Dehydroepiandrosterone Combined with Exercise Improves Muscle Strength and Physical Function in Frail Older Women

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Abstract and Introduction

Abstract

Objectives: To investigate the effects of dehydroepiandrosterone (DHEA) combined with exercise on bone mass, strength, and physical function in older, frail women.
Design: Double-blind, randomized, placebo-controlled trial.
Setting: A major medical institution.
Participants: Ninety-nine women (mean age 76.6 ± 6.0) with low sulfated DHEA (DHEAS) levels, low bone mass, and frailty.
Intervention: Participants received 50 mg/d DHEA or placebo for 6 months; all received calcium and cholecalciferol. Women participated in 90-minute twice-weekly exercise regimens.
Measurements: Hormone levels, bone mineral density (BMD), bone turnover markers, body composition, upper and lower extremity strength, physical performance.
Results: Eighty-seven women (88%) completed 6 months. There were no significant changes in BMD or bone turnover markers. DHEA supplementation resulted in gains in lower extremity strength (from 459 ± 121 N to 484 ± 147 N; P=.01). There was also improvement in Short Physical Performance Battery score, a composite score that focuses on lower extremity function, in those taking DHEA (from 10.1 ± 1.8 to 10.7 ± 1.9; P=.02). There were significant

changes in all hormone levels, including DHEAS, estradiol, estrone, and testosterone, and a decline in sex hormone-binding globulin levels in those taking DHEA.
Conclusion: DHEA supplementation improved lower extremity strength and function in older, frail women involved in a gentle exercise program of chair aerobics or yoga. No changes were found in BMD either due to small sample size, short duration of study or no effect. The physical function findings are promising and require further evaluation as frail women are at high risk for falls and fracture.

Introduction

Dehydroepiandrosterone (DHEA) and its sulfate ester, DHEAS, are major secretory products of the human adrenal gland with known anabolic effects. DHEA and DHEAS undergo a significant reduction from peak levels reached in early adulthood, so that at age 70, levels are only 10% to 20% of those of young adults.[1] This age-associated decrease along with the associations between low DHEAS and mortality,[2] osteoporosis,[3] and frailty[4,5] led to speculation that DHEA supplementation may slow some typical age-related changes in bone, muscle, and physical function.

Preliminary studies found beneficial effects of DHEA on sense of well-being and energy in young individuals with primary and secondary adrenal insufficiency.[6,7] The studies evaluating the effects of DHEA supplementation in older adults are few, and the effects on bone and muscle function have been variable. Many of the studies have evaluated healthy men and women and have not selected individuals according to DHEAS level or physical capacity. DHEA supplementation has improved bone mineral density (BMD) in many but not all studies of healthy, older women and not consistently at all skeletal sites.[8–14] The data on body composition (e.g., sarcopenia), strength, and physical function are also not consistent,[10,11,13,15–19] but one study has suggested that DHEA benefits physical function when combined with exercise.[20] Most studies have been done

in healthy older adults, and function is not often measured. Thus, older women were selected for low DHEAS levels and the presence of frailty, focusing this study on a group at high risk for falls and fracture. DHEA supplementation was combined with exercise, choosing gentle, low-impact exercise (chair aerobics or yoga) that frail women could tolerate. It was hoped that the question of whether DHEA supplementation, in combination with gentle exercise, can improve function and decrease osteoporosis risk in frail, older women at high risk for falls and fractures would be answered.

Methods

The institutional review board at the University of Connecticut Health Center approved the study, and all women gave written informed consent before the screening evaluation. The women were recruited from the community. Women aged 65 and older were selected for DHEA levels below 550 ng/dL, which were the lower 50% of DHEAS levels from a previous study of older women,[21] BMD more than 1 SD below normal of a young adult, and at least one of the five frailty criteria defined by Fried and colleagues.[22] All women had had a normal mammogram within the prior year. Exclusion criteria were diseases or medications known to affect bone metabolism (Paget's disease, osteomalacia, hyperparathyroidism, corticosteroids, phenytoin, phenobarbital, methotrexate, selective estrogen receptor modulators, parathyroid hormone, bisphosphonates); use of psychiatric medications, including antipsychotic medications and selective serotonin uptake inhibitors; use of androgen, estrogen, or dehydroepiandrosterone in the preceding year; metastatic or advanced cancer or history of breast cancer; active cardiac ischemia (history of angina pectoris or myocardial infarction in the preceding 6 months).

Treatment

Women were randomized in a double-masked manner to receive DHEA supplementation (50 mg/d) or a matching placebo. Each subject was randomly

assigned to one of the four groups: DHEA+yoga, DHEA+aerobics, placebo+yoga, or placebo+aerobics, using a random number generator such that equal numbers were recruited into each group. The subjects were randomized in blocks of 20, so that for each set of 20, five subjects were assigned to each intervention group. A randomization list was provided to the research pharmacist, who had no direct contact with research participants. A subgroup of 11 women was randomly assigned to a wait list group to serve as a nonexercise control group. The women in the wait list group had baseline and 6-month assessment of all outcome measures. They were then randomized to DHEA or placebo and one of the exercise groups if they were willing to continue participation. Charles Hakala, PhD (Belmar Pharmacy, Lakewood, CO) supplied DHEA and placebo. All women were given 630 mg/d of calcium and 400 IU of cholecalciferol.

Exercise Prescription

The subjects were scheduled for two 90-minute sessions per week of yoga or chair aerobics. A certified practitioner with experience working with older adults conducted yoga classes following the Ivengar yoga method. The sessions began with breathing exercises and then postures focusing on balance and stretching and finished with relaxation. The yoga instructor demonstrated all postures, and individual instruction was provided throughout class to each woman to ensure proper positioning. Frequent posture modifications were required because of osteoarthritis or joint replacements. Participants became more proficient in yoga with time, and the classes progressed in difficulty as the participants improved. Chair aerobics used commercially available tapes with supervision by an exercise instructor. Participants were unable to follow the commercially available tapes because of deconditioning, so the instructor made a less-intense tape of chair aerobics for the first 4 to 6 weeks. Participants maintained moderate aerobic effort, and the difficulty of the tapes advanced to maintain a moderate level of activity. Class sizes were comparable, and an

instructor facilitated each session so that equal attention between exercise types was maintained. Attendance was recorded at each session for adherence.

Evaluations

A medical history was taken for each participant at screening, a physical examination was performed, and fasting DHEAS was measured. Baseline and 6-month assessments of outcome variables included serum DHEAS and other sex hormone levels, bone turnover markers, BMD and body composition according to dual X-ray absorptiometry (DXA), a frailty evaluation,[22] and physical strength and performance.

Biochemical Measurement

Blood was collected between 7:00 and 9:00 a.m. after a 10- to 12-hour fast and stored at −70°C. Blood samples were drawn in the morning before exercise participation. Markers of bone formation included bone-specific alkaline phosphatase (Metra Biosystems Inc., Palo Alto, CA), N-terminal type I procollagen peptide (Orion Diagnostica, Espoo, Finland) measured using enzyme-linked immunosorbent assay (ELISA), and osteocalcin measured using the Immulite 1000 (Siemens Medical Solutions Diagnostics, Los Angeles, CA). Average intra-assay variability was less than 5% for all measures of bone formation. Markers of bone resorption were crosslinked N-telopeptide of type I collagen measured using ELISA (Wampole Labs, Princeton, NJ) and free deoxypyridinoline crosslinks measured using the Immulite 1000. Intra-assay variability was less than 10% for measures of bone resorption.

DHEAS and sex hormone–binding globulin were measured using an immunoassay (Immulite 1000) with a sensitivity of 5 and 0.2 nmol/L, respectively. Testosterone and estradiol were measured using ELISA and estrone using radioimmune assay (RIA; Diagnostic Systems Lab, Inc., Webster, TX), with an intra-assay variability less than 6.5%. The detection limit of the estradiol assay is 0.6 pg/mL. Tests for 25 hydroxyvitamin D (25OHD), DHEAS,

and parathyroid hormone (PTH) were preformed in the General Clinical Research Center core laboratory using an EIA (IDS, Boldon, UK) for 25OHD and Immulite 1000 for PTH and DHEAS. The intra-assay variability was less than 10% for all assays.

Bone Mineral Density

BMD (g/cm^2) (Lunar DPX-IQ, Madison, WI) of the proximal femur, lumbar spine, and total body were obtained at baseline and 6 months. The coefficient of variation of BMD measurement at the proximal femur, spine, and total body was less than 1%, 1.5%, and 2%, respectively.

Body Composition, Strength Testing, and Physical Performance Testing Total and regional lean tissue masses of volunteers were determined using whole-body DXA using a DPX-IQ scanner (GE Medical Systems Lunar, Madison, WI); the same certified technician performed all scans. The whole-body scan measured total lean body mass (kg), total fat mass (kg), and total body bone mineral content (kg). Appendicular skeletal muscle mass was determined by combining the lean tissue mass of the arms and legs excluding all other regions from analysis.[23]

Physical performance was assessed according to hand grip strength (Jamar handheld dynamometer); lower extremity strength (N) and power (W) (Kaiser sitting leg press, 1-repetition maximum);[24] Short Physical Performance Battery (SPPB), which includes ability to rise from a chair, static balance, and the 8-foot walk;[25] the Get Up and Go test;[26] and the Berg Balance Scale.[27]

Frailty Evaluation The frailty phenotype evaluation, based on that described by Fried and colleagues,[22] included self-reported weight loss of 10 pounds or more in the preceding year, grip strength measured using a handheld Jamar dynamometer, sense of exhaustion as evaluated by two questions from the Center of Epidemiologic Studies Depression Scale,[28] walking speed on an 8-foot walk, and level of physical activity reported in kcal/wk from the Physical

Activity Scale in the Elderly.[29] Individuals were reported to be frail if they met criteria in three or more of the five characteristics and intermediate frail if they met criteria in one or two of the characteristics.

Statistical Analysis

Analysis was performed on individuals who had completed the 6-month study (n=87 women; 44 on placebo vs 43 on DHEA). Reanalysis was performed using the individuals that remained on study medications throughout the 6 months (n=77), but intention-to-treat analyses of 87 finishers were presented; there were no significant differences in the results between the samples of 77 and 87. Baseline and clinical characteristics for DHEA and placebo were compared using one-way analysis of variance and chi-square tests, respectively. Comparisons for exercise effect were made between wait-list controls and non-DHEA (placebo) exercisers. Using analysis of covariance, the effect of DHEA on the outcomes was tested after 6 months of drug intervention, covarying for the exercise intervention and baseline measures. A post hoc analysis was also done including 25OHD level in the model as a continuous variable and dichotomized on low (<50 nmol/L) or normal levels. Paired t-tests were used to detect change within each group over time. To correct for outliers and nonnormally distributed measures, the positive square root was calculated; variables that required square root conversion included fat mass, abdominal fat, and blood pressure readings. All analyses were done using SPSS version 16.0 (SPSS, Inc., Chicago, IL). Sample size estimates were made for changes in strength of 45 N. The study was underpowered to detect changes in BMD; an 8% change in femoral neck BMD would need to have occurred to have 80% power to detect the change.

Results

Two hundred fifty-five women attended the prescreening visit, but 156 were excluded because they did not have any frailty characteristics, they had DHEA

levels above the inclusion criteria or estrogen or bisphosphonate use, or they were unwilling to participate. Ninety-nine women were randomly assigned to treatment or placebo, yoga or aerobics. Data for analysis were available for 87 women (43 DHEA; 44 placebo); 12 women were lost to analysis for stroke, hip fracture, pelvic fracture, fall, car accident, and loss of interest in the study (Figure 1).

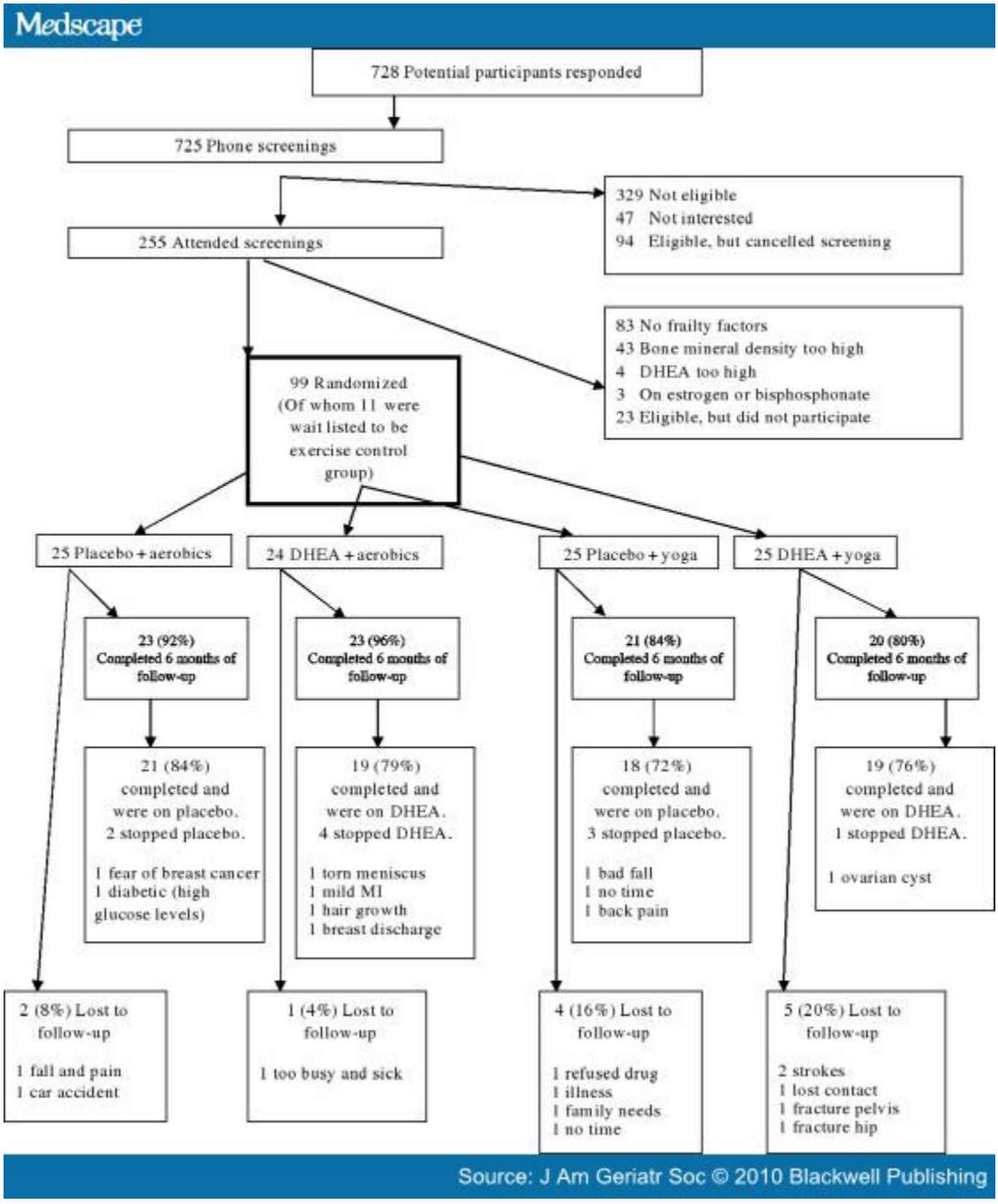

Figure 1. Recruitment and retention schema for study. DHEA=dehydroepiandrosterone.

The baseline characteristics for those given DHEA and placebo are in Table 1. No significant differences were found between the groups. Wait-list exercise controls were not different from the entire group on any characteristic shown in Table 1 (data not shown).

Table 1. Baseline Characteristics of Women Enrolled in the Study

Characteristic	DHEA (n=49)	Placebo (n=50)	Total Sample (N=99)	P-Value
Age, mean ± SD	76.4 ± 6.2	76.9 ± 5.8	76.6 ± 6.0	.68
Body mass index, kg/m^2, mean ± SD	27.5 ± 6.2	28.0 ± 6.8	27.7 ± 6.5	.67
Comorbidities, n (%)				
Coronary heart disease	6 (13)	7 (14)	13 (13)	.86
Diabetes mellitus	6 (13)	3 (6)	9 (9)	.25
Stroke	1 (2)	3 (6)	4 (4)	.32
Hypertension	19 (40)	23 (46)	42 (43)	.58
Depression (Center for Epidemiologic Studies Depression Scale score ≥16)	10 (21)	5 (10)	15 (16)	.15
Race, n (%)				.44
White	42 (89)	46 (92)	88 (91)	
Hispanic	1 (2)	0 (0)	1 (1)	
Black	4 (9)	2 (4)	6 (6)	

Other	0 (0)	2 (4)	2 (2)	
Education, n (%)				.10
High school	12 (26)	18 (36)	30 (31)	
College	18 (38)	19 (38)	37 (38)	
Postgraduate	17 (36)	13 (26)	30 (31)	
Marital status, n (%)				.47
Single	7 (15)	2 (4)	9 (9)	
Married	17 (36)	21 (42)	38 (38)	
Divorced or Separated	8 (17)	8 (16)	16 (16)	
Widowed	15 (32)	19 (38)	34 (34)	
Smoker, n (%)	2 (1)	0 (0)	1 (1)	.53
Estradiol, pg/mL, mean ± SD	22.6 ± 7.6	22.0 ± 6.5	22.3 ± 7.0	.69
Estrone, pg/mL, mean ± SD	31.6 ± 10.5	31.7 ± 13.6	31.7 ± 12.1	.95
Testosterone, pg/mL, mean ± SD	245.2 ± 123.4	251.0 ± 138.4	248.1 ± 130.6	.83
Sex hormone-binding globulin, nmol/L, mean ± SD	63.0 ± 25.2	56.4 ± 22.8	59.7 ± 24.1	.18
Dehydroepiandrosterone sulfate, μg/mL, mean ± SD	0.30 ± 0.13	0.32 ± 0.15	0.31 ± 0.14	.70
Frailty				
Prefrail	45 (92)	43 (86)	88 (89)	.36
Frail	4 (8)	7 (14)	11 (11)	

Frailty characteristics, n (%)				
Handgrip	41 (82)	38 (79)	79 (81)	.72
Depression	7 (25)	9 (31)	16 (28)	.61
Walk speed	4 (8)	6 (12)	10 (10)	.46
Weight loss	9 (18)	8 (16)	17 (17)	.82
Physical activity	7 (14)	5 (11)	12 (12)	.59

SD=standard deviation.

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Estrone, pg/mL, mean ± SD	31.6 ± 10.5	31.7 ± 13.6	31.7 ± 12.1	.95
Testosterone, pg/mL, mean ± SD	245.2 ± 123.4	251.0 ± 138.4	248.1 ± 130.6	.83
Sex hormone-binding globulin, nmol/L, mean ± SD	63.0 ± 25.2	56.4 ± 22.8	59.7 ± 24.1	.18
Dehydroepiandrosterone sulfate, μg/mL, mean ± SD	0.30 ± 0.13	0.32 ± 0.15	0.31 ± 0.14	.70

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Physical activity	7 (14)	5 (11)	12 (12)	.59

SD=standard deviation.

There were no significant changes in BMD or bone turnover markers between groups or within groups from 0 to 6 months, with the exception of a within-group increase in spine BMD from baseline in the DHEA and placebo groups (Table 2). A similar within-group increase in spine BMD was seen in the wait-list nonexercise controls during 6 months of observation (1.06 ± 0.37 to 1.10 ± 0.39 g/cm^2; P=.008), suggesting an effect of the calcium and vitamin D supplementation. Changes in 25OHD and PTH levels from baseline were found, although there were no between-group differences (Table 2). Hormonal response to 6 months of DHEA was evident, with all hormone levels (DHEA, estradiol, estrone, and testosterone) increasing. A significant decline in sex hormone–binding globulin accompanied these hormone changes, as expected, in the DHEA group (Table 2).

Table 2. Bone Mineral Density (BMD), Bone Markers, and Hormones After 6 Months of Dehydroepiandrosterone (DHEA) or Placebo Supplementation

Outcome	Mean ± Standard Deviation		

Outcome	Mean ± Standard Deviation				Beta (Standard Error)	P-Value
	DHEA (n=43)		Placebo (n=44)			
	Baseline	6 Months	Baseline	6 Months		
BMD						
Total femur, g/cm^2	0.85 ± 0.14	0.86 ± 0.14	0.86 ± 0.18	0.87 ± 0.18	−0.002 (0.005)	.71
Femoral neck, g/cm^2	0.80 ± 0.11	0.80 ± 0.12	0.80 ± 0.14	0.80 ± 0.15	−0.001 (0.006)	.81
Trochanter, g/cm^2	0.71 ± 0.13	0.71 ± 0.13	0.73 ± 0.15	0.74 ± 0.16	−0.007 (0.006)	.22
Spine L1–L4, g/cm^2	1.08 ± 0.24	1.09 ± 0.24*	1.07 ± 0.23	1.09 ± 0.24*	0.001 (0.007)	.89
Spine L2–L4, g/cm^2	1.12 ± 0.26	1.13 ± 0.26*	1.10 ± 0.24	1.11 ± 0.25*	0.001 (0.009)	.91
Whole body, g	2,121+386	2,124+386	2,072+398	2,074+406	1.66 (13.35)	.90
Bone turnover markers						
N-telopeptide/creatinine nM of bone collagen equivalents per mM	19.0 ± 4.4	18.3 ± 4.6	22.2 ± 15.0	22.1 ± 18.0	−0.11 (0.76)	.89
Bone-specific alkaline phosphatase, U/L	25.7 ± 9.9	24.9 ± 8.4	25.6 ± 9.4	24.3 ± 8.3	0.51 (0.87)	.56
Osteocalcin,	9.4 ± 4.9	8.9 ± 5.6	10.3 ±	10.2 ±	−0.51	.61

ng/mL			6.6	7.4	(1.00)	
Immunoreactive parathyroid hormone, pg/mL	48.4 ± 21.9	48.5 ± 19.2	48.9 ± 23.0	44.3 ± 19.7*	4.5 ± (2.6)	.09
Vitamin D, nmol/L	102.6 ± 46.2	112.9 ± 36.8*	88.5 ± 28.4	100.5 ± 29.9*	4.0 ± 5.2	.45
Hormones						
DHEA sulfate, ug/mL	0.30 ± 0.12	1.60 ± 1.15*	0.31 ± 0.15	0.37 ± 0.49	1.24 ± 0.19	<.001
Estradiol, pg/mL	21.2 ± 6.2	29.4 ± 10.2*	21.4 ± 6.5	21.7 ± 8.7	7.9 ± 1.6	<.001
Estrone, pg/mL	30.8 ± 10.1	56.2 ± 22.9*	30.9 ± 12.7	30.9 ± 15.7	25.4 ± 3.5	<.001
Testosterone, pg/mL	230.3 ± 116.2	571.4 ± 320.3*	247.1 ± 141.8	252.3 ± 150.9	332.3 ± 48.6	<.001
Sex hormone–binding globulin, nmol/L	62.0 ± 25.4	54.5 ± 24.1*	56.8 ± 22.7	58.5 ± 22.2	−8.5 ± 2.3	<.001

Outcomes were evaluated using analysis of covariance controlling for baseline measures and the exercise intervention; DHEA vs placebo was the primary predictor.

* P<.05 using paired t-tests within groups.

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ng/mL			6.6	7.4	(1.00)	
Immunoreactive parathyroid hormone, pg/mL	48.4 ± 21.9	48.5 ± 19.2	48.9 ± 23.0	44.3 ± 19.7*	4.5 ± (2.6)	.09
Vitamin D, nmol/L	102.6 ± 46.2	112.9 ± 36.8*	88.5 ± 28.4	100.5 ± 29.9*	4.0 ± 5.2	.45
Hormones						
DHEA sulfate, ug/mL	0.30 ± 0.12	1.60 ± 1.15*	0.31 ± 0.15	0.37 ± 0.49	1.24 ± 0.19	<.001
Estradiol, pg/mL	21.2 ± 6.2	29.4 ± 10.2*	21.4 ± 6.5	21.7 ± 8.7	7.9 ± 1.6	<.001
Estrone, pg/mL	30.8 ± 10.1	56.2 ± 22.9*	30.9 ± 12.7	30.9 ± 15.7	25.4 ± 3.5	<.001
Testosterone, pg/mL	230.3 ± 116.2	571.4 ± 320.3*	247.1 ± 141.8	252.3 ± 150.9	332.3 ± 48.6	<.001
Sex hormone–binding globulin, nmol/L	62.0 ± 25.4	54.5 ± 24.1*	56.8 ± 22.7	58.5 ± 22.2	−8.5 ± 2.3	<.001

Outcomes were evaluated using analysis of covariance controlling for baseline measures and the exercise intervention; DHEA vs placebo was the primary predictor.

* P<.05 using paired t-tests within groups.

There were significant differences in lean mass between the DHEA and placebo groups and a trend toward a difference in appendicular skeletal mass. No differences were noted between groups in body fat (Table 3). There were significantly greater improvements in sitting leg strength and composite SPPB score in those receiving DHEA supplementation than in those receiving placebo.

No differences between exercise interventions were found in the analyses, and no differences in wait-list exercise controls and placebo exercising women (aerobics or yoga) were found for body composition, strength, or physical performance (data not shown).

Table 3. Body Composition and Physical Performance Measures After 6 Months of Dehydroepiandrosterone (DHEA) or Placebo Supplementation

Outcome	Mean ± Standard Deviation				Beta (Standard Error)	P-Value
	DHEA (n=43)		Placebo (n=44)			
	Baseline	6 Months	Baseline	6 Months		
Body composition						
Percentage fat	39.6 ± 7.5	39.7 ± 6.8	38.8 ± 7.6	38.8 ± 7.7	0.16 (0.41)	.55
Lean mass, kg	39.5 ± 6.4	39.6 ± 6.1	38.4 ± 5.4	38.1 ± 5.2	0.49 (0.24)	.048
Appendicular skeletal muscle mass, kg	16.1 ± 3.1	16.1 ± 3.0	15.6 ± 3.1	15.4 ± 2.9*	0.28 (0.15)	.07
Physical performance						
Handgrip average, kg	15.4 ± 4.5	17.5 ± 5.0*	15.7 ± 5.7	16.4 ± 5.7	1.3 (0.9)	.20
Leg press strength, N	459 ± 121	484 ± 147*	477 ± 186	447 ± 128*	50 (20)	.015
Leg press power, W	166 ± 73	176 ± 76	154 ± 64	160 ± 67	6.5 (11.1)	.56

Physical Activity Scale for the Elderly						
Kilocalories	963 ± 691	829 ± 530	770 ± 484	804 ± 618	−69.1 (107.7)	.52
Score	234 ± 118	244 ± 116	156 ± 102	180 ± 102	24.4 (21.8)	.27
Short Physical Performance Battery score	10.1 ± 1.8	10.7 ± 1.9*	10.1 ± 1.4	10.1 ± 1.8	0.7 (0.3)	.016
8-foot walk, m/s	0.98 ± 0.20	1.01 ± 0.22	0.91 ± 0.17	0.89 ± 0.15	0.01 (0.05)	.81
Chair rise time, seconds	14.4 ± 6.4	13.7 ± 8.1	13.7 ± 4.3	13.2 ± 6.3	−0.16 (1.2)	.89
Single leg stance, seconds	10.0 ± 8.2	9.3 ± 7.2	7.7 ± 7.5	7.8 ± 7.2	0.5 (1.3)	.69
Get Up and Go, seconds	10.5 ± 5.2	10.6 ± 4.3	11.0 ± 2.2	10.5 ± 2.1*	0.4 (0.5)	.39

Outcomes were evaluated using analysis of covariance, controlling for baseline measures and the exercise intervention; DHEA vs placebo was the primary predictor.

* P<.05 using paired t-tests within groups.

Whether baseline 25OHD status or change in 25OHD status affected strength and physical performance outcomes was evaluated. When 25OHD was dichotomized to deficient (<50 nmol/L) and normal, no effect were found (data not shown). Added as a continuous variable, 25OHD contributed to the model for SPPB score (B=0.008, P=.03) but did not markedly change the contribution of DHEA B=0.594, P=.04 compared with B=.708, P=.02 when 25OHD was not in the model.

There was 88.9 ± 22.4% adherence to DHEA and placebo supplements and 73.1 ± 24.2% adherence to exercise interventions in the study.

Discussion

It was found that DHEA supplementation combined with exercise in women selected for low DHEAS levels improved lower extremity muscle strength, which translated to improvement in lower extremity physical performance. A cross-sectional analysis of physical performance and hormone status found an association between physical performance (physical performance test and chair rise time) and DHEA levels in men.[30] A few other studies have evaluated physical performance but have found no change in physical performance in men[15] or women.[16] There could be sex differences in effects of DHEA on muscle and function. DHEA supplementation increases testosterone levels in most studies of women and may contribute to changes in muscle strength and function. The study that did not find changes in function in women studied young postmenopausal women, and only 25 women received DHEA supplementation.[16] Other studies that measured strength found no improvement in older women.[10,13,18]

The differences may also be due to use of exercise in all women. It was not found that exercise made a difference in strength or function compared with wait-list controls or in the multivariate analysis, but the DHEA supplement was given to frail women engaging in exercise. Another study[20] showed improvement in strength in a group of healthy older adults only after adding high-resistance training to DHEA supplementation. Improvement in strength and function may require a combination of DHEA and exercise, although was not seen in all studies.[17]

Furthermore, the changes were made in a group selected for some level of frailty or poor physical performance, although their overall function was relatively good, with most of the sample demonstrating prefrailty. A

prospective 4-year study demonstrated that participants with a baseline SPPB score of 8 had greater subsequent decline in function[31] than the mean SPPB score of 10 in the current study. It is unclear whether DHEA and exercise benefits would be found in a more-robust or a more-impaired group.

Small but significant changes in lean body mass and a trend for a change in appendicular skeletal mass were found, consistent with findings of greater strength and function. A previous study found that total body mass and lean body mass increased in 10 healthy postmenopausal women receiving 100 mg DHEAS per day.[13] One study demonstrated an increase in muscle mass,[32] whereas using magnetic resonance imaging (MRI), another found no changes after 12 weeks of supplementation in 12 women.[16] Many other studies of DHEA supplementation have not found changes in body composition measured using DXA.[8,10,11,18] The differences may be due to evaluation technique using MRI, which is more sensitive to small changes than DXA.

No changes in body fat were found. Two studies by one group[12,32] found changes in body fat measured as did another study[10] when measured using MRI. Again, the differences may be due to evaluation technique.

Minimal changes were found in BMD in this 6-month intervention, with an increase in lumbar BMD, although not different from placebo or in nonexercise wait-list controls. Similarly, changes in bone turnover markers were small and not different from placebo; all participants received calcium and vitamin D supplementation (including the nonexercise wait-list controls) and some type of exercise. The majority of DHEA supplementation studies that include older adults have found changes in BMD, although not at all sites and typically only in women. The largest studies of older adults found significant increases in spinal BMD in women,[19] as did another study,[11] and another study found increased BMD at the femoral neck in women aged 60 to 69 and in the radius in women aged 70 to 79.[9] A previous study found an increase in the distal radius in women.[10] All studies used 50 mg/d of DHEA supplementation for 1 to 2

years. A small study of 50 mg of DHEA for 6 months found an increase in whole-body and lumbar spine BMD in men and women.[12] Two uncontrolled studies of healthy postmenopausal women have found increased markers of bone formation and decreased markers of bone resorption after oral[18] and topical[20] DHEA replacement. Other small studies of older adults receiving 100 mg/d of DHEA supplementation[13] or men receiving 50 mg/d of supplementation[14] failed to find changes in BMD. The current study may have missed changes in BMD because of the short study duration. Women with low DHEAS levels at baseline, a group that it was determined would have been at high risk for low bone density from epidemiological studies and studies of adrenal insufficiency,[5–7] were selected. It is unclear whether the benefits seen in other studies are due to the increase estrogen levels in bone[33,34] or increased testosterone levels acting on bone or other target tissues such as muscle.[20] This study of women selected for low DHEAS level and some level of frailty found no dramatic effects on bone, although the duration of the study was short and the sample size too small to reliably detect changes less than 8% at the femoral neck.

There was no effect of exercise on bone or muscle function in this study when compared with the wait-list controls for exercise. Low-intensity, non-weight-bearing exercise was chosen, in contrast to many of the other exercise programs that have used progressive resistance training or weight-bearing exercise with a focus on lower-extremity strength. Other exercise studies using progressive resistance training have found that exercise can increase BMD.[24,35,36] A meta-analysis of exercise found that walking was insufficient to preserve BMD at the spine, although it had a positive effect at the hip.[37] Another meta-analysis found bone preservation when adequate skeletal loading targeted to the lower extremities was provided (jogging, resistance training, or stair climbing).[38] Similarly, exercise studies using progressive resistance training or focused on lower extremity strength and function have demonstrated improved strength and physical function,[39–42] although not all studies of exercise have

been beneficial.[43] The exercise regimen in the current study focused not on weight bearing (chair aerobics and yoga, including chair yoga) but on gentle, low-impact exercise that frail, older women could accomplish. Others have described graduated exercise beginning gently to accommodate frail adults.[40] The current study found an improvement in strength and function with DHEA supplementation, but exercise, even at low intensity, may have been a requisite for this effect, as others have found in nonfrail subjects.[20] Further studies will be required to explore this preliminary finding.

DHEA supplementation increased the concentration of all sex hormones studied, indicating a good therapeutic response. DHEAS levels increased five times, equal to those seen in a typical young adult[44] and similar to increases seen in other studies of older adults using 50-mg/d supplementation with DHEA.[10,12,17,18,20,32,45] Other studies have reported increases in estrogen and testosterone levels similar to those reported here.[10,17,18,45] The increases in estradiol and estrone levels reached those seen in premenopausal women, and the levels of testosterone were greater than in premenopausal women.[46]

Conclusion

DHEA supplementation improved lower extremity strength and function in older, frail women involved in a gentle exercise program of chair aerobics or yoga. These findings are promising and require further evaluation because frail women are at high risk for falls and fracture.

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