lipoprotein in combination with the low-density lipoprotein (LDL). The fraction containing LDL was isolated by increasing the plasma density to 1.063 g/mL with sodium bromide (21,22). The plasma was then centrifuged, with a Beckman LB-70 ultracentrifuge with a 70.1 Titanium rotor, for 2.34×10^6 ghr. After centrifugation, the visible floating fraction (containing LDL) was aspirated, and the remaining plasma contained high-density lipoprotein (HDL). The concentration of total plasma cholesterol and cholesterol in each fraction was determined with the assay described above. The total amount of cholesterol in the fractions was compared with the total plasma cholesterol to determine a percent recovery for each assay. Making the assumption that the percent lost or gained was similarly distributed within the LDL- and HDL-containing fractions, the cholesterol concentrations for these fractions were adjusted to equal 100% of the measured total plasma cholesterol. The percent recovery of cholesterol in the LDL and HDL fractions for the dogs receiving DHEA was 91 ± 3 and 92 ± 4, and for the dogs receiving placebo, it was 85 ± 3 and 94 ± 4 for pretreatment and on treatment, respectively.

Data Analysis

The results of this study were analyzed by comparing findings on all dogs receiving DHEA with findings on all dogs receiving placebo. In addition, each of the treatment groups were divided into two groups, dogs that were mild or moderately obese (15% to 40% overweight, hereafter referred to as ≤40% overweight) and dogs that were grossly obese (>40% overweight). These groupings were based on definitions of obesity in humans, relating body mass index with percent overweight, that correlated with obesity-associated morbidity (15,41). Results of these subgroups were also compared by treatment. Comparisons made between groups were analyzed with a Student's *t*-test. Comparisons made within groups were analyzed with a Student's paired *t*-test. A p value of less than 0.05 was considered significant. All results are reported as mean ± standard error.

Results

Fifty-three dogs were evaluated for entry into this study. Of these, 10 were excluded: 9 were found to be hypothyroid and 1 had hyperadrenocorticism (Cushing's disease). Forty-three dogs were randomized to receive caloric restriction combined with either DHEA or with placebo. After randomization, three dogs were removed from the study for various reasons: one dog developed a thyroid tumor, one dog developed eosinophilic pneumonia, and one dog was determined to have been less than 15% overweight at the time of entry into the study. There were 40 cases available for evaluation.

Descriptions of the treatment groups with regard to the number of dogs and their sex and age are shown in Table 1. There were a total of 27 dogs that received DHEA and 21 that received placebo. In the ≤40% overweight group, 21 dogs received DHEA and 11 received placebo. In the >40% overweight group, 6 dogs received DHEA and 10 received placebo. Four dogs receiving DHEA were lost to follow-up after 4, 4.5, 5.5, and 6 months on treatment. The owners of 10 dogs receiving DHEA elected to stop treatment at 2, 6.5, 8, 9, 10 (2 dogs), 11.5, 12, 12.5, and 13 months. Nine dogs receiving placebo were lost to follow-up at 3.5 (two dogs), 4.5, 5, 6 (two dogs), 6.5, 7, and 11 months on treatment. The owners of three dogs receiving placebo elected to stop treatment at 6, 9, and 19.5 months.

Our findings with regard to weight loss are shown in Figure 1. Dogs receiving DHEA (n = 27) lost an average of 0.70 ± 0.11 kg/month, or 10.7 ± 1.7% of their excess bodyweight per month. This was significant compared with dogs receiving placebo (n = 21), which lost an average of 0.39 ± 0.08 kg/month ($p = 0.041$), or 5.54 ± 0.85% ($p = 0.016$) of their excess bodyweight per month. When we analyzed the dogs according to their percent excess bodyweight, we found that the most marked weight loss observed was in the ≤40% overweight group. Dogs in this group receiving DHEA (n = 21) lost 0.79 ± 0.12 kg/month, or 13.02 ± 1.9% of their excess bodyweight per month, compared with the placebo group (n = 11), which lost 0.49 ± 0.14 kg/month ($p = 0.148$), or 6.85 ± 1.12% of their excess bodyweight per month ($p = 0.032$). There was no significant difference with regard to weight loss between the DHEA (n = 6) and placebo (n = 10) groups for dogs that were >40% overweight (0.392 ± 0.23 kg/month, or 2.75 ± 1.32% excess bodyweight per month, and 0.282 ± 0.08 kg/month, or 4.1 ± 1.17% excess bodyweight per month, respectively).

A total of 14 dogs reached their ideal bodyweight, 13 of which had received DHEA and one of which had received placebo. All of these dogs were in the ≤40% overweight

Table 1. Number, sex, and age of dogs in each treatment group

Treatment	n	Females		Males	Mean age	Age range
		Neutered	Intact	Neutered		
DHEA						
≤40% Overweight	15	8	2	5	6.8	2.5–13
>40% Overweight	4	0	0	4	4.1	2.0–6
Placebo						
≤40% Overweight	11	9	1	1	6.1	2.0–10
>40% Overweight	10	7	0	3	6.8	1.5–11.5
Crossed over placebo to DHEA						
≤40% Overweight	3	3	0	0	7.5	6.5–9
>40% Overweight	5	3	0	2	6.9	1.5–11.5

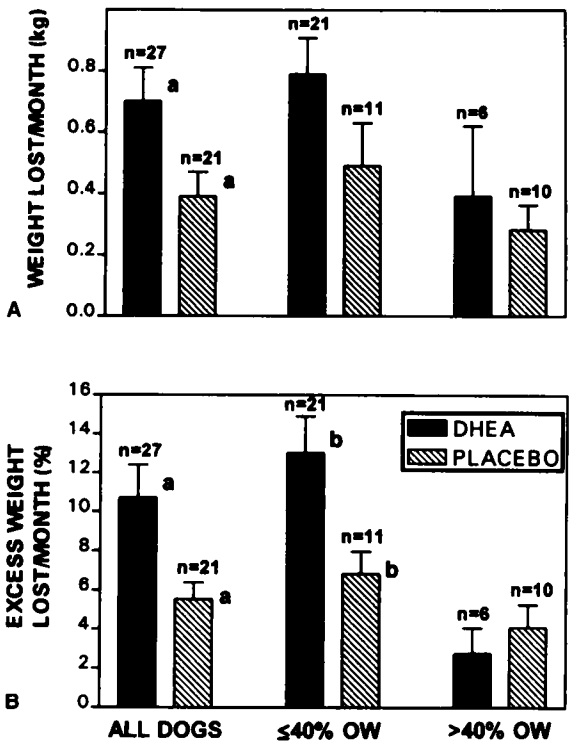

Figure 1: Rate of weight loss in dogs on a low-calorie/high-fiber diet combined with DHEA or placebo. OW, overweight (A) Actual weight lost per month (kg). a, significant difference between DHEA- and placebo-treated dogs ($p = 0.041$). (B) Percent excess weight lost per month. a and b, significant difference between DHEA- and placebo-treated dogs (a, $p = 0.016$; b, $p = 0.032$).

group. The duration of treatment for the dogs that reached their ideal bodyweight varied from 3 months to 12 months. None of the dogs in the >40% overweight group reached their ideal bodyweight after being on treatment for 2 months to 11.5 months.

The effect of DHEA on serum cholesterol concentration is shown in Figure 2. Serum cholesterol concentrations were assessed in 27 dogs receiving DHEA and in 20 dogs receiving placebo (Figure 2A). For DHEA-treated dogs, serum cholesterol was significantly decreased ($p<0.002$) at 2 (165 ± 15 mg/dL, n = 26), 4 (165 ± 12 mg/dL, n = 23), 6 (170 ± 20 mg/dL, n = 15), and 8 months (187 ± 18 mg/dL, n = 11) when compared with pretreatment (243 ± 13 mg/dL, n = 27). At 10 and 12 months of treatment, serum cholesterol was decreased compared with pretreatment and this decrease was borderline significant at 10 months (188 ± 19 mg/dL, n = 9, $p = 0.0514$) and not significant at 12 months (218 ± 48 mg/dL, n = 3, $p = 0.5861$). Placebo-treated dogs also showed a significant decrease ($p<0.03$) at 2-months (232 ± 18 mg/dL, n = 17) and 4 months (229 ± 18 mg/dL, n = 18), but not at 6 months (240 ± 26 mg/dL, n = 9) compared with pretreatment serum cholesterol (263 ± 20 mg/dL, n = 20). At 8, 10, and 12 months of treatment, serum was collected on a limited number of dogs (two, one, and two dogs, respectively) receiving placebo; thus, comparisons to pretreatment were not performed. DHEA-treated dogs had significantly lower serum cholesterol at 2, 4, and 6 months of treatment compared with placebo-treated dogs ($p<0.043$). Comparisons of serum cholesterol between treatment groups at 8, 10, and 12 months were not performed because of the small number of dogs in each group.

When dogs in the treatment groups were evaluated by percent overweight, we found that DHEA-treated dogs that were ≤40% overweight had significantly decreased serum cholesterol at 2 (n = 20), 4 (n = 18), 6 (n = 13), and 8 (n = 9) months of treatment ($p<0.036$), but not at 10 (n = 7) or 12

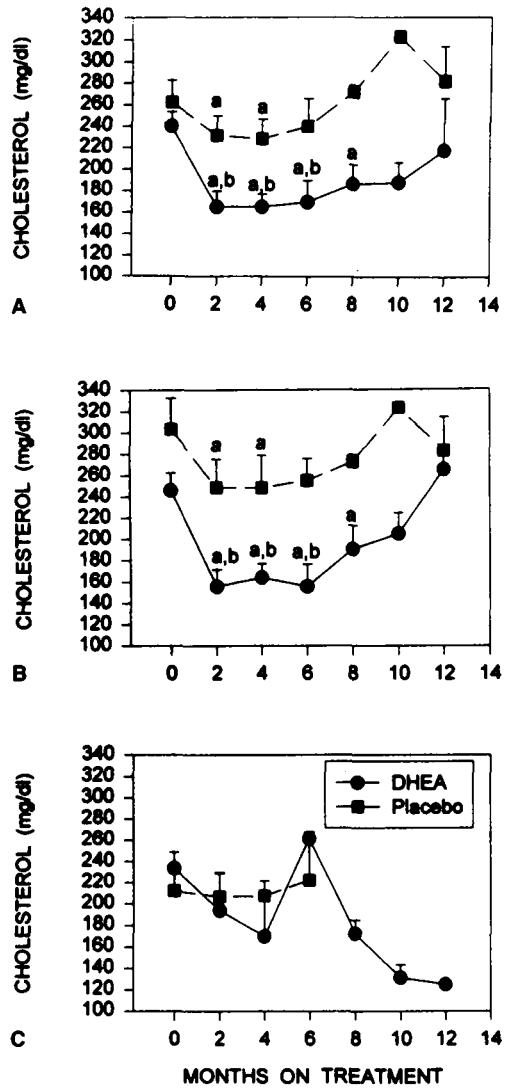

Figure 2: Serum cholesterol concentrations for dogs on a low-calorie/high-fiber diet combined with DHEA or placebo. (A) All dogs, regardless of percent obesity. a, significantly lower compared with pretreatment (month 0) ($p<0.03$); b, DHEA-treated dogs had significantly lower cholesterol than placebo-treated dogs ($p<0.05$). (B) Dogs ≤40% overweight. a, significantly lower compared with pretreatment (month 0) ($p<0.0352$); b, DHEA-treated dogs had significantly lower cholesterol than placebo-treated dogs ($p<0.0211$). (C) Dogs >40% overweight. No significant differences were observed.

(n = 2) months (Figure 2B). Placebo-treated dogs that were ≤40% overweight had significantly decreased serum cholesterol at 2 (n = 10) and 4 (n = 10) months on treatment ($p<0.014$), but not at 6 (n = 5), 8 (n = 2), 10 (n = 1), or 12 (n = 2) months. When DHEA-treated dogs were compared with placebo-treated dogs in this group, DHEA-treated dogs had significantly lower serum cholesterol at months 2, 4, and 6 of treatment ($p<0.022$). There were only two dogs in the placebo-treated group at 8 months and beyond; thus, a comparison to the DHEA dogs could not be made at these times. Dogs >40% overweight showed no significant changes in serum cholesterol for either the DHEA- or the placebo-treated dogs at 2 (n = 6 and n = 7, respectively) and 4 (n = 5 and n = 8, respectively) months. Comparison at 6 months (n = 2 and n = 4, respectively), was not performed because the number of dogs in the groups was too small. At 8, 10, and 12 months, there were two, two, and one dogs, respectively, in the DHEA-treated group and no dogs in the placebo group; thus, comparisons between the groups could not be made for those times (Figure 2C).

The effects of treatment on total plasma cholesterol and on cholesterol in the fractions of plasma containing the HDL and LDL are shown in Table 2. Evaluations were performed before the initiation of treatment and during treatment (between 4 and 10 months on treatment) and were obtained on 25 dogs receiving DHEA and 15 dogs receiving placebo. Some dogs had more than one evaluation performed during treatment. Changes in plasma cholesterol were observed at the first postinitiation of treatment sample collected and remained stable after that. For this reason, for each dog, only results from one postinitiation of treatment sample are shown. Reductions in total plasma cholesterol for DHEA- and placebo-treated dogs were similar to the reductions observed for serum cholesterol.

The decrease in total plasma cholesterol was due in part to a decrease in cholesterol in the lipoprotein fraction containing HDL (Table 2). Dogs receiving DHEA (n = 25) had a significant (27%) reduction in cholesterol. Dogs receiving placebo (n = 15) also had a significant (11%) reduction. DHEA-treated dogs had significantly lower cholesterol in this fraction while on treatment compared with the placebo-treated dogs ($p = 0.002$). Evaluation of cholesterol in this fraction for DHEA-treated dogs by percent overweight showed a pattern similar to that seen for total plasma cholesterol: dogs ≤40% overweight (n = 20) had a significant (28%) reduction, and dogs >40% overweight (n = 5) had a significant (22%) reduction. In the placebo group, there was a significant (12%) reduction in cholesterol for dogs ≤40% overweight (n = 9), but no significant reduction was observed for dogs >40% overweight (n = 6). In the ≤40% overweight group, the DHEA-treated dogs had significantly lower cholesterol than the placebo-treated dogs before treatment ($p = 0.0441$) and while on treatment ($p = 0.0030$).

We observed a marked decrease in cholesterol in the lipoprotein fraction containing the LDL cholesterol for dogs receiving DHEA (Table 2). These dogs had a significant (50%) reduction. However, it was only the DHEA-treated dogs in the ≤40% overweight group that showed a statistically significant reduction (52%). The >40% overweight group had a nonsignificant (27%) reduction ($p = 0.8161$). It

Table 2. Total plasma and lipoprotein cholesterol concentrations, pretreatment and during treatment

Treatment group	Total cholesterol (mg/dL) Pretreatment*	During treatment	p Value†	HDL cholesterol (mg/dL) Pretreatment	During treatment	p Value	LDL cholesterol (mg/dL) Pretreatment	During treatment	p Value
All dogs									
DHEA (n=25)	196 (10)	134 (9)‡	0.001	154 (6)	113 (7)‡	0.001	42 (6)	21 (4)‡	0.001
Placebo (n=15)	217 (17)	198 (13)	ns§	171 (8)	152 (9)	0.019	46 (11)	47 (9)	ns
≤40% Overweight									
DHEA (n=20)	202 (11)‡	135 (10)‡	0.001	156 (7)‡	113 (8)‡	0.001	46 (7)	22 (4)‡	0.002
Placebo (n=9)	249 (21)	218 (15)	ns	182 (10)	160 (11)	0.041	67 (14)	59 (12)	ns
>40% Overweight									
DHEA (n=5)	170 (15)	132 (27)	ns	144 (11)	113 (19)	0.039	26 (8)	19 (9)	ns
Placebo (n=6)	170 (12)	168 (19)	ns	154 (8)	140 (13)	ns	16 (5)	28 (9)	0.046

*Numbers are means ± standard error (in parentheses).
†Comparisons made are between pretreatment and postinitiation of treatment (Student's paired *t*-test).
‡$p<0.05$, DHEA-treated dogs compared with placebo-treated dogs (Student's *t*-test).
§ns, not significant.

is of interest to note that the dogs in both treatment groups that were >40% overweight had a much lower pretreatment LDL cholesterol level than did dogs that were ≤40% overweight. For dogs in the >40% overweight placebo group, there was a significant (75%) increase in LDL cholesterol. There was no difference in cholesterol when all dogs receiving placebo were analyzed together, nor was there any change observed for the placebo dogs that were ≤40% overweight. Compared with the placebo-treated dogs, DHEA-treated dogs had significantly lower cholesterol in this fraction while on treatment ($p=0.0039$), and this difference was only observed in the dogs that were ≤40% overweight ($p=0.001$).

Serum T4, T3, and cortisol concentrations were analyzed before treatment and during treatment (between 4 and 8 months on treatment) (Table 3). The number of dogs available for evaluation at these time were: for T4, 22 dogs receiving DHEA and 13 dogs receiving placebo; for T3, 19 dogs receiving DHEA and 12 dogs receiving placebo; and for cortisol, 22 dogs receiving DHEA and 14 dogs receiving placebo. There were significant decreases in T4, T3, and cortisol for dogs receiving DHEA. When the DHEA group

Table 3. Serum T4, T3, and cortisol concentrations pretreatment and during treatment

Treatment group	T4 (ng/mL) Pretreatment*	During treatment	p Value†	T3 (ng/mL) Pretreatment	During treatment	p Value	Cortisol (ng/mL) Pretreatment	During treatment	p Value
All Dogs									
DHEA	16 (1)	9 (1)‡	0.001	0.82 (0.04)	0.68 (0.04)‡	0.006	49 (8)	20 (3)‡	0.001
Placebo	15 (1)	18 (2)	ns§	0.87 (0.04)	0.82 (0.04)	ns	51 (8)	42 (9)	ns
≤40% Overweight									
DHEA	16 (1)	9 (1)‡	0.001	0.81 (0.04)	0.67 (0.04)‡	0.005	46 (8)	20 (3)	0.002
Placebo	15 (2)	17 (2)	ns	0.89 (0.05)	0.84 (0.07)	ns	39 (10)	26 (9)	0.010
>40% Overweight									
DHEA	16 (2)	8 (2)	ns	0.91	0.94	1 dog	80 (26)	22 (18)	ns
Placebo	15 (2)	20 (5)	ns	0.84 (0.07)	0.79 (0.03)	ns	68 (12)	63 (12)	ns

*Numbers are means ± standard error (in parentheses).
†Comparisons made are between pretreatment and postinitiation of treatment (Student's paired *t*-test).
‡$p<0.03$, DHEA-treated dogs compared with placebo-treated dogs (Student's *t*-test).
§ns, not significant.

was divided by percent overweight, these observed decreases were statistically significant for the dogs in the ≤40% overweight group (n = 20, 18, and 20 for T4, T3, and cortisol, respectively). There were too few dogs in the >40% overweight group (n = 2, 1, and 2 respectively) in which these assays were performed; therefore, no conclusions can be made for this subset of dogs. When all dogs receiving placebo were evaluated together, no changes in T4, T3, or cortisol concentrations were observed (n = 13, 12, and 14, respectively). When the placebo group was divided by percent overweight, the only significant decrease noted was a reduction in cortisol concentration for dogs in the ≤40% overweight group (n = 8). Compared with placebo-treated dogs, DHEA-treated dogs had significantly lower T4 ($p = 0.0001$), T3 ($p = 0.0283$), and cortisol ($p = 0.0084$) concentrations while on treatment. This difference was also observed for dogs ≤40% overweight for T4 ($p = 0.0002$) and T3 ($p = 0.0295$), but not for cortisol.

Serum insulin concentrations were either unchanged for some dogs, or too variable throughout the study for us to be able to meaningfully analyze the results. Serum DHEAS concentrations were also very variable throughout the study. From a previous study in rhesus monkeys (21), we know that serum DHEAS concentrations approach baseline at 12 hours post–DHEA administration. Mean pretreatment serum DHEAS concentration for all dogs was 61 ± 13 ng/mL. We observed up to a 7-fold increase in serum DHEAS while dogs were receiving DHEA. We also observed a 1.7-fold increase in serum DHEAS after 2 months on placebo. At 4 months on placebo, serum DHEAS concentrations returned to pretreatment levels. There were no remarkable changes in serum biochemistry profiles (other than cholesterol).

Dog owners were questioned at each recheck as to the dog's food intake, and in addition, owners kept weeklong diaries of what the dogs were fed each day and how much they ate each day for the week before recheck. Information provided by the owners indicated that food intake, as prescribed by the investigators, remained constant for all dogs throughout the study. There were no reports by the owners of food spillage.

Discussion

It is estimated that up to 50% of pet dogs are overweight (12,13,23). Similar to humans, obesity is detrimental to a dog's health. Obesity in dogs is associated with a higher incidence of diabetes mellitus; skeletal, cardiac, and respiratory problems; impaired reproduction efficiency; cancer; skin disease; and increased risks associated with anesthesia and surgery (20,45). Similarities between dogs and humans, and the desire of many pet dog owners to control obesity in their dogs, make the dog a useful model for the study of factors that affect weight gain and loss.

The findings in this study support the antiobesity activity of DHEA observed in our previous study in spontaneously obese dogs (18), as well as the findings reported of many studies in mice, rats, and humans (2,7,34). Studies in several strains of mice reported that DHEA administration resulted in a decreased weight gain without a reduction in food intake (36,38,49,50). Similar findings were reported in genetically obese Zucker rats (8,9,33). DHEA treatment of obese adult rats has resulted in weight loss (10,29). It has been reported that high (compared with the dose in this study) doses of DHEA administration (200 mg/kg per day intraperitoneally or 0.6% of the diet) to Zucker rats resulted in decreased food intake (46,47). In the study reported here, dogs received a much lower dose of DHEA (60 mg/kg per day) and were fed a prescribed amount of food. As reported by the dogs' owners, DHEA did not reduce the intake of the food offered to the dogs. Men of normal weight treated with DHEA (1600 mg/day) for 28 days had no change in total bodyweight but did have a decrease in total body fat and in LDL cholesterol (33). Other studies in men and women without obesity showed no effect of DHEA (1600 mg/day) on bodyweight (31,44). Postmenopausal women who were not obese treated with DHEA did show a marked decline in serum cholesterol, HDL, and LDL (31). Men with obesity receiving DHEA for 28 days at 13 mg/kg to 20 mg/kg daily had no change in bodyweight, body fat, or lipoproteins (40). It is important to note that the dose of DHEA in these studies of men and women of normal weight and men with obesity was approximately one-third the dose used in our study in dogs presented here.

We found it particularly interesting that the dogs that were most obese (>40% overweight) lost weight at a much slower rate than the dogs that were in the ≤40% overweight group. It is our hypothesis that dogs that are extremely overweight are physiologically or metabolically dissimilar from dogs with mild or moderate obesity. It is not clear from the results of this study if the dogs that were the most obese failed to lose weight because of an abnormality that led to the severe obesity or because of the obese state.

Our finding of the cholesterol-lowering effect of DHEA confirms results from our previous study in dogs (18). We have also shown that DHEA significantly lowered cholesterol in rhesus monkeys that were obese (4) and nonobese (16). As in the dog (18) and men who were nonobese (33), but not men who were obese (40), the lipoprotein fraction containing LDL in the rhesus monkey was the most affected by this reduction in cholesterol (4,16). It is well established that high cholesterol levels are associated with increased risk of atherosclerosis and heart disease (3). In men, decreased DHEAS levels have been associated with a higher risk of cardiovascular disease (1). This may be in part because of the effect of androgens, which are known to raise LDL cholesterol levels and reduce HDL cholesterol (14,25,30,39). Estrogen has been found to lower LDL cholesterol and increase HDL cholesterol (17,30,42,43). The

cholesterol-lowering effect of DHEA may be related to its role as a precursor of estrogen (11,37).

The reduction in serum T4 that we observed in the DHEA-treated dogs is in agreement with other studies. In our previous study in the dog, we found that DHEA significantly lowered basal serum T4 (18). In one study of BHE/cdb rats treated with DHEA, there was a 40% decrease in T4 (26). Another study in rats with obesity treated with DHEA reported no change in T4 levels, but there was a reduction in T3 levels after 2 weeks of DHEA treatment (29). In our previous study in rhesus monkeys, we found that DHEA had no affect on T4 (16). It appears that the decrease in T4 observed in this study resulted from the administration of DHEA and not weight loss. The relationship between DHEA, weight loss, and thyroid hormones is a complex one requiring further investigation.

Serum cortisol concentrations declined in dogs ≤40 overweight in both treatment groups; however, the decline was significantly greater for dogs receiving DHEA. In our previous study in dogs that were not on a prescribed restricted diet, we found a nonsignificant decrease in serum cortisol (18). It is possible that in the study reported here, diet alone resulted in a decrease in serum cortisol and that this effect was enhanced by DHEA. Cortisol remained unchanged in our study of DHEA-treated rhesus monkeys that were obese (4) and nonobese (16). We have been unable to obtain information regarding the effect of DHEA on cortisol from reports of studies of DHEA treatment in mice, rats, and humans.

Recent reviews of the mechanism of action of the antiobesity effect of DHEA suggest that no one mechanism is solely responsible (2,17,34). The liver plays a central role in mediating the activity of DHEA. It has been suggested that the antiobesity activity of DHEA may in part be due to its effect on futile fatty acid cycling. Studies in rodents have shown that DHEA treatment results in the induction of a substrate futile cycle of deacylation/reacylation of long-chain fatty acyl-coenzyme A (5,24). DHEA has also been shown to increase hepatic mitochondrial protein, resulting in increases in mitochondrial respiration rates (6,19,20). These energy-consuming metabolic processes may contribute to the weight-controlling effect of DHEA.

In summary, our findings show that caloric restriction, with a low-calorie/high-fiber diet, in combination with DHEA is an effective method for controlling obesity in dogs that are ≤40% above their ideal bodyweight. In addition, this combination results in a marked decrease in serum cholesterol and plasma lipoproteins, particularly in the fraction containing LDL. We also observed decreases in serum concentrations of T4 and T3 in dogs treated with DHEA, but not in those receiving placebo. Caloric restriction alone had a moderate effect on weight loss in dogs ≤40% overweight; however, the rate is slower than that seen with DHEA. Caloric restriction alone did result in a decrease in serum cholesterol, although it was not significantly less than that observed with DHEA. There was minimal effect on plasma lipoproteins for dogs on caloric restriction alone. DHEA has important potential as an antiobesity agent, and perhaps even greater potential as an antihypercholesterolemic agent. The findings of studies in the rodent, monkey, and dog warrant further investigation into the mechanism of action of DHEA and its potential therapeutic value.

Acknowledgments

We thank Mr. Joel Armstrong of the Radionuclide Laboratory of the School of Veterinary Medicine and, in our laboratory, Ms. Cynthia Broderick and Ms. Arlene Haffa for their technical assistance.

This work was supported by the Morris Animal Foundation (Grant No. 88CA-29), Englewood, CO.

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