PRELIMINARY COMMUNICATION

Effect of DHEA on Abdominal Fat and Insulin Action in Elderly Women and Men

A Randomized Controlled Trial

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Context Dehydroepiandrosterone (DHEA) administration has been shown to reduce accumulation of abdominal visceral fat and protect against insulin resistance in laboratory animals, but it is not known whether DHEA decreases abdominal obesity in humans. DHEA is widely available as a dietary supplement without a prescription.

Objective To determine whether DHEA replacement therapy decreases abdominal fat and improves insulin action in elderly persons.

Design and Setting Randomized, double-blind, placebo-controlled trial conducted in a US university-based research center from June 2001 to February 2004.

Participants Fifty-six elderly persons (28 women and 28 men aged 71 [range, 65-78] years) with age-related decrease in DHEA level.

Intervention Participants were randomly assigned to receive 50 mg/d of DHEA or matching placebo for 6 months.

Main Outcome Measures The primary outcome measures were 6-month change in visceral and subcutaneous abdominal fat measured by magnetic resonance imaging and glucose and insulin responses to an oral glucose tolerance test (OGTT).

Results Of the 56 men and women enrolled, 52 underwent follow-up evaluations. Compliance with the intervention was 97% in the DHEA group and 95% in the placebo group. Based on intention-to-treat analyses, DHEA therapy compared with placebo induced significant decreases in visceral fat area (–13 cm^2 vs +3 cm^2, respectively; $P=.001$) and subcutaneous fat (–13 cm^2 vs +2 cm^2, $P=.003$). The insulin area under the curve (AUC) during the OGTT was significantly reduced after 6 months of DHEA therapy compared with placebo (–1119 μU/mL per 2 hours vs +818 μU/mL per 2 hours, $P=.007$). Despite the lower insulin levels, the glucose AUC was unchanged, resulting in a significant increase in an insulin sensitivity index in response to DHEA compared with placebo (+1.4 vs –0.7, $P=.005$).

Conclusion DHEA replacement could play a role in prevention and treatment of the metabolic syndrome associated with abdominal obesity.

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THE ACCUMULATION OF ABDOMINAL fat increases with advancing age, and there is extensive evidence that abdominal obesity increases the risk for development of insulin resistance, diabetes, and atherosclerosis.[1-4] In addition to insufficient exercise and overeating, hormonal/metabolic changes that occur with aging may contribute to the increase in abdominal fat that generally occurs during middle and old age. One such change is the decline in production of the adrenal hormone dehydroepiandrosterone (DHEA). The blood level of DHEA, most of which is present in the sulfated form (DHEAS), peaks at approximately 20 years of age and declines rapidly and markedly after age 25 years.[5]

Administration of DHEA to rats and mice reduces visceral fat accumulation in both genetic[6,7] and diet-induced obesity[8,9] and results in a smaller increase in body fat with advancing age.[10] In rats, DHEA also has a protective effect against both the insulin resistance induced by a high-fat diet[9] and the decrease in insulin responsiveness that occurs with advancing age.[10] A possible explanation for these findings is that DHEA is an activator of peroxisome proliferator-activated receptor α (PPARα), a transcription factor that belongs to the steroid hormone nuclear receptor family.[11,12] Activation of PPARα induces transcriptional up-regulation of fatty acid transport proteins that facilitate fatty acid entry into cells and the enzymes involved in the β-oxidation of fatty acids.[13-15] Activation of PPARα also results in decreased expression of fatty acid synthase and acetyl-coenzyme A carboxylase.[13] These adaptations favor increased fat oxidation and reduced fat deposition. The absence of PPARα in PPAR (–/–) mice results in late-onset obesity.[16]

Dehydroepiandrosterone is widely available as a dietary supplement without a prescription. However, it is not known whether DHEA decreases abdominal obesity in humans as it does in rats and mice. In this context, the purpose of this preliminary study was to test

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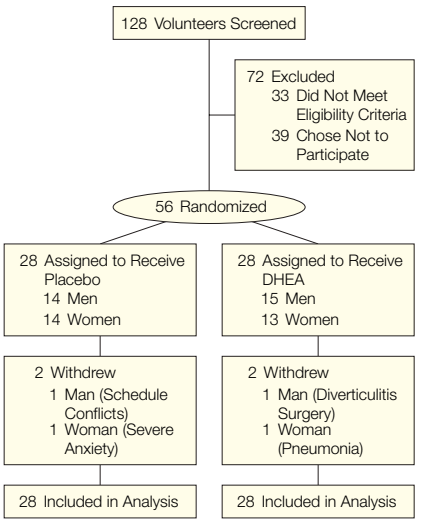
Figure. Study Flow



DHEA indicates dehydroepiandrosterone.

the hypothesis that DHEA replacement therapy results in a decrease in abdominal fat and an improvement in insulin action in elderly humans.

METHODS

Study Participants

The study was conducted at Washington University School of Medicine (WUSM) from June 2001 to February 2004. Men and women aged 65 to 78 years were recruited from the community using direct mailing and mass media to participate in a study of DHEA replacement therapy. Participants provided written informed consent to participate in the study, which was approved by the WUSM institutional review board.

We screened 128 volunteers (FIGURE). The screening evaluation included a medical history, physical examination, analyses of blood chemistry, and urinalysis. Of the 128 volunteers, 33 were excluded because they did not meet our eligibility criteria. Exclusion criteria included hormone therapy within the past year, a history of hormone-dependent neoplasia, a prostate-specific antigen (PSA) level above 2.6 ng/mL, or active serious illness. An additional 39 chose not to participate. The remaining 56 volunteers were randomly assigned to receive DHEA (15 men, 13 women) or placebo (14 men, 14 women) using a computer-generated block random-permutation procedure stratified for sex.[17] None of the participants smoked. They had received stable medications for at least 6 months, and had maintained stable body weight (±2 kg) for the past year. None exercised regularly. The participants were asked not to alter their diets or physical activity during the study.

Study Design

We conducted a randomized, double-blind, placebo-controlled study of the effects of 6 months of DHEA replacement therapy. The dose was 50 mg of DHEA per day taken at bedtime. The DHEA was synthesized by Schering-Plough (Munich, Germany); we obtained the DHEA and placebo capsules from the Life Extension Foundation (Fort Lauderdale, Fla). Placebo and active capsules were identical in appearance. The randomization algorithm was generated by a member of the WUSM Biostatistics Division and maintained by a member of the research team who did not interact with the participants. The participants, the individual performing the tests and measurements, the person dispensing the capsules, and those assessing the outcomes were blinded to group assignment.

Compliance was checked by pill counts at monthly intervals. Adverse effects were monitored by interview, physical examinations, and standard laboratory tests, including serum PSA measurements in the men at 1, 3, and 6 months after starting the study. Assessments of abdominal fat, oral glucose tolerance, and hormone and lipid levels were performed at baseline and after 6 months of treatment.

Magnetic Resonance Imaging

Proton magnetic resonance imaging of the abdominal region was obtained to quantify abdominal fat. Axial images were acquired at the level of L3-4 using a 1.5-T superconducting magnet (Siemens, Iselin, NJ) and a T1-weighted pulse sequence. Images were acquired with 134 phase-encoding steps to form 256 × 256 images that were stored in a 16-bit format. Consistent slice localization was accomplished by performing coronal scouting images to identify the starting point for image acquisition (L3-4 interspace). Eight 8-mm–thick axial images were acquired with no intersection gap. All images were analyzed by the same experienced technician using the Image analysis program (NIH, Bethesda, Md). Total abdominal area was expressed as the average total cross-sectional area derived from the mean of the 8 slices. The area of subcutaneous fat was calculated as the difference between the total abdominal area and an area inside a continuous digitized line demarcating the subcutaneous fat from the abdominal wall and paraspinal muscles. Abdominal visceral fat was identified using the density slicing mode of the Image program, in which the separation of fat from nonfat is performed using interactive level detection with the thresholds set by an experienced technician blinded to the participant's identity and treatment status. The coefficients of variation for visceral and subcutaneous fat areas from repeated blinded analysis of scans performed on 11 individuals were 3.6% (SD, 2.5%) and 2.6% (SD, 2.9%), respectively.

Oral Glucose Tolerance Test

A standard 75-g oral glucose tolerance test (OGTT) was performed after an overnight fast. Venous blood samples were obtained in the fasted state and 30, 60, 90, and 120 minutes after glucose ingestion for determination of plasma glucose (glucose oxidase method) and insulin[18] concentrations. The glucose and insulin areas under the curve (AUC) were calculated using the trapezoid method.[19] An insulin sensitivity index[20] was calculated using the formula: insulin sensitivity index = 10 000/square root of [(fasting glucose × fasting insulin) × (mean glucose × mean insulin during OGTT)]. This index correlates (r = 0.73) with the rate of whole-body glucose disposal during a euglycemic insulin clamp.[20]

Hormones, Lipids, and PSA

Serum levels of DHEAS were measured by enzyme-linked immunosorbent as-

Table 1. Baseline Characteristics

Characteristic	Mean (SD)					
	All		Men		Women	
	Placebo (n = 28)	DHEA (n = 28)	Placebo (n = 14)	DHEA (n = 15)	Placebo (n = 14)	DHEA (n = 13)
Age, y	71 (4)	71 (4)	70 (4)	72 (3)	71 (5)	71 (5)
White race, No. (%)*	26 (93)	25 (89)	13 (93)	14 (94)	13 (93)	11 (85)
Weight, kg	78.2 (13.1)	81.1 (16.8)	87.4 (7.4)	89.6 (16.9)	69.7 (11.4)	71.5 (10.7)
Height, cm	170.7 (7.9)	171.6 (10.1)	177.0 (5.1)	177.4 (4.8)	163.8 (3.1)	162.8 (3.1)
Body mass index†	27.2 (3.9)	28.04 (4.6)	27.9 (2.9)	28.2 (5.7)	27.0 (4.7)	27.7 (3.3)
Serum DHEAS, ng/mL	691 (425)	714 (439)	668 (132)	746 (128)	639 (928)	679 (348)

Abbreviations: DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate.
*Race data obtained per National Institutes of Health requirement. Race was self-reported using options defined by the participants.
†Calculated as weight in kilograms divided by the square of height in meters.

say (Diagnostic Systems Laboratory, Webster, Tex). Levels of testosterone, sex hormones–binding globulin, and insulin-like growth factor–binding protein 3 were measured by enzyme-linked immunosorbent assay; estradiol levels were measured by ultrasensitive radioimmunoassay (Diagnostic Systems Laboratory). Levels of insulin-like growth factor 1 (IGF-1) were measured by radioimmunoassay[21] by the core laboratory of the Diabetes Research Training Center at Washington University. The coefficients of variation of these assays were all less than 10%. Levels of PSA were determined using a monoclonal antibody assay (Hybritech Inc, San Diego, Calif).

Diet and Physical Activity

The participants completed 3-day food records at the beginning and end of the 6-month study period under the supervision of a dietitian. Records were analyzed using Nutritionist IV (First Databank, San Bruno, Calif). Physical activity was assessed using a physical activity questionnaire[22] at baseline and at the end of the study.

Statistical Analysis

Based on a preliminary study of the effects of DHEA on abdominal visceral fat in older women and men,[23] the mean (SD) difference between the placebo and DHEA groups was projected to be 10 (7) cm^2. Thus, for the projected sample sizes, the estimated power to detect significant effects of DHEA was 98% for visceral fat.

Data analysis was carried out in an intention-to-treat fashion. When follow-up data were not available (n=4), the last observation was carried forward. Data were analyzed using a 2×2 analysis of variance to evaluate the effects of group (DHEA vs placebo) and sex on the change between baseline and the results at 6 months. Paired *t* tests were performed to determine if there were significant changes within a group. Data were analyzed using SPSS version 12.0 (SPSS Inc, Chicago, Ill), and $P<.05$ was used to determine statistical significance. All values are presented as mean (SD).

RESULTS

Of the 56 women and men enrolled, 52 underwent follow-up evaluations (Figure). Two participants in the placebo group (1 woman, 1 man) dropped out and refused final testing for personal reasons; 2 participants in the DHEA group (1 woman, 1 man) dropped out for medical reasons unrelated to the study. The percentage of prescribed doses taken by those in the placebo group who completed the study averaged 95% (SD, 9%). Compliance in the DHEA group was 97% (SD, 10%).

There were no significant differences in baseline characteristics between the placebo and the DHEA groups (TABLE 1). On average, the participants were overweight. Compared with placebo, the 6 months of DHEA replacement resulted in a decrease in body weight (–0.9 [2.4] kg vs 0.6 [2.2] kg; $P=.02$), with no difference in response between men and women ($P=.74$).

Diet and Physical Activity

There were no significant changes in energy intake or physical activity assessed using diet records and a physical activity questionnaire. Energy intake averaged 2271 (338) kcal/d for the placebo group and 2219 (518) kcal/d for the DHEA group at baseline, and 2191 (527) kcal/d for the placebo group and 2156 (427) kcal/d for the DHEA group at the end of the study. Physical activity scores averaged 50 (33) for the placebo group and 48 (37) for the DHEA group at baseline, and 54 (34) for the placebo and 49 (42) for the DHEA group at the end of the study.

Serum Hormone and IGF-1 Levels

The DHEA replacement therapy raised the participants' serum DHEAS concentrations into the young normal range (TABLE 2). In the women, DHEA replacement significantly increased testosterone concentration, while in the men there was no effect of DHEA on testosterone level. Estradiol concentration increased significantly in both men and women in response to DHEA therapy. DHEA replacement also resulted in small but significant increases in IGF-1 concentration. There were no significant changes in sex hormones–binding protein or insulin-like growth factor–binding protein 3 (data not shown).

Abdominal Fat

Significant decreases in abdominal visceral fat occurred during the 6 months of DHEA replacement (TABLE 3). These decreases were of similar magnitude in the men and women in absolute terms.

The decrease in visceral fat relative to initial values averaged 10.2% in the women and 7.4% in the men. The DHEA therapy also resulted in a significant decrease in abdominal subcutaneous fat, averaging approximately 6% in both the men and women.

Glucose Tolerance

The insulin AUC during the OGTT was significantly reduced after 6 months of DHEA replacement therapy (TABLE 4). Despite the lower insulin levels, the glucose AUC was unchanged, providing evidence for an improvement in insulin action. This improvement is reflected in a significant increase in the insulin sensitivity index (Table 4). There was an inverse correlation between the changes in insulin sensitivity index and visceral fat area (R=–0.50, P=.003).

Adverse Events

There were no significant adverse effects of the DHEA replacement. Mean PSA levels for the men in the DHEA group were 1.7 (0.9) ng/mL at baseline and 1.6 (0.8) ng/mL after 6 months of DHEA replacement. For the men in the placebo group, mean PSA values were 1.4 (0.6) ng/mL at baseline and 1.8 (1.3) ng/mL at the end of the study.

COMMENT

In this randomized, double-blind, placebo-controlled study of 6 months of DHEA replacement therapy, we found that DHEA induced significant decreases in both visceral and subcutaneous fat in elderly men and women. The DHEA replacement also resulted in a significant improvement in insulin action that correlated with the reduction in visceral fat. These findings provide evidence that DHEA replacement may partially reverse the aging-related accumulation of abdominal fat in elderly people with low serum levels of DHEAS. They also raise the possibility that long-term DHEA replacement therapy might reduce the accumulation of abdominal fat and protect against development of the metabolic/insulin resistance syndrome.

An improvement in insulin action has also been reported by Kawano et al[24] in a study of the effect of DHEA therapy in

Table 2. Effects of DHEA Replacement Therapy on Serum Hormone Levels

	Mean (SD)					
	Men			Women		
Hormone	Placebo	DHEA	Usual Young Range	Placebo	DHEA	Usual Young Range
DHEAS, ng/mL						
Baseline	668 (132)	746 (128)		639 (298)	679 (348)	
Final	464 (36)	3578 (410)*‡	2477-4247	721 (162)	3589 (413)*‡	2339-4104
Testosterone, ng/mL						
Baseline	5.2 (1.4)	4.8 (1.4)		0.3 (0.1)	0.4 (0.4)	
Final	5.3 (1.2)	5.2 (1.1)	2.9-9.9	0.3 (0.1)	1.4 (0.5)*‡	0.3-2.3
Estradiol, pg/mL						
Baseline	20.0 (3.3)	22.9 (6.7)		13.1 (3.2)	13.3 (5.9)	
Final	19.7 (3.6)	30.9 (8.4)*‡	5.6-50.1	15.6 (7.0)	28.0 (8.3)*‡	38-300
IGF-1, ng/mL						
Baseline	151 (64)	166 (43)		144 (49)	157 (55)	
Final	141 (54)	186 (36)†§	114-492	143 (41)	188 (61)†§	114-492

Abbreviations: DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; IGF-1, insulin-like growth factor 1.
SI conversion factors: To convert DHEAS to µmol/L, multiply by 0.0027; testosterone to nmol/L, multiply by 3.47; estradiol to pmol/L, multiply by 3.67; IGF-1 to nmol/L, multiply by 0.131. *P<.001 for the comparisons with the change in the placebo group. †P=.03 for the comparisons with the change in the placebo group. ‡P<.001 for the comparisons with baseline value. §P=.05 for the comparisons with baseline value.

Table 3. Effects of DHEA Replacement Therapy on Abdominal Fat

	Mean (SD)								
	All			Men			Women		
Abdominal Fat	Placebo	DHEA	P Value	Placebo	DHEA	P Value	Placebo	DHEA	P Value
Visceral fat area, cm^2									
Baseline	158 (70)	166 (89)		195 (71)	204 (104)		123 (51)	123 (36)	
Final	161 (72)	153 (87)*	.001	198 (71)	191 (101)†	.04	126 (55)	110 (34)†	.02
Change	3 (15)	–13 (18)		3 (20)	–14 (18)		3 (12)	–13 (19)	
Subcutaneous fat area, cm^2									
Baseline	205 (84)	220 (73)		185 (59)	219 (84)		224 (101)	221 (62)	
Final	207 (85)	207 (70)*	.003	185 (60)	206 (79)‡	.03	227 (101)	208 (60)†	.04
Change	2.0 (9)	–13 (22)		0.3 (6)	–13 (19)		3 (12)	–13 (25)	
Total abdominal area, cm^2									
Baseline	716 (177)	770 (200)		812 (151)	846 (220)		627 (162)	683 (162)	
Final	721 (170)	740 (20)*	.006	812 (164)	813 (231)‡	.06	638 (155)	656 (125)†	.05
Change	5 (32)	–31 (56)		–0.4 (16)	–33 (61)		11 (41)	–27 (54)	

Abbreviation: DHEA, dehydroepiandrosterone.
*P<.01 for the comparisons with baseline value. †P<.05 for the comparisons with baseline value. ‡P=.07 for the comparisons with baseline value.

middle-aged men with hypercholesterolemia. To our knowledge, only 1 other study has examined the effect of DHEA on abdominal fat in humans.[25] In that study, DHEA was administered to women in the form of skin cream and had no effect on abdominal fat measured by computed tomography. A possible explanation for the lack of effect is that the cream increased serum levels of DHEAS to only approximately 700 ng/mL, compared with the value of approximately 3600 ng/mL in the present study. In a previous study, 6 months of DHEA therapy in elderly men and women resulted in a 1.4-kg decrease in total body fat mass and a 0.9-kg increase in fat-free mass, measured by dual-energy x-ray absorptiometry (DXA).[26] In contrast, Jedrzejuk et al,[27] in a crossover study of 3 months of DHEA replacement in 12 men aged approximately 59 years, found no effect on body composition measured by DXA or on fasting levels of serum insulin and glucose. Flynn et al[28] also found no change in body composition measured using potassium K 40, or in fasting glucose or insulin levels in a crossover study of 3 months of DHEA therapy in older men. Similarly, Arlt et al[29] found no change in body composition measured using bioimpedence analysis and waist-hip ratio in a crossover study of 4 months of DHEA treatment. Possible explanations for the differences between the results of these 3 studies and the present study include the relative insensitivity, compared with magnetic resonance imaging, of potassium K 40, bioimpedence, and DXA in detecting small changes in visceral fat; the shorter durations of DHEA treatment in these previous studies; and the use of the insulin and glucose responses to an OGTT to evaluate insulin action in the present study.

The results of epidemiologic studies of the relationship between DHEA and abdominal fat have been conflicting. Haffner et al,[30,31] in studies on middle-aged men, found that DHEAS level was significantly inversely related to abdominal obesity and insulin concentration. In contrast, in a study by Barrett-Connor and Ferrara[32] on postmenopausal women, DHEAS levels were positively associated with waist-hip ratio, leading the authors to conclude that DHEA does not protect against obesity. The seeming discrepancy between this finding and the present results is probably explained by the difference in DHEAS levels. In the study that led Barrett-Connor and Ferrara to conclude that DHEA does not protect against obesity, the women in the highest quartile of waist-hip ratio had a mean serum DHEAS level of approximately 490 ng/mL, while those in the lowest quartile had a DHEAS level of approximately 420 ng/mL, compared to a DHEAS level of approximately 3600 ng/mL in women receiving DHEA replacement in the present study.

Table 4. Response to an Oral Glucose Tolerance Test

	Mean (SD)		
	Placebo	DHEA	*P* Value
Glucose area under the curve, mg/dL per 2 h			
Baseline	20839 (5226)	21542 (6527)	.79
Final	20655 (4331)	19572 (8152)	
Change	–183 (3083)	–418 (3378)	
Insulin area under the curve, μU/mL per 2 h			
Baseline	8052 (2472)	8399 (5220)	.007
Final	8871 (5337)	7251 (5015)*	
Change	818 (3190)	–1119 (1665)	
Insulin sensitivity index†			
Baseline	4.5 (2.5)	4.1 (2.5)	.005
Final	3.8 (1.6)	5.5 (3.3)‡	
Change	–0.7 (2.1)	1.4 (2.6)	

Abbreviation: DHEA, dehydroepiandrosterone.
*P=.007 for the comparisons with baseline value.
†Insulin sensitivity was calculated using the whole body insulin sensitivity index formula of Matsuda and DeFronzo.[20]
‡P=.04 for the comparisons with baseline value.

With regard to its mechanism of action, DHEA is a PPARα agonist[11,12] and serves as a precursor of testosterone and estrogens. It also increases the concentration of circulating IGF-1.[26,33] PPARα induces expression of the mitochondrial enzymes involved in fatty acid oxidation and suppresses expression of enzymes involved in fat synthesis.[13-15] Tenenbaum et al[34] showed that the PPARα receptor ligand bezafibrate reduced the incidence and delayed the onset of type 2 diabetes in patients with impaired fasting glucose levels. In laboratory rodent models, PPARα agonists have been shown to reduce adiposity, decrease triglyceride stores in liver and muscle, and improve insulin sensitivity.[35-37] In rats or mice, DHEA administration reduces fat accumulation in both genetic[6,7] and diet-induced obesity[8,9] and has a protective effect against the insulin resistance induced by a high-fat diet[9] as well as the decrease in insulin responsiveness associated with aging.[10] We think it likely that this mechanism, ie, activation of PPARα, is also involved in the decrease in abdominal fat and improvement in insulin action in response to DHEA in this study.

As in previous studies,[33,38,39] DHEA replacement therapy increased serum testosterone concentration in women but had no significant effect on testosterone level in men. Also in keeping with earlier studies,[39,40] DHEA replacement resulted in increases in serum estradiol concentration. There was also an increase in serum IGF-1 concentration in both men and women in response to DHEA. The magnitude of this increase, approximately 12% in men and 18% in women, was similar to that found in previous studies.[33,41] There is evidence suggesting that estrogen therapy protects postmenopausal women against abdominal fat accumulation[42] and that increasing IGF-1 levels reduces abdominal fat.[43,44] Thus, it is possible that the increases in estradiol and IGF-1 levels could have played a role in the decrease in abdominal fat induced by DHEA in our study.

Limitations of our study include the relatively small number of participants and the short duration of DHEA

replacement. Therefore, our findings should be considered preliminary. Furthermore, the long-term effects of the small but significant increases in IGF-1 and estradiol levels in both men and women, and in levels of testosterone in women, caused by DHEA replacement are not known. Larger-scale and longer-term studies are needed to determine whether DHEA replacement has any adverse effects.

We found in this preliminary study that DHEA reduced abdominal fat and improved insulin sensitivity index. Larger studies, however, will be needed to verify our findings and should include patient groups that are fully representative of the population at risk.

Author Contributions: Drs Villareal and Holloszy had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.
Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtained funding; study supervision: Villareal, Holloszy.
Statistical analysis: Villareal.
Administrative, technical, or material support: Holloszy.
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