DHEA in Elderly Women and DHEA or Testosterone in Elderly Men

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ABSTRACT

BACKGROUND

Dehydroepiandrosterone (DHEA) and testosterone are widely promoted as antiaging supplements, but the long-term benefits, as compared with potential harm, are unknown.

METHODS

We performed a 2-year, placebo-controlled, randomized, double-blind study involving 87 elderly men with low levels of the sulfated form of DHEA and bioavailable testosterone and 57 elderly women with low levels of sulfated DHEA. Among the men, 29 received DHEA, 27 received testosterone, and 31 received placebo. Among the women, 27 received DHEA and 30 received placebo. Outcome measures included physical performance, body composition, bone mineral density (BMD), glucose tolerance, and quality of life.

RESULTS

As compared with the change from baseline to 24 months in the placebo group, subjects who received DHEA for 2 years had an increase in plasma levels of sulfated DHEA by a median of 3.4 μg per milliliter (9.2 μmol per liter) in men and by 3.8 μg per milliliter (10.3 μmol per liter) in women. Among men who received testosterone, the level of bioavailable testosterone increased by a median of 30.4 ng per deciliter (1.1 nmol per liter), as compared with the change in the placebo group. A separate analysis of men and women showed no significant effect of DHEA on body-composition measurements. Neither hormone altered the peak volume of oxygen consumed per minute, muscle strength, or insulin sensitivity. Men who received testosterone had a slight increase in fat-free mass, and men in both treatment groups had an increase in BMD at the femoral neck. Women who received DHEA had an increase in BMD at the ultradistal radius. Neither treatment improved the quality of life or had major adverse effects.

CONCLUSIONS

Neither DHEA nor low-dose testosterone replacement in elderly people has physiologically relevant beneficial effects on body composition, physical performance, insulin sensitivity, or quality of life. (ClinicalTrials.gov number, NCT00254371.)

Ith the rapid increase in the population of people 60 years of age and older, considerable research is being focused on how to prevent or delay age-related disabilities. One approach is to replace hormones whose levels decline with age. Levels of dehydroepiandrosterone (DHEA) and its sulfated form, the most abundant steroid hormone in the circulation, decline from the third decade onward.[1,2] Studies in animals have shown beneficial effects of DHEA on many age-related changes in body composition and in conditions such as diabetes mellitus and cardiovascular disease.[3] These findings in experimental models have generally been supported by observational studies in humans.[2,4,5] Moreover, longevity in healthy humans[6] and nonhuman primates is associated with relatively high levels of DHEA,[7] a finding that has led to extensive promotion of DHEA as an antiaging agent by the lay media. However, the applicability of findings in rodents to humans is open to question, since rodents have very low levels of DHEA.[8] Furthermore, a review of the literature indicated that most studies showing positive effects in humans have been short-term or have used pharmacologic doses of DHEA.[8]

DHEA modestly increases testosterone levels in women, although in the absence of overt hypogonadism, DHEA replacement has a minimal effect on testosterone levels in men.[9] It is unclear whether testosterone supplementation has a benefit in elderly men with a modest reduction in the level of "bioavailable" testosterone (i.e., the fraction of circulating testosterone that is not bound to sex hormone–binding globulin). Therefore, there is a growing debate about whether to treat the substantial proportion of elderly men (up to 90% in some reports)[10] whose level of bioavailable testosterone is below that of young men. Moreover, testosterone replacement in elderly men may be associated with risks, especially of prostate cancer and progression of benign prostatic hypertrophy.[11] This uncertainty recently prompted the Institute of Medicine to conclude that additional well-controlled studies examining the risks and benefits of testosterone replacement in elderly men should be performed before large-scale, long-term clinical trials are undertaken.[12] In postmenopausal women, studies show that conventional estrogen replacement has substantial adverse effects; trials of ultralow estrogen replacement have demonstrated beneficial effects.[13]

We conducted a 2-year, randomized, placebo-controlled, double-blind study to determine the effects of full DHEA replacement and low-dose testosterone replacement on body composition, physical performance, bone mineral density (BMD), and glucose tolerance in elderly people with low androgen levels. We also determined whether receiving this hormone-replacement therapy had adverse effects related to the prostate.

METHODS

SUBJECTS

Subjects were eligible to participate in the study if they were at least 60 years of age. Eligibility criteria included, for men, a level of bioavailable testosterone that was less than 103 ng per deciliter (3.6 nmol per liter) and a sulfated DHEA level that was less than 1.57 μg per milliliter (4.3 μmol per liter), and for women, a sulfated DHEA level that was less than 0.95 μg per milliliter (2.6 μmol per liter). These cutoff values, which represented the 15th percentile of levels for normal young men and women,[2] were chosen to ensure that a sufficient number of healthy elderly people could participate in the study. All volunteers underwent a medical history taking and physical examination and were excluded if there was evidence of clinically important coexisting illnesses or conditions that could have an effect on outcome measures.

In addition, we evaluated 38 healthy young women and 37 healthy young men between the ages of 18 and 31 years once in order to obtain a baseline for a comparison of outcome measures. Elderly men underwent a digital rectal examination and ultrasonography to quantify the size of the prostate and to detect any nodules, and all elderly men with a level of prostate-specific antigen (PSA) above the age-adjusted normal level were excluded.

STUDY DESIGN

The study was approved by the institutional review board of the Mayo Foundation, and all subjects gave written informed consent. The study was designed and conducted entirely by the study team without industry support. Randomization schedules were prepared by study statisticians. Study groups included elderly men receiving a DHEA tablet (75 mg per day) and a transdermal placebo patch, a placebo tablet and a transdermal testosterone patch (5 mg per day; D-TRANS, Alza), or

a placebo tablet plus a placebo transdermal patch. Elderly women received either a DHEA tablet (50 mg per day) or a placebo tablet. Identical-appearing blue capsules contained either DHEA (which was 95.5% pure on analysis) or placebo with lactose as filler. Only the statisticians and pharmacists had access to the coded treatment assignments. We randomly assigned 92 men and 60 women to the study groups (Fig. 1).

Elderly subjects initially received a placebo tablet and placebo skin patch for 1 month in order to exclude those in whom allergic reactions developed to the tablet or patch preparations. No subjects were excluded after this test. At the end of 1 month, baseline studies were performed and subjects were randomly assigned to the respective treatment groups. Blood samples were collected every 3 months for the measurement of liver enzymes, hematocrit, testosterone, sulfated DHEA, and (among men) PSA. Every 3 months, the subjects received a new supply of tablets and patches.

If we observed an increase in the PSA level of 0.75 ng per milliliter or more, we repeated the PSA measurement in 3 months. If the PSA level remained elevated, the subject was examined by a urologist who was unaware of the subject's treatment assignment. A digital examination, ultrasonography, and a biopsy of the prostate were performed if such procedures were clinically warranted.

OUTCOME MEASURES

Primary outcome measures were physical performance, the peak aerobic capacity, body composition, BMD, and levels of plasma insulin and glucose after an overnight fast. Additional measurements included body weight, the proportion of body fat, the insulin-sensitivity index, quality of life, levels of various hormones, and levels of alkaline phosphatase, alanine aminotransferase, aspartate transferase, and hemoglobin. Adverse effects, including increases in the PSA, were assessed.

Measures of physical performance included muscle strength and the peak aerobic capacity, as reflected by the maximum volume of oxygen consumed per minute (VO_2). The peak VO_2 was measured during a graded-intensity treadmill-walking test, with expired gas exchange assessed as previously described.[14] Isometric torque of the knee extensors was measured (the best of five maximal voluntary contractions) on the dominant leg while the subject was seated and the knee angle was fixed at 60 degrees of flexion. The one-repetition maximum (the highest weight that can be lifted one time) for the double leg press and chest press was determined from a progressive series of attempts on adjustable weight-stack machines. All subjects were familiarized with the equipment and procedures on a separate visit preceding the data collection, and all tests were supervised by exercise specialists.
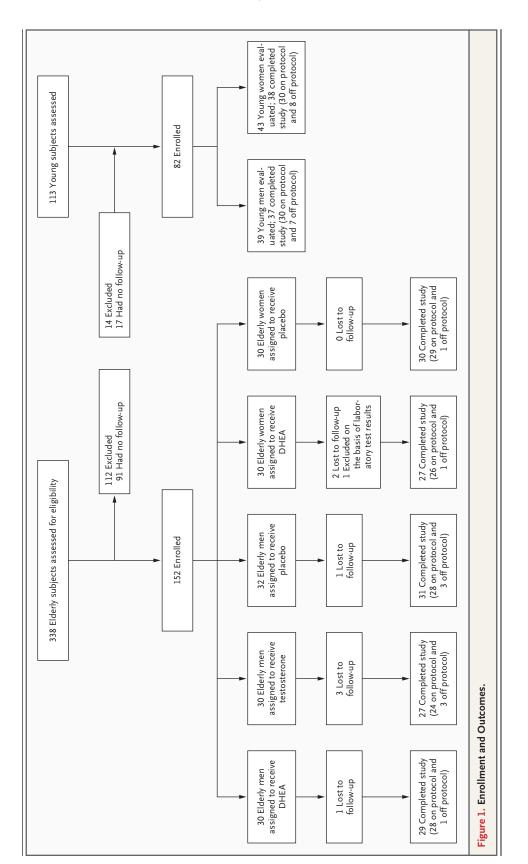
Body composition and BMD, including the proportion of abdominal visceral fat and the fat-free mass, were measured with the use of dual-energy x-ray absorptiometry (DPX-IQ, Lunar),[15] and the thigh-muscle area was measured with computed tomography.[16] Abdominal visceral fat was measured as previously described.[15,17] BMD was obtained at the anteroposterior mass of the lumbar spine (L2 to L4), femoral neck, total hip, distal radius, and ultradistal radius.

After an overnight fast, subjects ingested a mixed meal consisting of 45% carbohydrate, 40% fat, and 15% protein, totaling 10 kcal per kilogram of body weight.[18] Arterialized venous blood was sampled at regular intervals for 30 minutes before and 6 hours after the meal to measure levels of glucose, insulin, and C peptide. The oral glucose minimal model[19] was used to calculate the insulin-sensitivity index.

Ultrasonography of the prostate was performed with the use of a probe and biplanar imaging.

Levels of sulfated DHEA, total and bioavailable testosterone, follicle-stimulating hormone, and estradiol were measured by competitive chemiluminescence immunoassay (with a high-sensitivity competitive chemiluminescence immunoassay for subjects with low levels of estradiol); sex hormone–binding globulin was measured by solid-phase, two-site chemiluminescence immunometric assay (Immulite, Diagnostic Products). In subjects with low testosterone levels, values were obtained with the use of high-sensitivity competitive chemiluminescence immunoassay (ACS-180, Bayer Diagnostics); bioavailable testosterone and bioavailable estradiol were measured on the basis of differential precipitation of sex hormone–binding globulin by ammonium sulfate after the equilibration of serum samples with tracer amounts of tritium-labeled testosterone and estradiol.

We used the Health Status Questionnaire (HSQ) to evaluate subjects' quality of life.[20] The HSQ adds three questions to the Medical Outcomes Study 36-item Short General Form Health Survey (SF-36)[21]

Figure 1. Enrollment and Outcomes.

to provide a further assessment of emotional function. Although the HSQ gives rise to eight dimensions, or scales, of health status, it can also be scored to generate the two factor-derived scores from the SF-36 questionnaire (the physical component and the mental component). Each summary score is assigned a mean (±SD) score of 50±10 on the basis of an assessment of a general U.S. population without chronic conditions; individual scores were then compared with the normalized scores for the general population.[21]

STATISTICAL ANALYSIS

On the basis of preliminary estimates of the corresponding standard deviations, we determined that 30 subjects would be required in each group for the study to have a statistical power of 90% to detect clinically meaningful differences between groups. We therefore planned to enroll 150 elderly subjects (90 men and 60 women) during a 5-year period, with all subjects followed for 24 months. Difficulties in recruiting volunteers in a timely manner resulted in an extension of the study to 6 years. Recruitment was terminated on June 30, 2002; follow-up was terminated on December 31, 2003. Thus, not all subjects had their last follow-up visit at a full 24 months. For men receiving DHEA, the median duration of treatment was 23.2 months (interquartile range, 22.6 to 23.5); for men receiving testosterone, the median was also 23.2 months (interquartile range, 22.2 to 23.8); and for men receiving placebo, the median was 23.1 months (interquartile range, 22.7 to 24.0). For women receiving DHEA, the median duration of treatment was 23.0 months (interquartile range, 22.7 to 23.7), and for women receiving placebo, the median was 23.3 months (interquartile range, 22.4 to 23.5).

Changes in the end points of interest were calculated by comparing the value at baseline with that at the last measurement. The value at the last follow-up visit was used for subjects who were followed for less than 24 months but not less than 12 months. Univariate and multivariate associations of these changes for each end point were calculated for each treatment group with the use of multiple regression analysis. Independent variables included the group, the length of follow-up, the age of the subject, and the baseline value of the end point of interest. The dependent variable was the change (from lowest to highest) from baseline to 24 months. Four subjects for whom no data were available at or after 12 months were not included in the analysis. Two-sided tests were used, and P values of less than 0.05 were considered to indicate statistical significance.

Randomization and maintenance of the project database, data editing, and data analysis were carried out in the Division of Biostatistics at the Mayo Clinic.

RESULTS

BASELINE CHARACTERISTICS

The characteristics of the elderly men and women did not differ significantly among the groups at baseline (Table 1). (Additional details are listed in Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm. org.) Baseline characteristics of young subjects are listed in Table 2 of the Supplementary Appendix.

HORMONE AND METABOLIC VARIABLES

Subjects in the DHEA groups (but not the placebo groups) had a significant increase from baseline to 24 months in levels of sulfated DHEA and estradiol (both total and bioavailable forms), and women had an increase in levels of total testosterone (Fig. 2; additional details are shown in Table 3 of the Supplementary Appendix). Men in the testosterone group had a significant increase in levels of bioavailable testosterone and total testosterone, as compared with men in the placebo group. Neither men nor women in the DHEA group had significant changes in the levels of follicle-stimulating hormone or luteinizing hormone; men in the testosterone group had significantly lower levels of both hormones (data not shown). Subjects in both the DHEA group and the testosterone group had no significant changes in fasting plasma glucose or in the insulin-sensitivity index. Significant changes in fasting insulin levels were noted in the testosterone group but not in the placebo group. Taken together, men and women in the DHEA group had significant reductions in the levels of high-density lipoprotein cholesterol, but no other measures of lipids were affected by treatments.

BODY COMPOSITION AND PHYSICAL PERFORMANCE

Among the primary outcome measures, only fat-free mass differed significantly between the treatment groups and placebo groups. When men and women in the DHEA group were considered separately, no significant changes were seen in body-

Table 1. Baseline Characteristics of the Subjects.*

Characteristic	Elderly Women			Elderly Men				
	Placebo (N=30)	DHEA (N=27)	P Value	Placebo (N=31)	DHEA (N=29)	P Value†	Testosterone (N=27)	P Value†
	median (interquartile range)			*median (interquartile range)*			*median (interquartile range)*	
Demographic and body-composition characteristics								
Age — yr	70.4 (65.6–74.5)	68.4 (65.6–71.3)	0.37	67.1 (63.6–72.6)	68.4 (66.7–72.4)	0.32	66.2 (61.8–72.3)	0.55
Weight — kg	72.5 (63.0–80.0)	70.0 (59.0–78.0)	0.37	86.0 (79.0–98.0)	84.5 (74.0–92.5)	0.14	86.0 (78.0–92.0)	0.47
Body-mass index	27.9 (25.7–30.4)	26.4 (24.7–28.8)	0.19	27.4 (25.9–30.0)	27.1 (24.5–28.9)	0.31	28.4 (25.7–30.3)	0.80
Body fat — %	42.4 (39.3–45.5)	42.3 (37.6–46.4)	0.82	29.1 (23.8–32.0)	26.0 (21.8–30.0)	0.26	27.0 (24.3–29.7)	0.46
Ratio of visceral fat to total body fat‡	0.13 (0.11–0.16)	0.12 (0.09–0.15)	0.19	0.20 (0.15–0.21)	0.20 (0.16–0.23)	0.39	0.21 (0.18–0.27)	0.12
Visceral fat — g§	3892 (2681–4771)	3436 (1719–5020)	0.16	5395 (3303–6330)	4059 (3615–5929)	0.59	4800 (3307–6150)	0.97
Fat-free mass — kg	39.7 (37.5–42.5)	38.9 (36.9–42.2)	0.47	62.2 (56.9–64.6)	59.7 (56.2–64.3)	0.46	59.7 (56.3–64.3)	0.38
Thigh-muscle area — cm²	188 (179–204)	176 (164–189)	0.04	283 (237–308)	290 (250–317)	0.71	302 (277–325)	0.09
BMD — g/cm²								
Anteroposterior spine‡	1.1 (0.9–1.2)	1.2 (1–1.4)	0.10	1.2 (1.2–1.4)	1.2 (1.1–1.4)	0.48	1.3 (1.1–1.4)	0.55
Femoral neck‡	0.8 (0.7–0.9)	0.9 (0.8–0.9)	0.05	1.0 (0.9–1.0)	0.9 (0.9–1.0)	0.04	0.9 (0.9–1.1)	0.35
Total hip‡	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.12	1.1 (1.0–1.2)	1.1 (1.0–1.2)	0.34	1.1 (1.0–1.2)	0.53
Ultradistal radius‡	0.4 (0.3–0.4)	0.3 (0.3–0.4)	0.80	0.5 (0.5–0.6)	0.5 (0.5–0.5)	0.98	0.5 (0.5–0.6)	0.65
Physical performance								
Peak VO₂ — ml/kg‡¶	37.6 (33.6–39.8)	39.6 (34.0–43.0)	0.38	40.4 (35.6–42.5)	41.7 (38.8–47.1)	0.11	40.7 (36.9–45.0)	0.64
Seated chest press — kg‡	31.8 (24.9–34.0)	29.5 (27.2–31.8)	0.49	52.2 (49.9–59.0)	51.0 (45.4–63.5)	0.96	56.7 (49.9–59.0)	0.33
Isometric knee extension — kg‡	27.7 (22.4–31.5)	25.3 (21.8–28.9)	0.35	42.3 (38.1–49.4)	43.4 (39.0–48.9)	0.77	45.9 (41.0–52.2)	0.21
Double leg press — kg‡	31.8 (27.2–36.3)	45.9 (41.0–52.2)	0.55	40.8 (36.9–54.3)	45.4 (38.6–52.2)	0.51	49.9 (40.8–59.0)	0.055
Quality of life‖								
HSQ SF-36 mental component score	57.8 (54.5–59.4)	56.8 (52.1–60.0)	0.87	56.7 (53.9–58.9)	58.0 (54.9–60.5)	0.39	57.3 (54.2–61.0)	0.35
HSQ SF-36 physical component score	52.7 (47.9–55.2)	50.4 (41.1–55.5)	0.41	51.3 (48.7–54.9)	51.6 (46.7–55.1)	0.76	51.9 (50.2–55.9)	0.63

Hormone and metabolic values

Sulfated DHEA — μg/ml	0.3 (0.3–0.4)	0.4 (0.3–0.5)	0.44	0.7 (0.5–1.2)	0.6 (0.4–1.0)	0.47	0.7 (0.4–0.9)	0.57
Total testosterone — ng/dl	30.3 (26.8–35.0)	28.3 (27.5–31.9)	0.40	398.4 (296.1–472.6)	389.3 (250.9–440.2)	0.33	357.3 (281.5–464.7)	0.49
Bioavailable testosterone — ng/dl	NA	NA	NA	52.8 (46.3–63.7)	62.3 (52.4–69.0)	0.08	56.1 (44.4–65.3)	0.77
Fasting insulin — μU/ml	4.0 (3.1–4.8)	3.5 (2.7–5.4)	0.76	4.3 (3.2–5.4)	3.7 (2.9–5.3)	0.39	3.8 (3.2–5.4)	0.80
Insulin-sensitivity index**	9.3 (6.4–16.3)	12.2 (5.5–17.7)	0.97	11.4 (6.1–14.1)	12.7 (7.2–17.0)	0.21	9.6 (7.3–15.3)	0.60
Fasting glucose — mg/dl‡	94.2 (89.0–97.1)	89.9 (86.1–94.7)	0.06	93.6 (89.2–99.4)	89.9 (86.1–94.7)	0.95	92.7 (89.7–97.5)	0.44
Estradiol — pg/ml	8.5 (6.0–12.7)	7.3 (5.6–13.0)	0.89	23.6 (19.6–28.3)	20.7 (16.0–24.0)	0.04	20.2 (16.6–25.2)	0.19
Bioavailable estradiol — pg/ml	2.8 (1.6–5.2)	2.6 (1.6–6.2)	0.66	9.2 (7.0–11.8)	8.3 (7.0–10.8)	0.63	8.8 (6.8–11.4)	0.64

Lipids and PSA

PSA — mg/dl	NA	NA	NA	1.6 (0.6–3.6)	1.2 (0.8–3.6)	0.59	1.4 (0.9–2.8)	0.72
HDL cholesterol — mg/dl	47 (41–58)	49 (39–60)	0.68	36 (32–47)	41 (33–48)	0.39	35 (28–43)	0.39
LDL cholesterol — mg/dl	124 (95–147)	115 (96–131)	0.69	102 (90–128)	116 (96–128)	0.57	109 (93–137)	0.33
Triglycerides — mg/dl	121 (99–144)	121 (68–145)	0.41	112 (76–149)	103 (78–139)	0.91	132 (88–153)	0.34

* To convert values for sulfated DHEA to micromoles per liter, multiply by 2.714. To convert values for total and bioavailable testosterone to nanomoles per liter, multiply by 0.03467. To convert values for insulin to picomoles per liter, multiply by 6. To convert values for the insulin-sensitivity index to picomoles per liter, divide by 6. To convert values for estradiol and bioavailable estradiol to picomoles per liter, multiply by 3.671. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol to millimoles per liter, multiply by 0.0259. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. NA denotes not applicable. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
† P values are for the comparison between the treatment group and the placebo group.
‡ The category is a primary outcome variable.
§ Visceral fat was measured by dual-energy x-ray absorptiometry and computed tomography.
¶ The peak volume of oxygen (VO₂) consumed per minute was measured by treadmill walking.
‖ Quality-of-life scores for the HSQ SF-36 were compared with normalized scores for the general U.S. population, for which the mean score was 50±10. Higher scores indicate a better quality of life.
** The insulin-sensitivity index was calculated from an oral glucose minimal model[19] on the basis of liver and peripheral tissue.
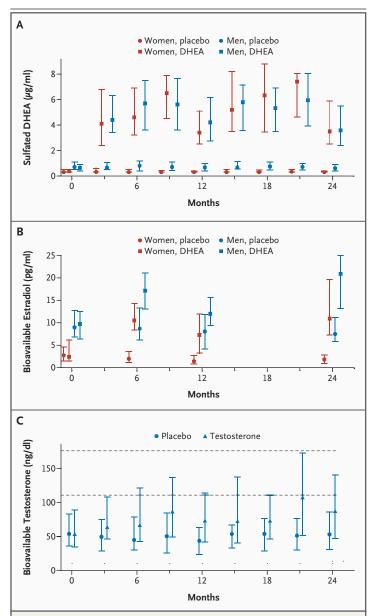
Figure 2. Changes from Baseline to 24 Months in Sulfated DHEA, Bioavailable Estradiol, and Testosterone Levels in Elderly Subjects Receiving DHEA, Testosterone, or Placebo.

Panel A shows a significant increase in median plasma levels of sulfated DHEA in elderly men and women after treatment with DHEA, as compared with placebo (P<0.001). Sulfated DHEA levels after treatment in elderly people were in the high-normal range for young men and women (see Table 2 of the Supplementary Appendix). Panel B shows a significant increase in median plasma levels of bioavailable estradiol after DHEA treatment, as compared with placebo, in both men and women (P<0.001). Panel C shows a significant increase in levels of bioavailable testosterone in elderly men after testosterone treatment, as compared with placebo (P<0.001). The dashed lines indicate the normal range of testosterone values in young men. For data in all panels, measurements were performed at a single, rather than at multiple, times during a 24-hour period at baseline and at 24 months. I bars indicate interquartile ranges.

composition measurements. When men and women were combined, the DHEA group had a slight but significant increase in fat-free mass (less than 0.5 kg) and a decrease in the proportion of body fat (less than 1.5%). Men in the testosterone group had a significant increase in fat-free mass. The changes in the peak VO_2 and the measures of muscle strength were similar in the combined DHEA group and the placebo group, as well as in the testosterone group and the placebo group.

BMD

In the DHEA group, women had a slight, but significant increase in the BMD of the ultradistal radius, and men had a slight, but significant increase in the BMD of the femoral neck. Men in the testosterone group had a significant increase in BMD only in the femoral neck. Subjects in neither the DHEA group nor the testosterone group had a significant increase in BMD at other sites.

QUALITY OF LIFE

Subjects in the DHEA and testosterone groups had no significant change in scores on the Physical Component Scale and the Mental Component Scale of the HSQ (Table 2, and Fig. 1, 2, and 3 of the Supplementary Appendix).

ADVERSE EVENTS

Measures of prostate volume, PSA levels, liver function, electrolyte levels, and hemoglobin levels were not significantly altered by treatment with either DHEA or testosterone (Table 3, and Tables 4, 5, and 6 of the Supplementary Appendix).

DISCUSSION

The administration of DHEA for about 23 months in elderly people with low androgen levels increased the levels of sulfated DHEA to values that would be considered in the high-normal range for young people. This therapy slightly increased levels of testosterone and estradiol in women and levels of estradiol in men. The administration of low-dose testosterone for just over 23 months significantly increased the levels of both total and bioavailable testosterone in men. However, treatment with neither DHEA nor testosterone had any detectable effect on physical performance, insulin sensitivity, or the physical and mental components of the quality of life. Testosterone replacement resulted in a small but significant increase in fat-free mass but no significant change in thigh-muscle area or

muscle strength. DHEA had no effect on fat-free mass in men or women when the groups were analyzed separately according to sex. The lack of a significant effect on thigh-muscle area, strength, or fitness largely discounts the relevance of the change in fat-free mass. Among the five sites measured for BMD, the women in the DHEA group had a small but significant increase in BMD of the ultradistal radius; men in both the DHEA and testosterone groups had an increase in BMD in the femoral neck. On the other hand, treatment with DHEA or testosterone caused no detectable harm, since side effects (including PSA levels and prostate volume) did not differ significantly between men in the treatment groups and those in the placebo group.

On the basis of the 95% CIs shown in Table 2, it is not likely that our negative findings can be attributed to the small number of subjects in the study. Specifically, these CIs indicate that the number of subjects was sufficient to establish that any treatment effects that might exist were not clinically meaningful. For example, the 95% CI in the DHEA group for the measure of fat-free mass in elderly men ranged from 0 to 1.78 kg, thus ruling out an effect greater than 1.8 kg. If the study had enrolled more subjects, the CI would have been even narrower. The upper limit of the 95% CI for the effect of DHEA on fat-free mass in elderly women was 1.35 kg, and for testosterone in men it was 2.15 kg.

Similarly, the number of subjects in the study appears to have been adequate to rule out clinically meaningful effect sizes for muscle strength, as measured by the upper limits of the 95% CI for the chest press (2.27 kg for both men and women in the DHEA group and 4.54 kg in the testosterone group), the fasting glucose level (1.37 mg per deciliter [0.08 mmol per liter] for men and 2.45 mg per deciliter [0.14 mmol per liter] for women in the DHEA group and 2.99 mg per deciliter [0.17 mmol per liter] in the testosterone group), and BMD at the femoral neck (0.04 g per square centimeter of body-surface area for men and 0.02 g per square centimeter for women in the DHEA group and 0.05 g per square centimeter in the testosterone group). Even though women in the DHEA group had a significant increase in BMD at the ultradistal radius (P=0.005), the number of subjects was adequate to establish that the magnitude of the effect was less than that reported with current treatments, such as bisphosphonates.[22] In contrast with our findings, 3 months of resistance exer-cise training increased chest-press strength by an average of 15 kg in older people.[23]

We administered 75 and 50 mg of DHEA per day to elderly men and women, respectively, to achieve circulating levels present in young people of the same sex.[24,25] Previous studies have examined the effects of DHEA doses ranging from 50 mg[26-28] to 1600 mg[29,30] given as a single dose or as repeated daily doses for up to 1 year.[25,31,32] These studies have had inconsistent results, with some reporting positive effects on body composition, muscle strength, BMD, and glucose tolerance, and others showing no effect.[8,9,21,25,27,29,33-41] The lack of a detectable effect of DHEA replacement on strength, peak VO$_2$, quality of life, or measures of insulin sensitivity does not preclude the possibility that DHEA had short-term effects on these measures or that pharmacologic doses could have a biologic effect. However, the current data indicate that if short-term restoration of DHEA levels in elderly subjects has favorable biologic effects, they are not sustained.

The effect of DHEA on BMD is less clear. Elderly women in the DHEA group had a small but significant increase in BMD of the ultradistal radius, and men in both the DHEA group and the testosterone group had an increase in BMD of the femoral neck. However, there was no significant increase in BMD at other sites in either group. Although this may have been a chance finding, an actual effect might have been influenced by the associated plasma estrogen levels. Since other well-tolerated and tested pharmacologic agents result in a far greater increase in BMD, the value of DHEA for either preventing or treating osteoporosis in elderly men or women is probably limited.

The administration of low-dose testosterone was associated with a small increase in fat-free mass but was not associated with a significant increase in the thigh-muscle area or with an improvement in any of the performance measures. In contrast to these results, a study of intramuscular testosterone therapy (at a dose of 200 mg every 2 weeks for 36 months)[42] demonstrated a larger increase in fat-free mass (6.7%) and a larger decrease in the proportion of body fat (17.3%). A previous study in elderly people in which testosterone levels were increased to values that were in the middle of the normal range for young people also did not show any effect on muscle strength.[43] Thus, although a pharmacologic dose of testosterone may have a marked effect on body composition and function, low-dose replacement has no

Table 2. Differences between Placebo and Treatment Groups in the Changes in Primary and Secondary Outcome Variables from Baseline to 24 Months.*

Variable	Elderly Women		Elderly Men			
	DHEA vs. Placebo *median difference (95% CI)*	P Value†	DHEA vs. Placebo *median difference (95% CI)*	P Value†	Testosterone vs. Placebo *median difference (95% CI)*	P Value†
Body composition						
Weight — kg	0 (−2 to 2)	0.73	0 (−2 to 2)	0.67	0 (−2 to 2)	0.77
Body-mass index	0 (−0.72 to 0.76)	0.72	0 (−0.63 to 0.54)	0.87	0 (−0.64 to 0.62)	0.93
Body fat — %	−1.36 (−2.71 to 0.45)	0.09	−0.19 (−1.57 to 1.09)	0.43	−1.04 (−2.36 to 0.32)	0.08
Ratio of visceral fat to total fat‡	0 (−0.01 to 0.01)	0.31	0 (−0.01 to 0.01)	0.62	0 (−0.01 to 0.01)	0.92
Visceral fat — g§	−158 (−518 to 292)	0.43	−44 (−468 to 418)	0.88	−180 (−554 to 263)	0.48
Fat-free mass — kg	0.62 (−0.05 to 1.35)	0.10	0.87 (0 to 1.78)	0.06	1.39 (0.65 to 2.15)	<0.001
Thigh-muscle area — cm²	10.9 (1.2 to 20.02)	0.10	−10.1 (−28.0 to 11.5)	0.42	−4.2 (−21.0 to 11.5)	0.89
BMD — g/cm²						
Anteroposterior spine‡	0.01 (−0.02 to 0.03)	0.63	0 (−0.02 to 0.03)	0.96	0.01 (−0.02 to 0.04)	0.38
Femoral neck‡	0 (−0.01 to 0.02)	0.69	0.02 (0 to 0.04)	0.045	0.03 (0.01 to 0.05)	0.002
Total hip‡	0.01 (−0.01 to 0.02)	0.38	0.01 (−0.01 to 0.02)	0.30	0.01 (−0.01 to 0.02)	0.26
Ultradistal radius‡	0.02 (0.01 to 0.03)	0.005	0 (−0.01 to 0.01)	0.58	0.01 (0 to 0.01)	0.06
Performance						
Peak VO_2 — ml/kg‡¶	−1.31 (−3.19 to 1.17)	0.26	−1.78 (−4.28 to 0.71)	0.45	0.48 (−2.00 to 3.15)	0.83
Seated chest press — kg‡	0 (−2.27 to 2.27)	0.94	0 (−2.27 to 2.27)	0.34	2.27 (0 to 4.54)	0.38
Isometric knee extension — kg‡	0.88 (−1.36 to 3.08)	0.54	0.29 (−3.26 to 3.81)	0.57	−0.27 (−4.22 to 3.54)	0.82
Double leg press — kg‡	0 (−2.27 to 4.54)	0.92	0 (−4.54 to 4.54)	0.46	0 (−4.54 to 4.54)	0.15

Quality of life ‖					
HSQ SF-36 mental component score	0.77 (−2.62 to 4.05)	0.61	−0.25 (−2.65 to 2.30)	0.59	0.39 (−2.23 to 3.23)	0.38
HSQ SF-36 physical component score	0.56 (−2.57 to 3.58)	0.91	−1.43 (−4.11 to 1.14)	0.12	−0.68 (−3.10 to 1.62)	0.36
Hormones and metabolic variables					
Sulfated DHEA (μg/ml)	3.8 (3.1 to 4.1)	<0.001	3.4 (2.9 to 3.8)	<0.001	0 (−0.1 to 0.1)	0.29
Total testosterone — ng/dl	19.8 (13.6 to 26.5)	<0.001	−23.1 (−58.6 to 8.3)	0.13	104.5 (39.5 to 172.7)	0.002
Bioavailable testosterone — ng/dl	NA	NA	5.8 (−4.4 to 15.4)	0.21	30.4 (11.9 to 50.0)	<0.001
Fasting insulin — μU/ml	−0.21 (−0.63 to 0.34)	0.41	−0.22 (−0.79 to 0.34)	0.53	−0.72 (−1.39 to −0.24)	0.003
Insulin-sensitivity index**	−1.80 (−5.02 to 1.10)	0.21	−0.06 (−3.41 to 3.20)	0.73	2.01 (−1.24 to 4.86)	0.22
Fasting glucose — mg/dl‡	0.11 (−2.50 to 2.45)	0.66	−0.60 (−2.72 to 1.37)	0.58	0.66 (−1.71 to 2.99)	0.77
Estradiol — pg/ml	20.4 (16.8 to 22.9)	<0.001	20.0 (15.2 to 24.4)	<0.001	1.4 (−2.0 to 4.9)	0.67
Bioavailable estradiol — pg/ml	9.52 (7.65 to 11.35)	<0.001	11.45 (8.60 to 14.72)	<0.001	2.43 (−0.11 to 5.05)	0.08
Lipids and PSA					
PSA — mg/dl	NA	NA	0 (−0.20 to 0.18)	0.95	0.09 (−0.14 to 0.31)	0.46
HDL cholesterol — mg/dl	−5 (−10 to 0)	0.003	−3 (−7 to 0)	0.06	1 (−2 to 5)	0.80
LDL cholesterol — mg/dl	4.4 (−10.4 to 20.0)	0.37	−4.8 (−17.4 to 9.0)	0.41	−6.4 (−18.2 to 4.8)	0.26
Triglycerides — mg/dl	3 (−12 to 19)	0.92	−5 (−21 to 13)	0.69	0 (−17 to 17)	0.91

* Levels of sulfated DHEA and bioavailable and total testosterone are mean values for measurements at multiple time points in a 24-hour sample. These 24-hour measurements were performed only at baseline and at 24 months. To convert values for sulfated DHEA to micromoles per liter, multiply by 2.714. To convert values for total and bioavailable testosterone to nanomoles per liter, multiply by 0.03467. To convert values for insulin to picomoles per liter, multiply by 6. To convert values for the insulin-sensitivity index to picomoles per liter, divide by 6. To convert values for estradiol and bioavailable estradiol to picomoles per liter, multiply by 3.671. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol to millimoles per liter, multiply by 0.0259. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. NA denotes not applicable.

† All P values are two-sided and are based on a multiple regression analysis in which the dependent variable was the change from baseline (with the use of a rank transformation) and the independent variables were the study group, sex, age at the time of randomization, length of follow-up, and baseline values.

‡ This category is a primary outcome variable.

§ Visceral fat was measured by dual-energy x-ray absorptiometry and computed tomography.

¶ The peak volume of oxygen (VO₂) consumed per minute was measured by treadmill walking.

‖ Quality-of-life scores for the HSQ SF-36 were compared with normalized scores for the general U.S. population, for which the mean score was 50±10.

** The insulin-sensitivity index was calculated from an oral glucose minimal model[19] on the basis of liver and peripheral tissue.

Table 3. Summary of Adverse Events.*

System Affected by Event	Placebo		DHEA		Testosterone	Total (N=151)
	Men (N=32)	Women (N=30)	Men (N=30)	Women (N=29)	Men (N=30)	
Cardiovascular	5	2	2	6	5	20
Gastrointestinal	1	0	0	2	2	5
Genitourinary†	6	3	4	1	8	22
Hematopoietic and lymphatic	2	1	0	3	2	8
Immunologic	2	1	0	3	6	12
Musculoskeletal	0	1	3	0	1	5
Nervous	2	1	2	1	1	7
Respiratory	3	1	3	2	2	11
Other system	4	0	2	2	1	9

* There were no significant differences between placebo and treatment groups.
† Adverse events associated with the prostate occurred in four men in the placebo group, three in the DHEA group, and five in the testosterone group.

demonstrable effect. Higher doses of testosterone that increase levels in older men to levels seen in young men may increase adverse effects (prostate enlargement and prostate cancer[11]), and any beneficial effects remain to be established.

It is reassuring that men in the DHEA, testosterone, and placebo groups had similar changes in both the PSA level and prostate size. However, the 2 years of observation may not be sufficient to detect subtle adverse effects of DHEA or testosterone on prostate growth and differentiation. Our study also does not preclude the possibility of adverse effects from higher doses of either of these agents. We therefore believe that the long-term safety of DHEA or testosterone therapy in elderly people remains uncertain.

In all, we found little if any beneficial effect of the restoration of DHEA levels in elderly men and women to those in healthy young people of the same sex. Although DHEA replacement has no detectable effect on body composition, physical performance, insulin action, or quality of life, it resulted in a minimal and inconsistent effect on BMD, the magnitude of which was far smaller than that of established therapies for osteoporosis. Additional long-term studies of testosterone are warranted to determine the risk–benefit ratio of higher doses. Taken together, our data provide no evidence that either DHEA or low-dose testosterone is an effective antiaging hormone supplement and argue strongly against the use of these agents for this purpose.

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