

Effects of dehydroepiandrosterone vs androstenedione supplementation in men

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ABSTRACT

WALLACE, M. B., J. LIM, A. CUTLER, and L. BUCCI: Effects of dehydroepiandrosterone vs androstenedione supplementation in men. *Med. Sci. Sports Exerc.*, Vol. 31, No. 12, pp. 1788–1792, 1999. **Purpose:** The purpose of this study was to compare the effects of short-term (12 wk) supplementation with androstenedione versus dehydroepiandrosterone (DHEA) on body composition, strength, and related hormones in middle-aged men. **Methods:** A randomized, placebo-controlled, double-blind design was used to study 40 healthy, trained (>1 yr weight training) male subjects (mean \pm SD: age 48.1 ± 3.9 yr; weight 79.8 ± 9.8 kg). Subjects were randomly assigned to one of three groups: placebo (P), DHEA (D), or androstenedione (A). Supplements (50 mg capsules) were ingested two times daily for 12 wk. All testing, including venous blood samples, body composition, and performance, was conducted at three time points: presupplementation (1 d), at 6 wk, and postsupplementation (12 wk). **Results:** Despite a small increase in lean body mass (0.8 ± 0.4 and 0.5 ± 0.3 kg) and mean strength (6.8 ± 2.7 and 5.7 ± 2.4 kg) in both D and A groups respectively, these changes were not significantly different from P. In D, there was a significantly greater increase in DHEA-S levels than in P ($P < 0.05$). There were no adverse side effects demonstrated during D or A supplementation including significant changes in PSA, liver function, or lipid levels ($P < 0.05$). **Conclusions:** The results of this study suggest that supplementation with $100 \text{ mg}\cdot\text{d}^{-1}$ of either androstenedione or DHEA does not independently elicit a statistically significant increase in lean body mass, strength, or testosterone levels in healthy adult men over a 12-wk period. **Key Words:** ANDROGENIC HORMONES, BODY COMPOSITION, STRENGTH TRAINING

Dehydroepiandrosterone (DHEA), its sulfate ester (DHEA-S), and androstenedione are androgenic hormones produced primarily by the adrenal glands, which serve as precursors in the endogenous production of both testosterone and estrogens (7,20). In the adrenal cortex, DHEA is converted to androstenedione that, in turn, can either be dehydrogenated in the liver to testosterone or aromatized to estrone (13). It is, in fact, their role in testosterone synthesis that has stimulated much of the recent interest in their potential as anabolic/ergogenic aids.

Like testosterone, the production of these hormones peaks in the mid-20s and then declines steadily with age after the third decade of life (19). It has been speculated, therefore, that supplementation with these "precursor" hormones may help keep androstenedione and/or testosterone levels elevated thereby optimizing the anabolic state and attenuating age-associated metabolic/hormonal changes and related sequelae (e.g., decrease in immune function, lean body mass, and strength levels; and increase in body fat, insulin resistance, and coronary artery disease). Several recent studies have, in fact, demonstrated age-related benefits with DHEA supplementation including increases in lean body mass and strength

(17,18,25) as well as a reduced risk of heart disease, improved lipid levels, and enhanced immune system function and glucose tolerance/insulin sensitivity (1,3,4,7,9,11,14,18,24,25). These findings have generated considerable interest in the potential health and longevity benefits of androgenic hormone supplementation.

However, studies with humans have produced equivocal results (22,23). These discrepancies may be related to a number of factors including: the basal physiologic milieu (initial hormonal/metabolic profile); body composition (lean body mass vs fat mass); nutritional status (quantity, composition, and timing); training index (frequency \times intensity \times volume); dosing criteria (timing, quantity, and route of administration); and age.

Supplementation with androgenic hormones also poses a potential risk for promoting growth of hormone-sensitive tumors, most notably prostatic hypertrophy, as well as promoting hepatotoxicity, and increasing the risk of cardiovascular disease (8,10,21). However, there is little evidence of acute toxicity associated with DHEA or androstenedione supplementation in humans. Further, there is little information regarding the effects of normal physiological doses in middle-aged men participating in a strength-training program. The purpose of this study, therefore, was to compare the effects of short-term (12 wk) DHEA versus androstenedione supplementation on body composition, strength levels, and hormonal profiles in middle-age men experienced in weight training. A key question to be addressed is

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whether or not such supplementation will induce any adverse side effects in these subjects.

METHODS

Subjects

Forty healthy men between the ages of 40 and 60 (mean \pm SD age: 48.1 ± 3.9 yr) experienced in weight training (>1 yr) participated in this study. All subjects completed a medical history, lifestyle and training inventory, and written informed consent before participation. All procedures were in compliance with human subject guidelines established by the U.S. Department of Health, Education, and Welfare and the American Physiological Society. Subjects were required to maintain their normal training index (frequency \times intensity \times volume), physical activity patterns, and dietary regimen (including no use of any other supplements) throughout the duration of the study.

Experimental Design

Subjects participated in one of three randomly assigned experimental trials. Each supplement phase consisted of blind assignment of either a placebo (P), DHEA (D), or androstenedione (A) capsules. Supplements were measured in 50-mg quantities and placed in generic capsules coded for identification. Capsules were ingested two times daily for 3 months (i.e., $100 \text{ mg}\cdot\text{d}^{-1}$). All measurements (including a body composition profile, blood chemistry and hormone profile, and performance measures) were made at three times points: presupplementation (1 d), 6 wk, and post-supplementation (12 wk).

Body Composition

Body composition was determined using hydrostatic-weighting techniques and corrected for residual volume using the helium dilution method. Body fat and fat free mass were calculated from body density values. The waist-to-hip ratio, an index of intra-abdominal adiposity, was calculated by dividing the circumference of the abdomen (at the level of the umbilicus) by the circumference of the buttocks where the hips are largest.

Blood Samples

Fasting blood samples (12 h) were taken from an antecubital vein by a trained phlebotomist between 0700 and 0800 on three consecutive days. Samples were immediately refrigerated and transported to the lab and analyzed for the following: a blood chemistry profile (including a lipid profile, liver function, and glucose); hormones (including testosterone, cortisol, DHEA-S, androstenedione, insulin-like growth factor-1 (IGF-1), and insulin; sex-hormone-binding-globulin (SHBG); and prostate-specific antigen (PSA). All hormone measurements for each subject were performed in the same assay. Total cholesterol, glucose, and triglycerides were determined using enzymatic methods/spectrophotometry; high-density lipoprotein (HDL)-C was determined by

phosphotungstic precipitation/spectrophotometry; and serum concentrations of DHEA-S, testosterone, insulin, SHBG, IGF-1, and androstenedione were measured by specific radioimmunoassays (RIA). The intra- and inter-assay coefficients of variation were 4 and 7% for DHEA-S, 5 and 8% for testosterone, 4 and 9% for androstenedione, 5 and 10% for IGF-1, 3 and 6% for SHBG, 2 and 3% for PSA, and 5 and 7% for insulin.

Performance

Each subject's maximal functional capacity was tested for both muscular strength and aerobic capacity.

Strength. Subjects were tested for one repetition maximum (1RM) upper-body (barbell bench press) and lower-body (leg press) strength. After two to three progressive warm-up sets, sets of 1RM were completed with increasing loads until the subject could not complete one repetition. Each set was followed by a 2- to 3-min rest period. The last successful weight lifted was determined to be the 1RM.

Aerobic capacity. A symptom-limited maximal exercise test was performed to assess cardiopulmonary and metabolic functional capacity, to screen for coronary artery disease (ischemic and arrhythmic responses), and to evaluate any potential contraindications to exercise training. All tests were performed using an electromagnetically braked cycle ergometer using a 25-W RAMP protocol. Each test consisted of 2 min of unloaded pedaling at 60 rpm, followed by a 2-min warm-up at 25 W and a subsequent constant rate of increase of power output ($25 \text{ W}\cdot\text{min}^{-1}$). An electrocardiogram was used to monitor cardiac rate and rhythm continuously throughout the test using standard 12-lead procedures. Metabolic and ventilatory responses were assessed using a digital computer based exercise system (SensorMedics, Yorba Linda, CA).

Training/Dietary Control

Subjects met individually with a nutritionist who instructed them to maintain their normal dietary pattern throughout the course of the study and to refrain from using any other supplementation. Compliance was monitored by analyzing 3-d food records pre-, mid-, and post-supplementation. Exercise logs/training programs were also reviewed at this time by an exercise physiologist to insure compliance with their training program. All subjects increased their training loads progressively over the course of the study to maintain an 8-12 RM intensity. A visual analog scale of libido and an open-ended questionnaire for self-assessment of well-being were administered pre- and post-supplementation. A 24-h history questionnaire consisted of questions related to factors such as sleep patterns, physical health, exercise levels, and general state of well-being.

Statistical Analysis

All results are reported as means \pm SE. Data were analyzed using a two-way (3×3 , time \times group) analysis of variance. Interactions were analyzed on pre/post scores

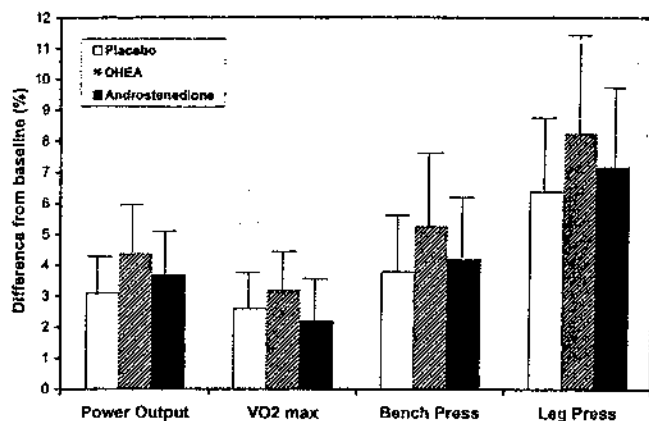


Figure 1—Percentage change of performance measures pre- to post-supplementation. No significant differences were demonstrated ($P < 0.05$).

using a *t*-test. Pearson product moment correlations were performed to determine significant correlations between variables. When significant effects were revealed, a Scheffe *post hoc* test was used to locate the pairwise differences among means. For all statistical tests, significance was accepted at the $P < 0.05$ level.

RESULTS

Performance Measures

Figure 1 summarizes the results of the maximal exercise test and 1RM testing for each trial. There were no significant differences (NS) demonstrated between groups on any baseline (pre-) measures. There was a small increase in power output (W) and $\dot{V}O_{2\max}$ ($L \cdot \min^{-1}$) for all groups that were not significantly different (NS) between groups. There was also an increase from baseline in both strength measures, bench press (4.3 ± 1.2 and 3.4 ± 1.0 kg), and leg press (13.0 ± 3.1 and 10.8 ± 2.4 kg) in both D and A, respectively, that were also not significantly different from changes in P or from each other ($P < 0.05$).

Body Composition

There were no significant differences observed between groups on baseline measures of body composition, including body mass (BM), percent fat (%), lean body mass (LBM), and fat mass (FM). As seen in Table 1, there was a small increase in LBM relative to baseline in D and A that was not significantly different from that demonstrated in P or from each other ($P < 0.05$).

Hormone Profile

Figure 2 summarizes the results of the salient (androgenic) hormonal changes. There were no significant differences observed between groups on any baseline hormone levels. Initial basal levels of all hormones were within the normal range for men. However, there was a significant correlation ($r = 0.56$) between baseline DHEA values and LBM that did not increase with supplementation. Further, there was a

significant increase in serum DHEA-S levels and a NS increase in IGF-1 demonstrated in D only ($P < 0.05$). No other statistically significant hormonal changes were observed in any group.

Risk Factor Profile

To monitor the occurrence of potential adverse side effects of supplementation, the following variables were determined: PSA, glucose, insulin, lipids, and liver function (ALT transaminase). Table 2 summarizes the results of this risk factor profile. There were no significant differences observed in any baseline "risk factor" measures. Small, NS decreases in glucose, cholesterol, and triglycerides were demonstrated in D. There were no significant differences reported for any of these risk factors relative to baseline or P.

Well-Being and Libido

A number of subjects reported an improved sense of well-being after supplementation (D = 4, A = 3, P = 3). Subjective statements included enhanced feelings of relaxation, sleep quality, and energy and stress management. Two subjects each in D and A, and one in P, reported improved feelings of libido. Further, two subjects in D reported a reduction in joint pain. Only one subject each in D and A reported an adverse effect on sleep quality. No other adverse effects were reported by any subjects.

DISCUSSION

The purpose of this study was to compare the effects of DHEA versus androstenedione supplementation in healthy, middle-aged men currently involved in a weight training program. The results demonstrate that supplementation did not significantly increase lean body mass or strength levels relative to changes observed in P. These results are consistent with previous studies reporting no increase in LBM or decrease in percent fat (23) but contradict others reporting an increase in both LBM and strength with DHEA supplementation (17,25). As mentioned, these discrepancies may

TABLE 1. Body composition measures pre- and post-supplementation; values are mean \pm SD.

Variable	Pre	Post
Body mass (kg)		
Placebo	80.2 \pm 10.2	80.7 \pm 11.0
DHEA	82.3 \pm 11.3	83.2 \pm 12.0
Androstenedione	78.4 \pm 9.1	79.1 \pm 9.9
Percent fat (%)		
Placebo	16.9 \pm 2.8	16.8 \pm 3.5
DHEA	17.4 \pm 3.0	17.2 \pm 4.3
Androstenedione	15.7 \pm 2.3	15.8 \pm 3.2
Lean body mass (kg)		
Placebo	66.7 \pm 5.9	67.1 \pm 7.4
DHEA	68.0 \pm 7.2	68.8 \pm 7.9
Androstenedione	66.1 \pm 6.3	66.6 \pm 7.0
Fat mass (kg)		
Placebo	13.5 \pm 2.1	13.6 \pm 3.5
DHEA	14.3 \pm 3.5	14.4 \pm 4.2
Androstenedione	12.3 \pm 2.6	12.5 \pm 3.0

* Statistically significant difference from baseline.

** Statistically significant difference from P, $P < 0.05$.

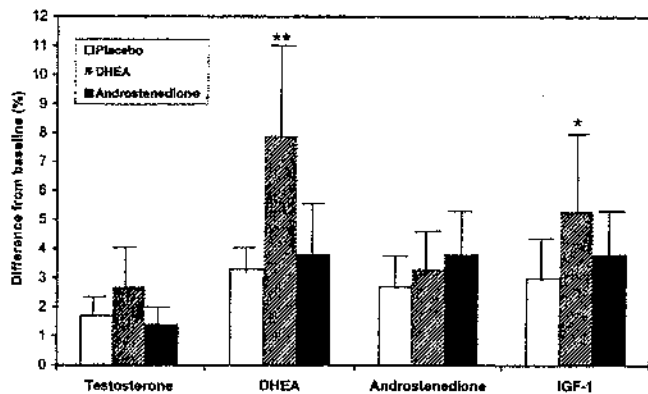


Figure 2—Percentage change of androgenic hormone profile pre- to post-supplementation. * Statistically different from baseline ($P < 0.05$). ** Statistically different from placebo ($P < 0.05$).

be related to a number of factors including: the basal physiologic milieu (e.g., initial hormonal/metabolic profile), body composition (lean body mass vs fat mass), nutritional status (quantity, composition, timing), training index (frequency \times intensity \times volume), dosing criteria (timing, quantity, route of administration), and age. Though of similar age and body mass, only two of our subjects (both in D) were below the normal reference range for serum DHEA and androstenedione concentrations. Such low levels may be critical to inducing a statistically significant response with replacement dose supplementation.

Though there is evidence that androstenedione can raise serum testosterone into normal range from low basal levels (2,13), in the present study, supplementation with androstenedione did not significantly increase serum androstenedione or testosterone levels. This lack of a conversion response in A may be related to the short half-life of androstenedione and its rapid conversion to estrogens in peripheral tissues (12). Further, it has been characterized as a weak androgen with only a minimal amount converted to testosterone and more to estrogen (16). Muscle, along with adipose tissue, is a major source of serum estrogens derived from androstenedione (15). In fact, increasing androstenedione levels in men may not provide the anabolic environment desired. Overproduction of androstenedione may cause feminizing signs such as gynecomastia, whereas elevated levels cause increased estrone levels. On the other hand, supplemental androstenedione in low doses is not prone to excess elevation of estrogen levels (13), particularly in hypogonadism. It also appears that a small additional amount of estrogen produced by supplemental androstenedione may trigger formation of more androgen receptors where they are wanted most—skeletal muscles (5). It is also likely that the body rapidly adapts to excess androstenedione and may down-regulate its production and subsequent conversion to testosterone or estrogens as needed. Finally, because androstenedione and DHEA have been shown to decrease with long-term strength training (2), supplementation may have been "sacrificed" to maintain testosterone levels and prevent overtraining. Replacement therapy may help reduce overtraining syndrome and prevent a deficiency induced by intense training and delayed strength plateaus normally ob-

served. Though the subjects in this study were involved in a weight training program 3–4 d \cdot wk $^{-1}$, the intensity and/or volume were not sufficient to elicit an overtraining syndrome.

In contrast to A, there was a significant increase in DHEA-S levels and a mild, NS increase in IGF-1 in D. Although the precise functions of DHEA (and thus the implications of an elevated DHEA level with supplementation) remain unclear (8), it has been postulated that it may play a role as a discriminator of life expectancy and aging (4). It has also been reported that DHEA-S level is independently and inversely predictive of death from any cause and from cardiovascular disease (3,4). Thus, it is tempting to speculate that supplementation with DHEA may help confer some protection against chronic disease and/or premature death. Future prospective studies would be needed to confirm this potential benefit.

Though smaller in magnitude, the increase in IGF-1 observed in this study is consistent with others' (17,25) who have suggested that an increased bioavailability to target tissues over time may manifest as improved capacity in physical and psychological performance in deficient subjects. However, this was not demonstrated in the present study nor was the increase in IGF-1 statistically significant relative to P. Although a number of subjects reported an improved sense of well-being after supplementation, the large majority of subjects did not report this benefit. Again, there may be a responder subset who may benefit with an enhanced sense of well-being and libido. Moreover, two subjects in P were convinced they were taking one of the hormone supplements, which, of course, demonstrates a significant placebo and/or seasonal effect. Results may have, in fact, been confounded by the timing of this study (spring-summer) which is often characterized by an improved sense of well-being and motivation.

TABLE 2. Risk factor profile pre- and post-supplementation; values are mean \pm SE.

Variable	Pre	Post
Glucose (mg \cdot dL $^{-1}$)		
Placebo	96.0 \pm 13.8	94.3 \pm 8.9
DHEA	90.6 \pm 12.5	87.5 \pm 10.8
Androstenedione	92.1 \pm 10.8	94.6 \pm 8.3
Cholesterol (mg \cdot dL $^{-1}$)		
Placebo	189 \pm 14	185 \pm 15
DHEA	179 \pm 12	175 \pm 12
Androstenedione	183 \pm 10	186 \pm 12
Triglycerides (mg \cdot dL $^{-1}$)		
Placebo	115 \pm 14	113 \pm 13
DHEA	122 \pm 13	117 \pm 12
Androstenedione	109 \pm 10	112 \pm 9
HDL-C (mg \cdot dL $^{-1}$)		
Placebo	44.9 \pm 3.2	45.7 \pm 4.0
DHEA	42.7 \pm 2.0	44.8 \pm 2.9
Androstenedione	40.5 \pm 4.1	41.0 \pm 4.5
ALT-transaminase (U \cdot L $^{-1}$)		
Placebo	23.0 \pm 2.8	25.3 \pm 2.3
DHEA	28.3 \pm 3.7	24.9 \pm 2.9
Androstenedione	26.8 \pm 4.2	27.3 \pm 3.3
PSA (ng \cdot mL $^{-1}$)		
Placebo	1.0 \pm 0.3	0.9 \pm 0.4
DHEA	1.2 \pm 0.5	1.3 \pm 0.7
Androstenedione	0.9 \pm 0.3	1.1 \pm 0.5

* Statistically significant difference from baseline.

** Statistically significant difference from P, $P < 0.05$.

Although several studies have reported that androgen levels may be related to insulin levels (18), there was not a significant relationship between fasting insulin and DHEA-S or androstenedione levels in this study. This confirms more recent studies also failing to demonstrate a relationship (6). The potential benefit of supplementation with these hormones may only be manifest in specific population subsets (characterized by low basal hormone levels and/or high-intensity training) using much longer supplementation periods. Researchers have, in fact, recently demonstrated the ability of DHEA supplementation to undergo biotransformation into potent androgens and estrogens in subjects with panhypopituitarism, characterized by the absence of adrenal and gonadal steroid secretion (26).

A key question to be addressed by this investigation was whether or not (replacement dose) supplementation with these androgenic hormones produces any adverse side effects. The results suggest that supplementation with 100 mg·d⁻¹ of either DHEA or androstenedione do not elicit any significant adverse side effects over a 3-month period. This includes changes in PSA, glucose, insulin, lipids, and liver function. In fact, it appears that even doubling serum androstenedione levels is not harmful (18). Moreover, bioavailability of oral steroid use is

only approximately 5% largely due to the effects of digestion, liver metabolism, and specific tissue enzyme activity. Like other fat-soluble nutrients, it is assumed that percent uptake also decreases with higher doses, thereby demonstrating another intrinsic safety mechanism.

In conclusion, despite several subtle physiologic "trends" in performance and hormone measures, any effect of supplementation in A or D was not statistically greater than that observed in P. Given the low bioavailability of these "weak" androgens coupled with internal feedback mechanisms (e.g., down-regulation), normal hormonal profiles, and potential placebo/seasonal affects, it is not surprising that significant differences were not observed in this relatively short-term study. Potential benefits would more likely be found with long-term supplementation and in special subset populations with very low initial basal levels and/or involved in high intensity training. Future studies should further delineate these populations and dosing criteria.

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