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# DHEA enhances effects of weight training on muscle mass and strength in elderly women and men

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**Villareal, Dennis T., and John O. Holloszy.** DHEA enhances effects of weight training on muscle mass and strength in elderly women and men. *Am J Physiol Endocrinol Metab* 291: E1003–E1008, 2006. First published June 20, 2006; doi:10.1152/ajpendo.00100.2006.—The plasma levels of dehydroepiandrosterone (DHEA) and its sulfated form (DHEAS) decline ~80% between the ages of 25 and 75 yr. Muscle mass and strength also decrease with aging. Published data on the effects of DHEA replacement on muscle mass and strength are conflicting. The goals of this study were to determine whether DHEA replacement increases muscle mass and strength and/or enhances the effects of heavy resistance exercise in elderly women and men. We conducted a randomized, double-blind, placebo-controlled study of the effects of 10 mo of DHEA replacement therapy with the addition of weightlifting exercise training during the last 4 mo of the study (DHEA + exercise group, $n = 29$; placebo + exercise group, $n = 27$). DHEA alone for 6 mo did not significantly increase strength or thigh muscle volume. However, DHEA therapy potentiated the effect of 4 mo of weightlifting training on muscle strength, evaluated by means of one-repetition maximum measurement and Cybex dynamometry, and on thigh muscle volume, measured by magnetic resonance imaging. Serum insulin-like growth factor concentration increased in response to DHEA replacement. This study provides evidence that DHEA replacement has the beneficial effect of enhancing the increases in muscle mass and strength induced by heavy resistance exercise in elderly individuals.

estradiol; insulin-like growth factor I; magnetic resonance imaging; testosterone; dehydroepiandrosterone

IN HUMANS, DEHYDROEPIANDROSTERONE (DHEA) and its sulfated form, DHEAS, are present in far higher concentrations in plasma than any of the other steroid hormones (22). More than 99% of the hormone in plasma is present as DHEAS, which is converted to DHEA by steroid sulfatases (21). DHEA and DHEAS [DHEA(S)] are secreted by the zona reticularis of the adrenal cortex only in humans and closely related primate species. Adrenal production of DHEA(S) begins during puberty and peaks at ~20 yr. Beginning at ~25 yr, plasma DHEA(S) begins to decline markedly and rapidly, so that, by age 75 yr, the plasma DHEA(S) level is ~80% lower than at 25 yr (2, 28, 29). This remarkable decline in DHEA(S) with age has led to considerable interest in the possibility that development of DHEA(S) deficiency plays a role in the deterioration in metabolic and physical function with advancing age as well as in development of aging-related disease processes.

One of the changes that occurs with aging is a progressive decline in muscle mass and strength, which can advance to the point of causing frailty (18, 34). The mechanisms responsible for this loss of muscle, which leads to the condition termed sarcopenia, have not been definitively identified. However, it seems likely that declines in anabolic hormones, growth factors, and physical activity are among the factors involved. The published data on the effects of DHEA replacement on muscle mass and strength are conflicting. Morales et al. (26) have reported that 6 mo of treatment with 100 mg DHEA/day increased muscle strength in 8 men but not in 10 women, aged 50–60 yr. Diamond et al. (14) reported that application of a 10% DHEA cream to the skin daily for 12 mo increased femoral muscle area, as assessed by computerized tomography (CT) scan in 15 women aged 60–70 yr. However, in a large study involving 140 men and 140 women, aged 60–80 yr, Percheron et al. (31) found that 50 mg of DHEA daily for one year had no effect on thigh muscle area, as assessed by magnetic resonance imaging (MRI), or on strength. The interaction between DHEA replacement and heavy resistance exercise has not been reported previously. DHEA replacement causes small increases in insulin-like growth factor I (IGF-I) and testosterone levels (13, 26, 39), and DHEA has been reported to have an anti-glucocorticoid effect (1, 24, 41). Although these effects might be insufficient to increase muscle mass or strength in sedentary people (31), it seemed possible that they might potentiate the response to weight training.

The goals of the present study were to determine whether DHEA replacement in elderly women and men increases muscle mass and strength and/or enhances the effects of heavy resistance exercise on muscle mass and strength.

## STUDY DESIGN AND METHODS

This study was approved by the Washington University School of Medicine Institutional Review Board. Study participants provided their written, informed consent to participate in the study.

Men and women aged 65–78 yr were recruited from the community, by use of direct mailing and mass media, to participate in a study of DHEA replacement therapy plus resistance exercise training. A total of 136 volunteers were screened. The screening evaluation included a medical history, physical examination, analyses of blood chemistry, urinalysis, and for the men prostate-specific antigen (PSA) analysis and for the women a mammogram. Exclusion criteria included hormone therapy within the past year, a history of hormone-dependent neoplasia, a PSA >2.6 ng/ml, and active, serious illnesses. Of the 136 volunteers screened, 33 were excluded because they did not meet our eligibility criteria. An additional 39 chose not to participate. The remaining 64 volunteers were randomly assigned to receive DHEA or placebo using a computer-generated block, random-permutation procedure stratified for sex (17). Fifty-six of the random-

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ized volunteers also participated in our study of the effects of 6 mo of DHEA replacement on abdominal fat and insulin action (39). None of the participants smoked. Those who were taking medications had been on stable medications for at least 6 mo. None of the volunteers exercised regularly, and all of them had maintained stable body weight (±2 kg for the past year).

*Study Design*

We conducted a randomized, double-blind, placebo-controlled study of the effects of 10 mo of DHEA replacement therapy with the addition of weightlifting exercise training during the last 4 mo of the study. The participants took either DHEA or placebo daily for 10 mos. All of the participants performed weight training three times per week for the last 4 mo of the study. A rationale for beginning weight training after 6 mo of DHEA replacement, rather than at the same time as the DHEA therapy, was to make it possible to distinguish between the effects of DHEA per se and the effects of DHEA on the response to weight training.

*DHEA Replacement Therapy and Randomization*

The dose of DHEA was 50 mg/day, taken at bedtime. We purchased the DHEA and placebo capsules from the Life Extension Foundation (Fort Lauderdale, FL). Placebo and active capsules were identical in appearance. The randomization algorithm was generated by a member of the Washington University School of Medicine Biostatistics Division and maintained by a member of the research team who did not interact with the participants. The participants, the individuals performing the tests and measurements, the person dispensing the capsules, and those assessing the outcomes were blinded to group assignment. Compliance was checked by pill counts at monthly intervals.

*Weightlifting Program*

All participants participated in a closely supervised weight-training program. They were expected to exercise three times per week, and missed sessions had to be made up, so that each of the participants performed a minimum of 48 sessions of weight training. The exercise sessions were conducted in our research facility and were supervised by exercise technicians. The training program consisted of nine exercises (squats, leg press, knee extension, knee flexion, seated row, upright row, seated chest press, biceps curl, and triceps extension) performed using a squat rack and Hoist machine (Hoist Fitness Systems, San Diego, CA). One-repetition maximums (1-RMs), the maximal amount of weight that can be lifted once, were measured to provide the information needed to adjust exercise intensity, i.e., the amount of weight lifted during the training sessions as the participants became stronger. Initially, the weightlifting sessions consisted of two sets of each exercise using a weight that allowed completion of six to eight repetitions of each exercise at ~65% of 1-RM. After ~6 wk, they had progressed to three sets of 8–12 repetitions performed at ~85% of initial 1-RM (4, 25).

*Assessments*

Strength, thigh muscle volume, serum hormones, and IGF-I were measured at baseline, after 6 mo, and again at the end of the study.

*MRI*

Proton MRI of the thigh region was used to quantify thigh muscle volume. Axial images were acquired using a 1.5-T superconducting magnet (Siemans, Iselin, NJ) and a T1-weighted pulse sequence. Images were acquired with 134 phase-encoding steps to form 256–256 images that were stored in a 16-bit format. Consistent slice localization was accomplished by performing coronal scouting images to identify the starting point for image acquisition (10 cm above the knee joint space). Eight 8-mm-thick axial images were acquired without intersection gap. All images were analyzed by the same blinded, experienced technician using the Image Analysis Program (National Institutes of Health, Bethesda, MD). The sum of the thigh muscle volume from the eight axial images was obtained to derive the total thigh muscle volume ($cm^3$). The coefficient of variation for repeated measures of total thigh muscle volume was <1.5%.

*Muscle Strength Testing*

*1-RM testing.* 1-RM testing was performed using the same Hoist machines used for training. The participants lifted increasingly heavy weights, and the maximal amount of weight that they could lift was recorded as the 1-RM for each exercise (4). Participants were initially given instructions and shown how to perform the exercises and then practiced during a trial session before the baseline measurements.

*Isokinetic Dynamometer Testing*

Knee extensor strength and flexor strength were also evaluated using a Cybex II isokinetic dynamometer (Lumex), while participants were seated with their backs supported and hips placed at 120° of flexion, as previously described (6). Tests were performed at 0°, 60°, and 180° per second. For the isometric test, the arm of the dynamometer was fixed at 45° of flexion. Cybex testing has the advantage that it minimizes the effects of neuromuscular learning on measurement outcomes, because the training program did not include Cybex exercise.

*Diet*

The participants completed 3-day food records under the supervision of a dietitian at baseline, at 6-mo, and at the end of the study. Records were analyzed using Nutritionist IV (First Databank, San Bruno, CA).

*Blood Hormones and PSA*

Serum DHEAS level was measured by enzyme-linked immunosorbent assay (Diagnostic Systems Laboratory, Webster, TX). Levels of testosterone, sex hormone-binding globulin (SHBG), and IGF-binding protein-3 (IGFBP-3) were measured by enzyme-linked immunosorbent assay; estradiol levels were measured by ultrasensitive radioimmunoassay (Diagnostic Systems Laboratory). IGF-I was measured by radioimmunoassay (9) by the core laboratory of the Diabetes Research Training Center at Washington University. The coefficients of variation of these assays were all <10%. Levels of PSA were determined using a monoclonal antibody assay (Hybritech, San Diego, CA). After the resistance training period, these blood tests were made ~40 h after the last bout of exercise.

*Statistical Analyses*

Baseline characteristics of the DHEA and control groups were compared using Student's *t*-test for unpaired samples for continuous variables and chi-square test for categorical variables. Repeated-measures analysis of variance (ANOVA) was used to compare treatment effects over time, with a group factor (treatment) and a trial factor (time). Age and gender were entered as covariates in the repeated-measures ANOVA. When a significant treatment-by-time interaction was observed, the changes from baseline to 6 mo, the changes from baseline to 10 mo, and the changes from 6 mo to 10 mo were compared with ANOVA using baseline and 6-mo values as covariates. Paired *t*-tests were also performed to determine whether there were significant within-group changes. Analyses were performed on subjects who completed the study. The primary outcome measures were changes in thigh muscle volume and strength. Secondary outcome measures were changes in hormone, IGF-I, and PSA concentrations. We estimated that a sample size of 20 in each group would be needed to detect a clinically meaningful 20 ± 11 $cm^3$ difference in change in thigh muscle volume, between groups, with a

power of 0.9 and α of 0.05. SPSS version 12.0 (SPSS, Chicago, IL) was used for all statistical analyses. *P* value ≤ 0.05 was considered to be statistically significant. Results are reported as means ± SD unless otherwise stated.

## RESULTS

Of the 64 participants enrolled, 56 completed the 10-mo-long study of DHEA therapy and resistance training. Five participants in the placebo group dropped out (3 for personal reasons and 2 for medical reasons unrelated to the study), and three participants in the DHEA group dropped out (1 for personal reasons and 2 for medical reasons unrelated to the study).

There were no significant differences in baseline characteristics between the groups randomized to placebo plus resistance exercise (PLB + EXER group) and to DHEA plus resistance exercise (DHEA + EXER group) (Table 1). In both groups, serum DHEAS levels were on average ~80% lower than the peak levels in young people established in our laboratory (~3,300 ng/ml), consistent with a large age-related decline in DHEAS. Body weight did not change significantly over the 10-mo study period (−0.9 ± 2.9 kg for PLB + EXER, and −1.1 ± 4.2 kg for DHEA + EXER).

The percentage of prescribed doses taken by the placebo group averaged 95 ± 9% at 6 mo and 93 ± 4% at 10 mo of the study. Compliance with the prescribed doses in the DHEA group was 97 ± 10% at 6 mo and 94 ± 6% at 10 mo of the study. Because all subjects were required to complete 48 exercise sessions, compliance with the exercise program was 100%. Average attendance was 2.8 ± 0.3 exercise sessions/wk for the DHEA group and 2.7 ± 0.5 sessions/wk for the placebo group. The training was completed over an average of 120 ± 10 days for the DHEA group and 125 ± 19 days for the placebo group.

### *Diet*

There were no significant changes in energy intake assessed using diet records. Energy intake averaged 2,199 ± 338 kcal/day for the PLB + EXER group and 2,260 ± 331 kcal/day for the DHEA + EXER group at baseline, and 2,127 ± 473 kcal/day for the PLB + EXER group and 2,276 ± 478 kcal/day for the DHEA + EXER group at 10 mo.

### *Muscle Thigh Volume*

MRIs were obtained on 48 participants (23 PLB + EXER and 25 DHEA + EXER). MRIs could not be obtained on eight participants because of metal in the body, pacemakers, or claustrophobia. There were no significant changes in thigh muscle volume in response to 6 mo of DHEA therapy or placebo. However, there were significant increases in thigh muscle volume in response to the subsequent 4 mo of resistance training in both the DHEA- and placebo-treated groups. The increase in thigh muscle volume in response to resistance training was significantly larger in the DHEA + EXER group (7.6 ± 7.3%) than in the PLB + EXER group (3.1 ± 5.5%) (Fig. 1).

Table 1. *Baseline characteristics*

| | Placebo + Resistance Training ($n$ = 27) | DHEA + Resistance Training ($n$ = 29) | $P$ Value |
|---|---|---|---|
| Age, yr | 71±4 | 72±4 | 0.277 |
| Male/female | 13/14 | 15/14 | 0.688 |
| Ethnicity, %Caucasian | 93 | 91 | 0.606 |
| Weight, kg | 82.5±12.9 | 81.5±17.7 | 0.885 |
| Height, cm | 168.7±8.7 | 171.1±12.1 | 0.410 |
| BMI, kg/m$^2$ | 29.0±4.4 | 27.9±4.5 | 0.351 |
| Serum DHEAS, ng/ml | 603.6±266.4 | 633.7±363.9 | 0.634 |

BMI, body mass index; DHEAS, sulfated form of dehydroepiandrosterone.

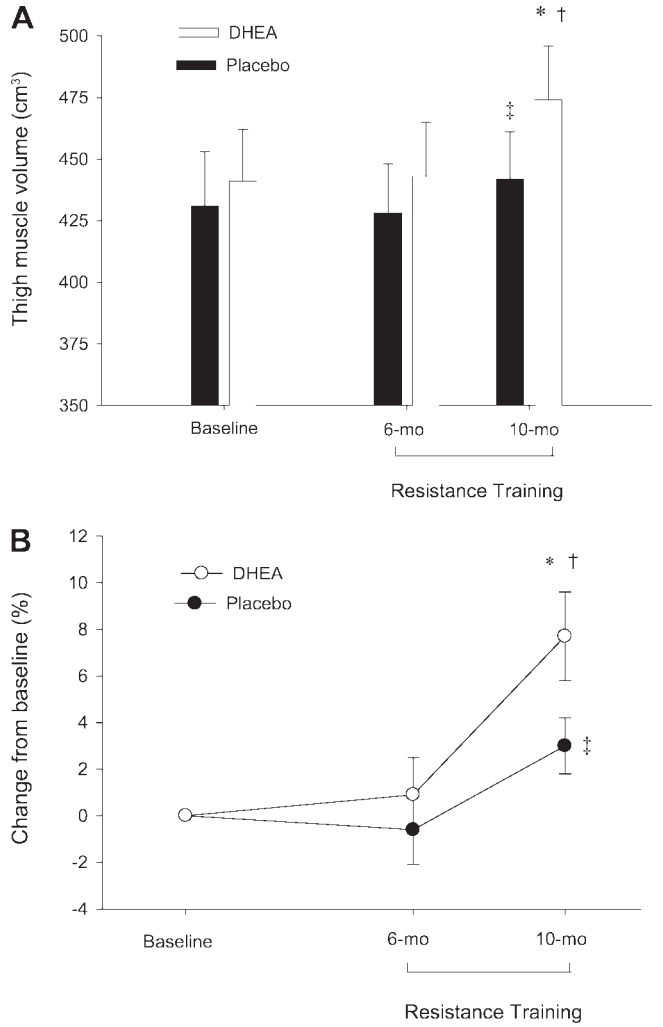


Fig. 1. Effect of dehydroepiandrosterone (DHEA) replacement therapy plus resistance training on thigh muscle volume assessed by magnetic resonance imaging. Participants were randomized to DHEA or placebo groups and given DHEA (50 mg/day) or placebo for 10 mo. For the last 4 mo of the study, all of the participants performed weight training 3 times/wk. *A*: thigh muscle volume in cm$^3$. *B*: changes in thigh muscle volume. Values are means ± SE. *$P < 0.05$ for between-group comparison of changes from baseline and from 6 mo. †$P < 0.01$ for within-group comparisons of changes from baseline and from 6 mo. ‡$P < 0.05$ for within-group comparisons of changes from baseline and from 6 mo.

### *Muscle Strength, 1-RM*

The 1-RM data on three participants in the DHEA group and two participants in the placebo group were internally inconsistent because of arthritis pain, muscle strains, and, in two individuals, unknown causes, and had to be discarded. Another participant in the placebo group could not perform the 1-RM testing because of foot surgery. The results of the 1-RM testing

Table 2. *Effects of DHEA + resistance exercise training on 1-RM strength measurements*

| | Placebo + Resistance Training ($n$ = 24) | | | DHEA + Resistance Training ($n$ = 26) | | | Treatment × Time |
|---|---|---|---|---|---|---|---|
| | Baseline | 6-mo | 10-mo | Baseline | 6-mo | 10-mo | $P$ Value |
| Leg press, lb | 114±35 | 115±40 | 134±38† | 116±37 | 117±40 | 149±44*† | 0.008 |
| Chest press, lb | 76±32 | 78±33 | 91±37† | 75±33 | 78±35 | 99±41*† | 0.022 |
| Biceps curl, lb | 38±18 | 41±17 | 51±25† | 36±18 | 40±20 | 55±25† | 0.605 |
| Seated row, lb | 86±28 | 89±28 | 115±37† | 89±30 | 94±34 | 124±41† | 0.463 |
| Knee flexion, lb | 100±37 | 102±34 | 126±41† | 99±29 | 103±36 | 136±49† | 0.222 |
| Knee extension, lb | 105±36 | 109±31 | 163±51† | 113±36 | 118±31 | 196±65*† | 0.027 |

1-RM, 1-repetition maximum. *$P < 0.05$ for between-group comparisons of the change from baseline value and of the change from 6-mo value; †$P = 0.001$ for within-group comparisons with baseline value and 6-mo value.

on the remaining 50 participants are shown in Table 2. No significant changes in muscle strength assessed by 1-RM were observed during the first 6 mo of the treatment with DHEA or placebo. Significant increases in 1-RM for all six exercises occurred in both groups in response to the 4 mo of weight training. However, the magnitudes of improvements in the 1-RM were greater in the DHEA group than in the placebo group, and for three of the exercises, leg press, chest press, and knee extension, the improvements were statistically significantly larger in the DHEA than in the placebo group (Table 2). The women and men responded similarly.

*Muscle Strength, Cybex Dynamometry*

No significant changes in strength assessed by Cybex dynamometry occurred during the first 6 mo of DHEA or placebo treatment. During the subsequent 4 mo of weight training, both the DHEA and placebo groups showed significant improvements. However, the increases in knee extension torque and knee flexion torque induced by training were significantly greater in the DHEA than in the placebo group for all the torque measurements, with the exception of isometric knee flexion (Table 3). The women and men showed similar improvements.

*Serum Hormone and IGF-I Levels*

The DHEA replacement therapy raised serum DHEAS levels into the young normal range (Table 4). Serum testosterone increased significantly (~3-fold) into the young normal range in the women in response to the DHEA replacement therapy but did not change significantly in the men. Serum estradiol increased ~30% in the men and ~70% in the women in response to DHEA therapy (Table 4). DHEA replacement also caused modest, but significant, increases in serum IGF-I. There were no significant changes in sex hormone-binding proteins or IGFBPs in response to DHEA replacement. SHBG averaged 129 ± 87, 130 ± 83, and 132 ± 83 nM for the PLB + EXER group and 123 ± 42, 116 ± 56, and 119 ± 60 nM for the DHEA + EXER group at baseline, 6 mo, and 10 mo, respectively ($P = 0.276$). IGFBP-3 averaged 4,008 ± 150, 41,464 ± 1,566, and 4,014 ± 1,529 ng/ml for the PLB + EXER group and 4,444 ± 1,646, 4,371 ± 1,630, and 4,339 ± 1,727 ng/ml for the DHEA + EXER group at baseline, 6 mo, and 10 mo, respectively ($P = 0.517$).

*Adverse Events*

There were no serious adverse events during the course of the study. Plasma PSA levels (baseline, 6 mo, and 10 mo) averaged 1.7 ± 1.1, 1.6 ± 1.2, and 1.5 ± 1.0 ng/ml for the men in the DHEA group and 1.4 ± 0.8, 1.8 ± 1.1, and 1.7 ± 1.1 ng/ml for the men in the placebo group, respectively.

## DISCUSSION

Our results show that DHEA replacement alone does not significantly increase muscle mass or strength in elderly men and women. This finding is in keeping with the results of the large study of DHEA replacement by Percheron et al. (31). In contrast, Morales et al. (26) reported an increase in strength in 8 men but not in 10 women in response to DHEA therapy. The reason for this discrepancy could be that Morales et al. used a dose of DHEA of 100 mg/day, whereas a dose of 50 mg/day was used in the present study and that by Percheron et al.

This study provides the new information that DHEA replacement significantly potentiates the effect of heavy resistance exercise on muscle hypertrophy and strength in elderly

Table 3. *Effect of DHEA + resistance exercise training on Cybex strength measurements*

| | Placebo + Resistance Training ($n$ = 27) | | | DHEA + Resistance Training ($n$ = 29) | | | Treatment × Time |
|---|---|---|---|---|---|---|---|
| | Baseline | 6-mo | 10-mo | Baseline | 6-mo | 10-mo | $P$ Value |
| Knee extension | | | | | | | |
| Isometric, ft-lb | 81±23 | 83±24 | 89±22‡ | 79±28 | 81±31 | 99±31*† | 0.008 |
| 60°, ft-lb | 87±19 | 84±21 | 89±19 | 85±28 | 84±24 | 95±23*† | 0.024 |
| 180°, ft-lb | 60±20 | 59±18 | 62±18‡ | 60±22 | 60±21 | 69±21*† | 0.012 |
| Knee flexion | | | | | | | |
| Isometric, ft-lb | 60±18 | 58±16 | 62±18 | 62±19 | 61±22 | 67±21‡ | 0.421 |
| 60°, ft-lb | 60±19 | 60±20 | 64±18‡ | 58±15 | 59±17 | 69±20*† | 0.029 |
| 180°, ft-lb | 43±19 | 47±19 | 49±18‡ | 47±17 | 47±18 | 58±19*† | 0.041 |

*$P < 0.05$ for between-group comparisons of the change from baseline value and of the change from 6-mo value; †$P = 0.001$ for within-group comparisons with baseline value and 6-mo value; ‡$P < 0.05$ for within-group comparisons with baseline value and 6-mo value.

Table 4. *Effects of DHEA replacement therapy on serum hormone levels*

| | Placebo + Resistance Training ($n$ = 27) | | | DHEA + Resistance Training ($n$ = 29) | | | Treatment × Time $P$ Value |
|---|---|---|---|---|---|---|---|
| | Baseline | 6-mo | 10-mo | Baseline | 6-mo | 10-mo | |
| DHEAS, ng/ml | | | | | | | |
| Men | 602±243 | 595±312 | 497±201 | 684±234 | 3,748±306*† | 3,218±346*† | |
| Women | 606±304 | 636±415 | 579±369 | 567±288 | 3,633±433*† | 3,401±469*† | <0.001 |
| Testosterone, ng/ml | | | | | | | |
| Men | 5.1±1.3 | 5.3±1.2 | 5.3±1.4 | 4.8±1.4 | 5.3±1.1 | 5.5±1.4 | |
| Women | 0.3±0.2 | 0.3±0.1 | 0.3±0.2 | 0.5±0.4 | 1.4±1.4*† | 1.5±1.9*† | 0.001 |
| Estradiol, pg/ml | | | | | | | |
| Men | 19.3±4.0 | 19.4±3.6 | 17.0±3.1 | 22.1±6.7 | 30.7±8.5*† | 29.1±7.5*† | |
| Women | 13.5±3.6 | 16.5±7.6 | 15.0±3.1 | 13.1±6.2 | 24.1±8.3*† | 22.3±7.3*† | <0.001 |
| IGF-I, ng/ml | | | | | | | |
| Men | 156±65 | 143±56 | 157±63 | 169±44 | 184±40*‡ | 193±40*‡ | |
| Women | 153±53 | 146±54 | 156±56 | 155±54 | 196±71*‡ | 202±51*‡ | 0.002 |

IGF, insulin-like growth factor. *$P < 0.05$ for between-group comparisons of the change from baseline value; †$P = 0.001$ for within-group comparisons with baseline value; ‡$P < 0.05$ for within-group comparisons with baseline value.

women and men. This research was an "add on" to an investigation of the effect of DHEA replacement on insulin action and glucose tolerance (39). Its purpose was to provide preliminary information on the effect of DHEA replacement on muscle mass and strength by itself and in combination with weightlifting exercise. The finding of a significant potentiating effect of DHEA on the increase in muscle mass and strength induced by weight training provides the rationale for additional studies specifically designed to elucidate the mechanisms by which DHEA replacement brings about this response.

One clue regarding a possible mechanism is provided by the finding that DHEA replacement results in an increase in serum IGF-I concentration (Table 4) (13, 26). Although this increase was small, it raises the possibility that DHEA replacement might also increase the IGF-I isoforms expressed in skeletal muscle. A particularly intriguing possibility is that DHEA replacement might potentiate the increase in the IGF-I isoform mechano-growth factor (MGF) that is induced by muscle contractions and has a powerful anabolic effect on muscle (19).

Testosterone has an anabolic effect on skeletal muscle (3, 5, 30) and powerfully potentiates the effects of heavy resistance exercise on muscle mass and strength (37, 38). DHEA replacement resulted in a threefold increase in testosterone level in the women in this study. This finding raises the possibility that the increase in testosterone might have played a role in potentiation of the effects of weight training on muscle mass and strength by DHEA replacement. Arguing against the possibility are the findings that the men, who had no significant increase in testosterone, showed the same potentiating effect of DHEA replacement as the women, and that the absolute level of testosterone, although increased, was still very low in the women receiving testosterone replacement.

Glucocorticoids have a catabolic effect on skeletal muscles, and plasma cortisol levels, as well as the increase in cortisol in response to physiological stressors, are increased in the elderly (27). DHEA has an anti-glucocorticoid effect (1, 24, 41). It seems possible that the enhancement of the effect of weight training on muscle mass and strength by DHEA replacement may be mediated, in part, by a countering of the catabolic effect of the increases in cortisol induced by exercise stress.

Studies in rodents have provided evidence that aging leads to chronic activation of NF-κB, resulting in increased production of inflammatory cytokines (10, 11, 33, 35). In humans, levels of IL-6, TNF-α, and C-reactive protein (CRP) increase with advancing age (7, 15, 20, 40). Elevated levels of IL-6 and acute phase proteins, including CRP, intercellular adhesion molecules (ICAM-1), and fibrinogen, the production of which is controlled by inflammatory cytokines, are predictors of disability (8, 16, 20). The inflammatory cytokines have a catabolic effect on skeletal muscle and are thought to play a role in the development of sarcopenia (34). DHEA is an activator of peroxisome proliferator-activated receptor-α (PPARα), a member of the steroid hormone nuclear receptor family (32, 33). Activated PPARα decreases inflammation by negatively regulating NF-κB transcriptional activity (12, 33, 36). Activated PPARα also exerts anti-inflammatory effects by antagonizing the activator protein-1 (AP-1) and STAT pathways (12, 23). Thus another mechanism by which DHEA could potentiate the effect of resistance exercise on muscle mass and strength is by decreasing inflammatory cytokine production in response to exercise.

It has previously been shown that DHEA replacement results in a decrease in intra-abdominal fat and improvements in insulin action and glucose tolerance (13, 39). The present results provide evidence that DHEA replacement has the additional beneficial effect of enhancing the increases in muscle mass and strength induced by heavy resistance exercise in elderly women and men.

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