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Effects of Dehydroepiandrosterone Replacement Therapy on Bone Mineral Density in Older Adults: A Randomized, Controlled Trial

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Context: Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) decrease with aging and are important androgen and estrogen precursors in older adults. Declines in DHEAS with aging may contribute to physiological changes that are sex hormone dependent.

Objective: The aim was to determine whether DHEA replacement increases bone mineral density (BMD) and fat-free mass.

Design, Setting, and Participants: A randomized, double-blinded, controlled trial was conducted at an academic research institution. Participants were 70 women and 70 men, aged 60–88 yr, with low serum DHEAS levels.

Intervention: The intervention was oral DHEA 50 mg/d or placebo for 12 months.

Measurements: BMD, fat mass, and fat-free mass were measured before and after intervention.

Results: Intent-to-treat analyses revealed trends for DHEA to increase BMD more than placebo at the total hip (1.0%, $P = 0.05$), trochanter (1.2%, $P = 0.06$), and shaft (1.2%, $P = 0.05$). In women only, DHEA increased lumbar spine BMD (2.2%, $P = 0.04$; sex-by-treatment interaction, $P = 0.05$). In secondary compliance analyses, BMD increases in hip regions were significant (1.2–1.6%; all $P < 0.02$) in the DHEA group. There were no significant effects of DHEA on fat or fat-free mass in intent-to-treat or compliance analyses.

Conclusions: DHEA replacement therapy for 1 yr improved hip BMD in older adults and spine BMD in older women. Because there have been few randomized, controlled trials of the effects of DHEA therapy, these findings support the need for further investigations of the benefits and risks of DHEA replacement and the mechanisms for its actions. **(*J Clin Endocrinol Metab* 91: 2986–2993, 2006)**

DEHYDROEPIANDROSTERONE (DHEA) and its sulfate (DHEAS) are the most abundant circulating C_{19} steroids in humans and are derived primarily from the adrenal glands (1). DHEAS is thought to be a good biomarker of aging because peak serum levels are achieved in early adulthood and decline steadily thereafter (1). By 70 yr, average serum DHEAS levels are about 20% of young adult levels. The biological role of these steroids in humans remains poorly understood.

The actions of DHEA in humans are thought to be mediated primarily through conversion to sex hormones (2). DHEA is the precursor for 30–50% of circulating androgens in older men (3) and more than 70% in older women (4). DHEA is a major source of estrogens in men and postmenopausal women (5). Thus, it has been postulated that the decline in DHEA with aging contributes to physiological changes that are dependent on sex hormones, such as the loss of bone and muscle mass. The few randomized, controlled trials that have evaluated changes in bone mineral density (BMD) or body composition in older women and men in response to DHEA replacement therapy at doses of 25–100 mg/d have yielded mixed results (6–13). Several factors probably contribute to the inconsistent outcomes among these eight trials: 1) only one included more than 43 participants (6); 2) only one was longer than 6 months (6); 3) only four restricted inclusion to individuals with low serum DHEAS levels (7, 8, 12, 13); and 4) none specified sex hormone therapy as an exclusion criterion.

The primary aim of this randomized, controlled trial was to determine the effects of 12 months of DHEA replacement therapy on BMD and body composition in 140 older women and men with low serum DHEAS levels at baseline. We hypothesized that DHEA would preserve or increase hip and spine BMD and fat-free mass when compared with placebo.

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Abbreviations: BMD, Bone mineral density; CV, coefficients of variation; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; DXA, dual-energy x-ray absorptiometry; SAE, serious adverse event.

Subjects and Methods

Study participants

Women and men aged 60+ yr were recruited from the Denver (Colorado) metropolitan area. Of the 599 volunteers who sought information about the study, 261 were assessed for eligibility, 140 were randomized to treatment, and 130 completed the study (Fig. 1).

Participants met the following eligibility criteria: serum DHEAS less than 140 μg/dl (3.8 μmol/liter); fasted serum triglycerides less than 400 mg/dl (4.52 mmol/liter); blood pressure less than 180/95 mm Hg; normal thyroid function; normal liver enzymes; Geriatric Depression Scale (14) score 20 or less; Mini-mental State Exam (15) score 24 or more.

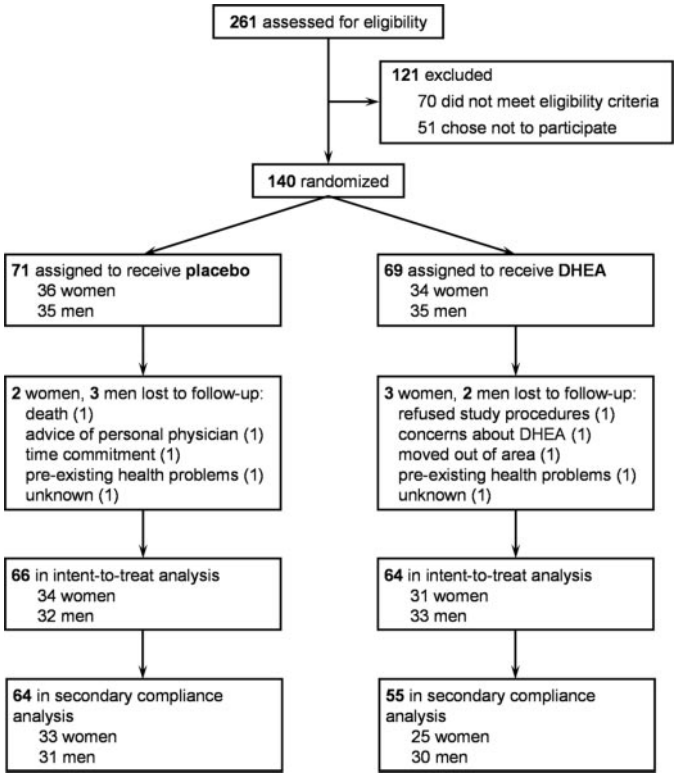

FIG. 1. Study flow chart.

Women had a normal mammogram and Pap test in the previous year, an endometrial stripe 5 mm or less, no history of breast cancer, and no other contraindications for sex hormone therapy. Men had a prostate-specific antigen less than 4.0 ng/ml, no history or evidence of prostate cancer or symptomatic benign prostatic hyperplasia, and no other contraindications for sex hormone therapy. Individuals were also excluded for: unstable health; type 1 or poorly controlled diabetes mellitus; use of prescribed or over-the-counter hormone therapies or oral glucocorticoids in the previous 6 months. The cohort was predominantly Caucasian (two Hispanic, two black, one American Indian, 11 other or unknown). The study was approved by the local Institutional Review Board. Written informed consent was obtained from all volunteers.

Intervention

Participants were randomly assigned with stratification by sex to receive oral DHEA 50 mg/d or placebo for 1 yr. The intervention was administered in a double-blinded manner. Identical DHEA and placebo pills were compounded by the Belmar Pharmacy (Lakewood, CO). The dose was selected because it has been reported to raise serum DHEAS levels of older adults into the normal range for young adults (6, 16). Compliance with the intervention was monitored by pill count and measuring serum DHEAS levels at 3-month intervals.

Procedures

Dual-energy x-ray absorptiometry (DXA). BMD of the proximal femur (total hip, neck, trochanter, and shaft regions) and lumbar spine (L_2-L_4) were measured by DXA at baseline and after 12 months of intervention using either a Lunar DPX-IQ (Lunar Co., Madison, WI) or a Hologic Delphi-W (Hologic, Inc., Bedford, MA) instrument. For each individual, baseline and 12-month measurements were obtained on the same instrument. There was equal distribution of treatment conditions for scans performed on the Lunar (48 placebo, 47 DHEA) and Hologic (23 placebo, 22 DHEA) instruments. The 12-month hip and spine scans were analyzed by comparing them with the baseline scans according to the recommendations of the manufacturer of the DXA instruments. Total body DXA scans were performed for the determination of fat mass and fat-free mass; fat-free mass did not include bone mineral content. In our laboratory, coefficients of variation (CVs) for lumbar spine, total hip, femoral neck, trochanter, and shaft BMD were 1.2 ± 0.8, 0.8 ± 0.6, 1.9 ± 0.9, 1.5 ± 1.0, and 1.1 ± 0.6%, respectively; CVs for fat-free mass and fat mass were 1.2 ± 0.8 and 1.8 ± 0.9%, respectively.

DHEAS. Serum DHEAS was measured at baseline, after 2 wk of therapy, and at 3-month intervals thereafter. Samples were stored at −80 C for subsequent batched analyses by RIA (Diagnostic Products Corp., Los Angeles, CA). The intra- and interassay CVs for DHEAS averaged 9.7 and 11.7%, respectively.

Calcium and vitamin D intake. Dietary and supplemental intake of calcium and vitamin D was assessed at baseline from 3-d diet records analyzed with Nutritionist V software (San Bruno, CA). Supplements were provided if calcium intake was less than 1000 mg/d and/or vitamin D intake was less than 400 IU/d.

Statistical analyses

The study was powered to detect the main effects of DHEA in women and men combined. The primary outcomes were the 12-month changes in hip and lumbar spine BMD and fat-free mass. Before statistical analyses, logarithmic transformations of the outcomes were considered but found to be unnecessary. Baseline characteristics of the treatment groups were compared using two-sample *t* tests in women and men separately. For intent-to-treat analyses, linear regression methods were used to analyze differences in the changes in BMD and body composition between treatment groups, with adjustment for sex and baseline value of the dependent variable.

The study was not powered to detect sex differences in the response to DHEA replacement therapy, but an exploratory aim of the study was to evaluate the sex-specific responses. This was done using the sex-by-treatment interaction in the linear regression models.

Inclusion of participants in the secondary compliance analyses was based on average serum DHEAS during the intervention. To define these groups, the average change from baseline in serum DHEAS was calculated for each individual from the 3-, 6-, 9-, and 12-month concentrations. The distribution of the average DHEAS changes for subjects in the placebo group revealed two obvious outliers whose average changes in DHEAS were more than 2 SD above the mean (+111 and +326 μg/dl, or +3.0 μmol/liter and +8.8 μmol/liter). These two cases were omitted from the placebo group for secondary analyses. Among the remaining cases in the placebo group, average changes in DHEAS ranged from −32 to +36 μg/dl (−0.9 to +1.0 μmol/liter). Compliance in the DHEA group was defined as an increase in average serum DHEAS that was at least 2-fold greater than the largest change among compliant participants in the placebo group (*i.e.* > 72 μg/dl, or > 2.0 μmol/liter). Based on this criterion, 55 cases were included in the DHEA group for secondary analyses (Fig. 1). A two-sided alpha level of 0.05 designated statistical significance. Data are presented as mean ± SD except where specified otherwise.

Results

Baseline characteristics (Table 1)

There were no significant differences between the placebo and DHEA groups in baseline characteristics, including alcohol, tobacco, and medication use. Antiresorptive drugs were predominantly bisphosphonates (n = 13 of 14). Body weight tended to be higher ($P = 0.06$) in men in the placebo arm when compared with men in the DHEA arm. There were no significant differences between the treatment groups at baseline in BMD, fat mass, or fat-free mass. Average baseline serum DHEAS levels were approximately 15% of the previously reported levels for young women (median, 324 μg/dl) and men (median, 420 μg/dl) (16). Of the 261 volunteers screened for participation, two women and 11 men had serum DHEAS levels that exceeded the inclusion criterion.

TABLE 1. Baseline characteristics

	Placebo	DHEA	*P* value
Women (n)	36	34	
Age (yr)	68.4 (6.5)	68.3 (7.3)	0.91
Serum DHEAS (μg/dl)	44.8 (25.6)	51.4 (35.2)	0.37
Weight (kg)	69.3 (15.2)	71.6 (15.4)	0.53
Height (m)	1.62 (0.06)	1.61 (0.06)	0.80
Fat-free mass (kg)	39.6 (5.2)	39.0 (5.8)	0.65
Fat mass (kg)	27.6 (11.3)	30.4 (10.1)	0.27
BMD (g/cm^2)			
Lumbar spine	1.000 (0.168)	1.043 (0.165)	0.27
Total hip	0.836 (0.149)	0.865 (0.134)	0.40
Femoral neck	0.760 (0.154)	0.779 (0.139)	0.60
Trochanter	0.668 (0.125)	0.705 (0.113)	0.20
Femoral shaft	0.981 (0.187)	0.999 (0.174)	0.69
Alcohol use (drinks/day)			
None	8 (22.2)	12 (35.3)	0.24
<1	23 (63.9)	15 (44.1)	
1–2	4 (11.1)	7 (20.6)	
>2	1 (2.8)	0 (0.0)	
Tobacco use			
Never	21 (58.3)	15 (44.1)	0.35
Previous	13 (36.1)	18 (52.9)	
Current	2 (5.6)	1 (2.9)	
Medication use			
HCTZ	8 (22.2)	3 (8.8)	0.23
Lipid-lowering	7 (19.4)	4 (11.8)	0.58
Thyroid	6 (16.7)	8 (23.5)	0.68
Antiresorptive	7 (19.4)	6 (17.6)	0.91
Calcium[a]	24 (66.7)	24 (70.6)	0.92
Vitamin D[a]	14 (38.9)	10 (29.4)	0.56
Men (n)	35	35	
Age (yr)	68.5 (6.4)	69.1 (6.7)	0.69
Serum DHEAS (μg/dl)	66.7 (29.1)	59.0 (27.0)	0.25
Weight (kg)	87.4 (12.7)	81.7 (12.2)	0.06
Height (m)	1.76 (0.06)	1.75 (0.06)	0.39
Fat-free mass (kg)	58.8 (6.0)	56.4 (5.7)	0.10
Fat mass (kg)	26.6 (9.4)	23.3 (8.2)	0.12
BMD (g/cm^2)			
Lumbar spine	1.240 (0.254)	1.263 (0.243)	0.71
Total hip	1.045 (0.144)	1.011 (0.138)	0.33
Femoral neck	0.965 (0.147)	0.915 (0.139)	0.16
Trochanter	0.883 (0.163)	0.879 (0.139)	0.91
Femoral shaft	1.204 (0.162)	1.150 (0.162)	0.17
Alcohol use (drinks/day)			
None	5 (14.3)	6 (17.1)	0.66
<1	14 (40.0)	18 (51.4)	
1–2	14 (40.0)	10 (28.6)	
>2	2 (5.7)	1 (2.9)	
Tobacco use			
Never	15 (42.9)	19 (54.3)	0.42
Previous	19 (54.3)	16 (45.7)	
Current	1 (2.9)	0 (0.0)	
Medication use			
HCTZ	7 (20.0)	4 (11.4)	0.51
Lipid-lowering	6 (17.1)	9 (25.7)	0.56
Thyroid	4 (11.4)	2 (5.7)	0.67
Antiresorptive	0 (0.0)	1 (2.9)	1.00
Calcium[a]	12 (34.3)	10 (28.6)	0.80
Vitamin D[a]	8 (22.9)	4 (11.4)	0.34

Values are mean (SD) for continuous variables and number (%) for categorical variables. HCTZ, Hydrochlorothiazide.

[a] Supplemental intake.

Calcium and vitamin D intake

In women in the placebo and DHEA groups for whom diet records were available (n = 31 and n = 29), total calcium intake at baseline averaged 1361 ± 566 and 1320 ± 545 mg/d and vitamin D intake averaged 459 ± 322 and 369 ± 220 IU/d. In men in the placebo and DHEA groups for whom diet records were available (n = 28 and n = 30), calcium intake at baseline averaged 1195 ± 549 and 1098 ± 509 mg/d and vitamin D intake averaged 457 ± 270 and 454 ± 264 IU/d. Calcium supplementation was initiated or increased in 14 subjects (seven women, seven men) in the placebo group and 14 subjects (four women, 10 men) in the DHEA group. Vitamin D supplementation was initiated or increased in 12 subjects (eight women, four men) in the placebo group and eight subjects (four women, four men) in the DHEA group.

Effects of DHEA: intent-to-treat analyses

Average serum DHEAS concentrations remained stable in women and men in the placebo group during the study (Fig. 2). In contrast, there was a 5-fold increase in serum DHEAS levels in the DHEA group. The average values after 2 wk of DHEA therapy were 365 ± 182 and 412 ± 226 μg/dl (9.9 ± 4.9 and 11.2 ± 6.1 μmol/liter) in women and men, respectively, and declined somewhat thereafter.

Pill count data were incomplete for 43 of the 130 participants who finished the trial. Based on the available data, pill compliance was 94 ± 11 and 93 ± 11% in the placebo and DHEA groups, respectively.

BMD and body composition in women and men combined (Table 2). There were strong trends for DHEA to have beneficial effects on BMD of the total hip ($P = 0.05$) and trochanter ($P = 0.06$) and shaft ($P = 0.05$) subregions but not the femoral neck ($P = 0.30$). The differences between the treatment groups in change in BMD for the total hip, trochanter, and shaft were 1.0, 1.2, and 1.2%, respectively. The difference between the DHEA and placebo groups in change in lumbar spine BMD was not significant (1.0%; $P = 0.11$). Changes in fat-free mass and fat mass in response to DHEA were not significantly different from the changes in the placebo group.

Sex-specific responses (Table 2). The lumbar spine was the only region for which there was a trend for a sex difference in the response to DHEA ($P = 0.05$ for the sex-by-treatment interaction). The change in lumbar spine BMD was significant in women (2.2%, $P = 0.04$) but not men (−0.2%, $P = 0.81$). The sex-by-treatment interactions for total hip, trochanter, and shaft BMD were not significant ($P = 0.60$–0.87). The magnitude of differences between the DHEA and placebo groups for the hip regions tended to be greater in women (1.1–1.4%) than men (0.6–1.1%). The sex-by-treatment interactions for changes in fat mass and fat-free mass were not significant.

Effects of DHEA: secondary analyses

BMD and body composition in women and men combined (Table 3). There were significant differences between the treatment groups, favoring DHEA, in the change in total hip (1.2%; $P = 0.01$), femoral trochanter (1.6%; $P = 0.02$), and femoral shaft (1.6%; $P = 0.02$) BMD. There was also a trend for an effect of DHEA on the change in lumbar spine BMD (1.2%; $P = 0.08$). There were no significant differences between the treatment groups in the change in fat mass or fat-free mass.

Sex-specific responses (Table 3). In sex-specific secondary analyses, none of the sex-by-treatment interactions reached sta-

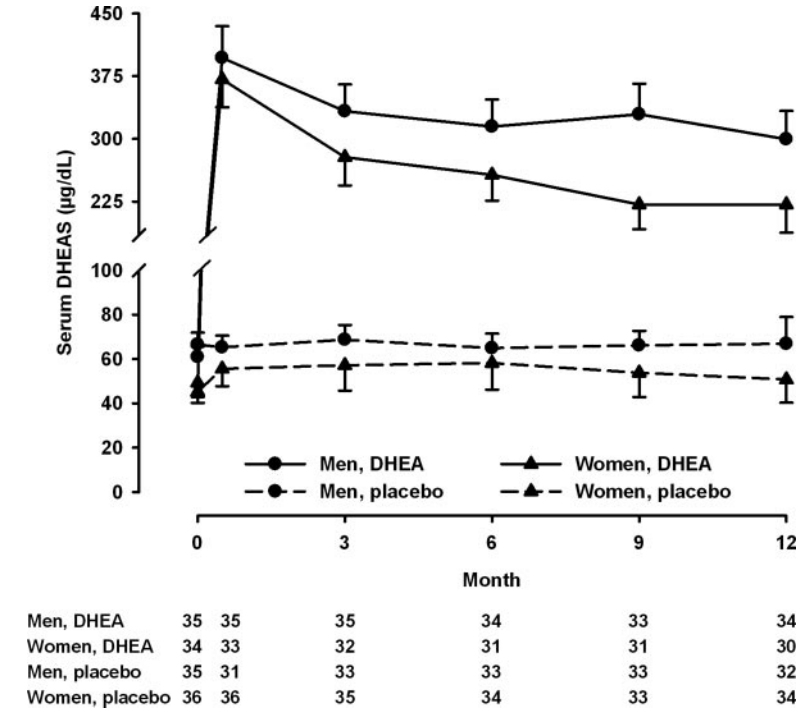

FIG. 2. Serum DHEAS concentrations (mean ± SE) at baseline and during the intervention in women and men randomized to placebo or DHEA therapy (conversion from micrograms per deciliter to micromoles per liter, multiply by 0.02714). *Numbers below the figure* indicate the number of subjects by sex and treatment group evaluated at each measurement time point (baseline, 2 wk, 3 months, 6 months, 9 months, and 12 months).

tistical significance (lumbar spine, $P = 0.09$; total hip, $P = 0.13$; trochanter, $P = 0.25$; shaft, $P = 0.41$), but the differences between the DHEA and placebo groups tended to be larger in women than men (lumbar spine: 2.3 *vs.* 0.1%; total hip: 2.0 *vs.* 0.5%; trochanter: 2.2 *vs.* 1.0%; shaft: 2.2 *vs.* 0.9%). However, these trends for sex differences appeared to be driven largely by differences between women and men in the placebo group rather than the DHEA group. In the DHEA group, the magnitudes of change in BMD were similar in women and men (Fig. 3; *black bars*, *top* and *bottom panels*). In contrast, the changes in BMD in women and men in the placebo group were quite different (Fig. 3; *gray bars*, *top* and

TABLE 2. Changes in BMD (%) and body composition (kg) over 12 months, based on intent-to-treat analyses

	Placebo		DHEA		Difference[a]		
	n	Mean (SD)	n	Mean (SD)	Difference	95% CI	*P* value
All							
Lumbar spine BMD	65	0.4 (4.0)	64	1.5 (3.4)	1.0	(−0.2, 2.3)	0.11
Total hip BMD	64	−0.4 (2.8)	62	0.6 (2.9)	1.0	(0.0, 2.0)	0.05
Femoral neck BMD	64	−1.3 (3.9)	62	−0.7 (3.0)	0.6	(−0.6, 1.9)	0.30
Trochanter BMD	64	−0.1 (4.0)	62	1.3 (3.7)	1.2	(−0.1, 2.6)	0.06
Femoral shaft BMD	64	−0.2 (3.3)	62	1.0 (3.9)	1.2	(0.0, 2.5)	0.05
Fat-free mass	66	0.0 (1.5)	64	0.1 (1.6)	0.1	(−0.4, 0.7)	0.64
Fat mass	66	−0.3 (2.8)	64	−0.5 (2.7)	−0.2	(−1.2, 0.8)	0.69
Women							
Lumbar spine BMD	33	−0.6 (4.2)	31	1.7 (3.8)	2.2	(0.1, 4.3)	0.04
Total hip BMD	33	−1.2 (2.7)	30	0.2 (3.7)	1.1	(−0.4, 2.7)	0.15
Femoral neck BMD	33	−1.8 (3.8)	30	−0.9 (3.5)	0.7	(−1.1, 2.5)	0.45
Trochanter BMD	33	−1.0 (3.9)	30	0.7 (4.6)	1.2	(−0.9, 3.3)	0.25
Femoral shaft BMD	33	−0.8 (3.8)	30	0.6 (4.7)	1.4	(−0.7, 3.5)	0.20
Fat-free mass	34	−0.2 (1.4)	31	0.3 (1.4)	0.4	(−0.3, 1.1)	0.23
Fat mass	34	0.0 (2.4)	31	−0.6 (2.2)	−0.5	(−1.7, 0.6)	0.37
Men							
Lumbar spine BMD	32	1.5 (3.4)	33	1.3 (3.0)	−0.2	(−1.8, 1.4)	0.81
Total hip BMD	31	0.4 (2.7)	32	1.0 (2.0)	0.6	(−0.6, 1.8)	0.31
Femoral neck BMD	31	−0.8 (4.0)	32	−0.4 (2.4)	0.4	(−1.3, 2.1)	0.63
Trochanter BMD	31	0.8 (3.9)	32	1.9 (2.6)	1.1	(−0.6, 2.8)	0.19
Femoral shaft BMD	31	0.5 (2.5)	32	1.4 (3.0)	0.9	(−0.6, 2.3)	0.23
Fat-free mass	32	0.1 (1.6)	33	−0.1 (1.8)	−0.2	(−1.0, 0.7)	0.70
Fat mass	32	−0.6 (3.2)	33	−0.5 (3.1)	0.1	(−1.5, 1.7)	0.91

CI, Confidence interval.

[a] Difference in 12-month change in BMD and body composition (DHEA minus placebo) adjusted for baseline measures of the outcome variable and sex (for the combined sex comparison).

TABLE 3. Changes in BMD (%) and body composition (kg) over 12 months, based on secondary compliance analyses

	Placebo		DHEA		Difference[a]		
	n	Mean (SD)	n	Mean (SD)	Difference	95% CI	*P* value
All							
Lumbar spine BMD	63	0.3 (3.9)	55	1.6 (3.5)	1.2	(−0.2, 2.6)	0.08
Total hip BMD	62	−0.4 (2.8)	53	0.9 (2.4)	1.2	(0.3, 2.2)	0.01
Femoral neck BMD	62	−1.2 (4.0)	53	−0.6 (2.7)	0.6	(−0.7, 1.9)	0.34
Trochanter BMD	62	−0.2 (4.0)	53	1.7 (3.3)	1.6	(0.3, 3.0)	0.02
Femoral shaft BMD	62	−0.2 (3.3)	53	1.3 (3.7)	1.6	(0.3, 2.8)	0.02
Fat-free mass	64	0.0 (1.5)	55	0.1 (1.7)	0.0	(−0.6, 0.6)	0.90
Fat mass	64	−0.2 (2.6)	55	−0.4 (2.6)	−0.2	(−1.2, 0.7)	0.64
Women							
Lumbar spine BMD	32	−0.6 (4.3)	25	1.8 (3.9)	2.3	(0.1, 4.6)	0.04
Total hip BMD	32	−1.1 (2.7)	24	0.8 (2.9)	2.0	(0.6, 3.4)	0.01
Femoral neck BMD	32	−1.6 (3.8)	24	−0.7 (3.0)	1.0	(−0.9, 2.8)	0.30
Trochanter BMD	32	−1.0 (3.9)	24	1.5 (4.1)	2.2	(0.2, 4.2)	0.03
Femoral shaft BMD	32	−0.8 (3.9)	24	1.3 (4.2)	2.2	(0.2, 4.3)	0.04
Fat-free mass	33	−0.1 (1.4)	25	0.3 (1.4)	0.4	(−0.4, 1.2)	0.31
Fat mass	33	−0.1 (2.4)	25	−0.5 (1.7)	−0.4	(−1.6, 0.8)	0.49
Men							
Lumbar spine BMD	31	1.3 (3.1)	30	1.4 (3.1)	0.1	(−1.5, 1.7)	0.91
Total hip BMD	30	0.4 (2.8)	29	0.9 (2.0)	0.5	(−0.8, 1.8)	0.44
Femoral neck BMD	30	−0.7 (4.1)	29	−0.5 (2.4)	0.2	(−1.6, 2.0)	0.79
Trochanter BMD	30	0.8 (4.0)	29	1.8 (2.5)	1.0	(−0.8, 2.8)	0.26
Femoral shaft BMD	30	0.4 (2.6)	29	1.3 (3.2)	0.9	(−0.6, 2.4)	0.23
Fat-free mass	31	0.1 (1.6)	30	−0.1 (1.9)	−0.3	(−1.2, 0.6)	0.53
Fat mass	31	−0.3 (2.8)	30	−0.4 (3.2)	0.0	(−1.6, 1.6)	0.98

CI, Confidence interval.

[a] Difference in 12-month change in BMD and body composition (DHEA minus placebo) adjusted for baseline measures of the outcome variable and sex (for the combined sex comparison).

bottom panels), with men exhibiting unexpected increases in BMD. In the intent-to-treat analyses, similar patterns were apparent in men in the placebo group (Table 2).

Serious adverse events (SAEs)

A total of seven SAEs occurred in six men. The death of a man in the placebo group was determined to be unrelated to the study. Other SAEs in the placebo group included two hospitalizations for exacerbation of chronic obstructive pulmonary disease (same participant) and one hospitalization for coronary artery stenting. SAEs in the DHEA group included one hospitalization for a transient ischemic attack, one hospitalization for a urinary tract infection, and one American Urological Association symptom score of 26, which exceeded the study-specific limit of 24.

Discussion

The primary aim of the study was to determine whether raising serum DHEAS has beneficial effects on BMD and body composition of older women and men with low endogenous DHEAS levels. The major finding was that, by intent-to-treat analyses, DHEA therapy tended to increase BMD in the hip (total, trochanter, and shaft regions). The trends for increased hip BMD became significant in secondary compliance analyses. There were no significant changes in fat mass or fat-free mass in response to DHEA in either intent-to-treat or secondary analyses.

An exploratory aim of the study was to evaluate whether women and men respond differently to DHEA replacement therapy. The only significant sex-specific response in the intent-to-treat analyses was the larger DHEA-mediated increase in lumbar spine BMD in women than men. However, the general tendency (Tables 2 and 3) was for the differences between the DHEA and placebo groups in changes in BMD to be larger in women. These findings should be considered preliminary and interpreted cautiously because the trial was not powered to detect sex differences.

The marked age-related decline in DHEAS (1) and the important role of DHEAS as a precursor for extragonadal sex steroid synthesis in older adults (3, 4) has led to speculation that DHEA therapy may prevent or attenuate age-related physiological changes that are mediated by the withdrawal of sex hormones, such as the loss of muscle and bone mass (17, 18). Indeed, studies of rodents provide compelling evidence for beneficial effects of DHEA on body composition (19, 20) and bone mass (21, 22). However, whether DHEA therapy would be expected to have similar effects in humans is questionable because DHEA production is markedly lower in rodents than humans (23).

DHEA therapy and BMD

Three randomized controlled trials (6, 9, 13) and two nonrandomized trials (16, 24) evaluated the effects of DHEA therapy on BMD in older adults. Casson *et al.* (13) found no significant changes in hip or spine BMD in postmenopausal women after 6 months of DHEA 25 mg/d (n = 7) when compared with placebo (n = 6). Morales *et al.* (9) also found hip and spine BMD to be unchanged in eight women and eight men, aged 50–65 yr, after 6 months of DHEA 100 mg/d in a randomized, controlled, crossover trial. The small numbers of participants in these trials, use of other sex steroids (*e.g.* estrogen-based hormone therapy), and the short duration of DHEA therapy may have limited the ability to detect changes in BMD. In the largest trial to date, Baulieu *et al.* (6)

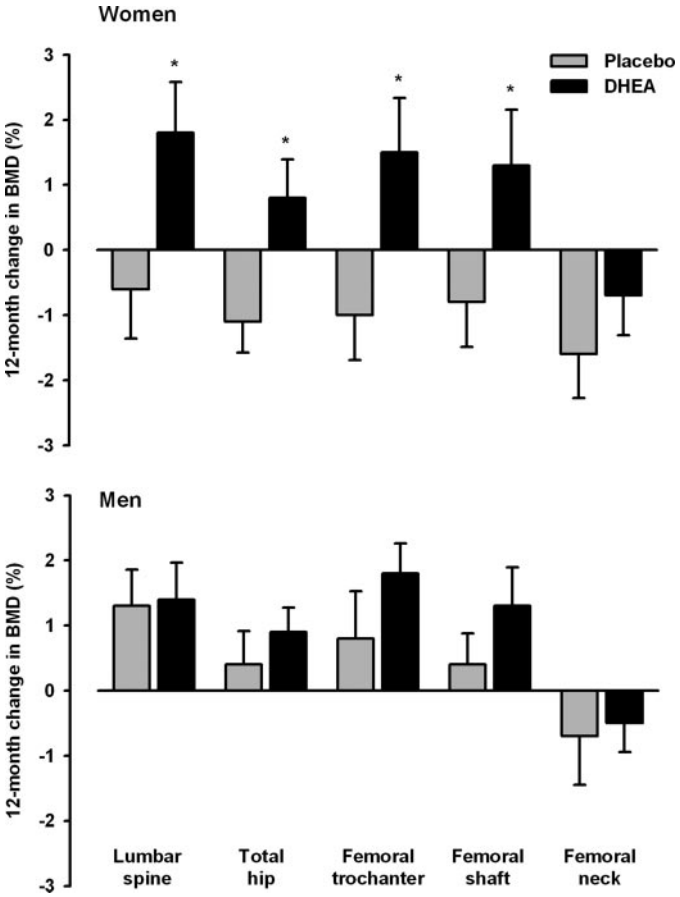

FIG. 3. Comparison of the effects of DHEA on BMD in women (*top panel*) and men (*bottom panel*) based on secondary compliance analyses. *Bars* represent the changes after adjustment for baseline BMD. *, $P < 0.05$.

measured changes in hip and radius BMD in 268 older adults who were stratified into four groups by sex and age category (*i.e.* 60–69 and 70–79 yr) and randomized to receive DHEA 50 mg/d or placebo for 12 months. Analyses were conducted only within each of the four groups (60–70 participants per group; half randomized to DHEA), thereby reducing the power to detect the effects of DHEA therapy. The only significant changes in response to DHEA were an increase in femoral neck BMD in 60- to 69-yr-old women and an increase in radius BMD in 70- to 79-yr-old women. Significant increases in BMD were also observed in the two nonrandomized trials of DHEA therapy (16, 24). In one, use of a skin cream containing DHEA for 12 months resulted in a significant increase in total hip BMD (1.9%) and a nonsignificant increase in spine BMD (1.2%) in 14 older women (24). In the other, 6 months of DHEA 50 mg/d resulted in a significant increase in lumbar spine BMD (2.7%) in 18 older women and men; increases in the men were as robust as in the women (16).

Compared with previous trials, strengths of the current trial included the relatively large number of participants, the inclusion of only those with low endogenous serum DHEAS, exclusion for use of sex hormone therapy, and the duration of intervention. There were strong trends in the intent-to-treat analyses for DHEA therapy to increase BMD of the total hip, trochanter, and shaft regions by 1.0–1.2%. The relative effect of DHEA on spine BMD was also 1.0%, but this was not significant. The improvements in BMD were somewhat smaller than the changes typically observed in response to osteoporosis therapies that have antifracture efficacy (25). For example, estrogen+progestin therapy increased total hip BMD 2.1% after 1 yr and 3.6% after 3 yr; relative risk for hip fracture was reduced by 33% (26). In postmenopausal women, alendronate increased total hip BMD about 2% after 1 yr and 4.7% after 3 yr; relative risk for hip fracture was reduced by 51% (27). In men with osteoporosis, alendronate increased total hip BMD by 1.6% at 1 yr and 3.9% after 3 yr (28). It is not known whether BMD would continue to increase with a longer duration of DHEA therapy because no trials have extended beyond 12 months. Because there is little correlation between the magnitude of increase in BMD and reduction in fracture risk (29), potential therapeutic benefits of DHEA to prevent fractures should not be ruled out simply because the effects on BMD were only modest in the current 1-yr trial.

The secondary compliance analyses based on changes in serum DHEAS corroborated, and strengthened, the trends in the intent-to-treat analyses for favorable effects of DHEA therapy on hip and spine BMD, although the latter did not achieve statistical significance. An exploratory aim of the study was to evaluate whether responses to DHEA therapy were similar in women and men. In this regard, the increases in BMD across regions of the femur and spine in the DHEA group were of similar magnitude in women and men (Fig. 3). This was consistent with observations in a small open-label trial of DHEA therapy (16). However, in sex-specific secondary analyses, the differences in hip BMD between the placebo and DHEA groups were significant in women only. It appears that a potential reason for the lack of an effect in the men was the unexpected increases in BMD in the placebo group. It was anticipated that BMD would decrease in both women and men in the placebo group. The annual rates of decline in total hip BMD for older Caucasian men have been reported to be −0.8% (30) and −0.3% (31). In contrast, the change for men in the placebo group in the current study was +0.4%. The increases in BMD in men in the placebo group did not appear to be related to calcium or vitamin D intake or supplementation, which were similar in the control and treatment groups. The results of the current trial suggest that DHEA therapy may be more beneficial for osteoprotection in women than men, but this finding must be considered preliminary. Additional controlled trials, designed to investigate sex-specific responses, will be necessary to determine whether DHEA is, indeed, more effective in increasing BMD in women than men, particularly in light of the unexpected BMD changes in men in the placebo group in the current trial.

The finding of significant increases in hip, but not lumbar spine, BMD in response to DHEA was surprising because it is the spine and other skeletal regions with a high trabecular bone content, such as the trochanter, that respond more robustly to estrogen (26) and testosterone (32). The smaller change in femoral neck BMD in response to DHEA, when compared with other regions of the hip or spine, is consistent with observations that this region also has a less robust response to other osteoporosis therapies

(33). Further studies will be required to elucidate the mechanisms by which DHEA influences BMD, which may involve the increases in serum testosterone, estradiol, and/or IGF-I that have been observed in older adults in response to DHEA therapy (7, 9, 34). However, identifying specific mechanisms of action in humans may prove challenging in light of the intracrinology hypothesis of Labrie *et al.* (35), that serum levels of testosterone and estradiol do not reflect the conversion of DHEA to active sex hormones within target tissues, such as bone.

DHEA therapy and body composition

Only two small trials (9, 16) have found small, but significant, improvements in body composition of older adults in response to DHEA therapy. Others found no significant changes in fat-free mass or fat mass (10, 11, 13). These studies involved only 3–6 months of therapy in small numbers of subjects. Although body composition was measured in the larger, 12-month trial of Baulieu *et al.* (6), results were not reported.

In the current trial, there were no significant effects of DHEA therapy on fat-free mass or fat mass in either primary or secondary analyses. It remains possible that DHEA therapy modulates the regional deposition of fat, which is strongly influenced by sex hormones (36). In a recent study, DHEA therapy significantly reduced abdominal adiposity in older adults (34). However, in another study (6), DHEA had no effects on thigh muscle or fat areas in older women. Based on available data, the effects of DHEA on regional body composition remain equivocal.

Summary

This was a randomized, double-blinded, controlled trial of the effects of DHEA therapy on BMD and body composition in older adults with low endogenous DHEAS levels. The study did not support observations from previous small trials that DHEA therapy increases fat-free mass or promotes fat reduction. However, DHEA therapy did improve hip BMD. Exploratory evaluations of the sex-specificity of this response suggested that DHEA may be more effective in women than men, but this requires further study. The increases in BMD were smaller than those typically observed in response to estrogen or other osteoporosis therapies, but this does not discount potential antifracture efficacy of DHEA therapy. A much larger and longer trial would be necessary to determine whether DHEA therapy reduces fracture risk. Whether such a trial is warranted is questionable, given that multiple therapies that effectively reduce fracture risk are available (25). However, one factor in favor of further investigation of DHEA therapy stems from the intracrinology concept of DHEA metabolism put forth by Labrie (37). Because DHEAS can be taken up and converted to potent androgens and estrogens in a tissue-appropriate manner, the benefit-to-risk ratio may be more favorable for DHEA therapy than for sex hormone therapy. If this is the case, it is possible that relatively long-duration DHEA therapy could be used safely to prevent the decline in serum DHEAS levels with aging and mitigate certain physiological changes that are mediated by age-related declines in sex hormones.

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