THE EFFECTS OF TREATMENT WITH PRASTERONE (DHEA) ON CIRCULATING HORMONES, BODY COMPOSITION AND MUSCLE STRENGTH IN MEN AND WOMEN

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Abstract. Nowadays many individuals are using “performance-enhancing” nutritional supplements. Many professional and nonprofessional athletes take the popular supplements, containing the hormone DHEA (Prasterone), to increase their testosterone levels and improve their performance. Even DHEA has been considered as a hormone with multiple effects, it is sold as a dietary supplement in many countries. Dehydroepiandrosterone (DHEA), a 19-carbon steroid, is situated along the steroid metabolic pathway. It is the most abundant circulating hormone in the body and can be converted to either androgens or estrogens. The physiological function of Dehydroepiandrosterone remains poorly understood and not enough analyzed. In this work we have analyzed the beneficial effects of a supplementation with Prasterone in order to alleviate its decrease in ageing and improve well-being. We have summarized the results of clinical trials including more than 1000 women and men.

Key Words: Dehydroepiandrosterone; Dehydroepiandrosterone sulfate; Prasterone; physical performance; muscle strength; sport; steroids; hormones; androgens; food supplements.

Abbreviation: Dehydroepiandrosterone (DHEA), Dehydroepiandrosterone sulphate (DS), insulin-like growth factor-I (IGF-I), muscle strength (MedX), growth hormone binding protein (GHBP), bone mineral density (BMD), testosterone (T), physical performance test (PPT), androstenedione (A), growth hormone binding protein (GHBP).

Introduction:

Human and some other primates are unique since their adrenals secrete large amounts of dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S), which are converted into androstenedione (4-dione) and then into potent androgens and estrogens in peripheral tissues, therefore providing autonomous intracrine control to target tissues that can adjust the formation and metabolism of active sex steroids according to local requirements. [25] Dehydroepiandrosterone (DHEA) is an endogenous steroid that is produced by the zona reticularis of the adrenal cortex.[19] It was first isolated in 1934 from urine by Butenandt and Dammenbaum. In 1944, Dehydroepiandrosterone sulfate (DHEA-S), DHEA’s sulfated metabolite, was isolated from the urine. In 1954, DHEA was isolated from the blood, and in 1959 the chemist E. Baulieu discovered that DHEA-S, which is the most abundant form of the hormone found in human plasma. In 1965, De Neve and Vermeulen reported an association between DHEA-S levels and aging; it was found that as people age, DHEA-S levels decline in a linear fashion [20][21]. This discovery led to numerous studies that focused on the link between DHEA and DHEA-S levels and the aging process.[18] DHEA is readily conjugated to its sulphate ester DHEAS, and they are designated as DHEA(S) here when used together.
Many hormonal changes may take place with aging but none is as marked as this. This “relative DHEA deficiency” resulted in DHEA being enthusiastically labeled by some as a fountain of youth or an antidote to aging that would prove to be the panacea they are seeking. Its use was also taken up enthusiastically by the athletic community and used as a prohormone in the belief or hope that it would be converted mainly to testosterone in the body. Dehydroepiandrosterone (DHEA) is a weak androgen also used to elevate testosterone levels, and is advertised as an anti-obesity and anti-aging supplement capable of improving libido, vitality and immunity levels. The age-related decline of Dehydroepiandrosterone and its sulfate ester levels is thought to be related to the development of age-associated usual modifications, such as neuromuscular function impairments. It is often claimed that individuals can enhance their muscular capacity by boosting Dehydroepiandrosterone levels through oral supplementation. Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS) represent the major androgens secreted by the adrenal gland. Various functions including metabolic, immune, and cognitive effects have been attributed to this steroid and are reviewed here. Since the levels of DHEA correlate with general good health, and aging is associated with a decline in the secretion of this steroid, a growing interest in replacement of DHEA in elderly people has developed. Administration of Dehydroepiandrosterone (DHEA), a precursor of sex steroid hormones, reduces total and visceral fat mass and elevates adipocytic adiponectin gene expression. Prasterone supplementation has been reported to increase testosterone and fat-free mass in nontrained populations.

Clinical studies, analyzing the effects of DHEA supplementation

Dehydroepiandrosterone, also known as androstenolone or prasterone is an important endogenous steroid hormone. Oral absorption of DHEA is excellent. The volume of distribution is 17.0-38.5 L for DHEA and 8.5-9.3 L for DHEAS. DHEA and DHEAS are converted into several active metabolites, including androstenedione, testosterone, estrone, estradiol, and estriol (Figure 1). The elimination half-life of DHEA is 15-38 minutes, whereas the half-life of DHEAS is 7-22 hours. Renal excretion accounts for DHEA metabolism.
for 51-73% of the elimination of DHEAS and its metabolites.[26,27,28,29] DHEA and DHEAS serve as the precursors of approximately 50% of androgens in men, 75% of active estrogens in premenopausal women, and 100% of active estrogens after menopause.[30]

Dehydroepiandrosterone (DHEA) therapy is controversial due to sensationalized reports of epidemiologic studies and the over-the-counter availability of DHEA. Human clinical trials have investigated the potential efficacy of DHEA therapy in multiple conditions with resultant inconsistencies in findings. DHEA is unique compared with other adrenal steroids because of the fluctuation in serum levels found from birth into advancing age. The lower endogenous levels of DHEA and DHEA sulfate found in advancing age have been correlated with a myriad of health conditions. Also, some studies suggest gender-specific actions of endogenous and exogenous DHEA.[23] We have summarized the results of some clinical trials included over 1000 men and women. In table 1 could be seen the design of these studies and the conclusions.

Physiological replacement dosages of oral DHEA in healthy people older than 40 years are in the range of 20-50 mg/day for men and 10-30 mg/day for women.[30] The researchers Tummala and Svec have described that incremental increases in serum DHEA and DHEAS levels appear to plateau at an oral DHEA dosage

### Table 1. Clinical studies about the beneficial effects of Prasterone (DHEA) supplementation.

<table>
<thead>
<tr>
<th>Design of the study and measurements</th>
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<td>Prospective, randomized, double-blind, and placebo-controlled phase III clinical trial has evaluated the effect of daily local intravaginal application of Prasterone for 12 weeks on the domains of sexual dysfunction, namely, desire/interest, arousal, orgasm, and pain at sexual activity, in 216 postmenopausal women with moderate to severe symptoms of vaginal atrophy.</td>
<td>A time- and dose-dependent improvement of the four domains of sexual function was observed. At the 12-week time interval, the 1.0% DHEA dose led, compared with placebo, to 49% ($P = 0.0061$) and 23% ($P = 0.0257$) improvements of the desire domains in the Menopause Specific Quality of Life and Abbreviated Sex Function questionnaires, respectively. Compared with placebo, the Abbreviated Sex Function arousal/sensation domain was improved by 68% ($P = 0.006$), the arousal/lubrication domain by 39% ($P = 0.0014$), orgasm by 75% ($P = 0.047$), and dryness during intercourse by 57% ($P = 0.0001$). By a local action in the vagina, DHEA applied daily at doses at which serum steroids remain well within normal postmenopausal values exerts relatively potent beneficial effects on all four aspects of sexual dysfunction.</td>
<td>[17]</td>
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<td>Healthy non-obese age-advanced (50-65 years of age) men ($n = 9$) and women ($n = 10$) were randomized into a double-blind placebo-controlled cross-over trial. Sixteen subjects completed the one-year study of six months of placebo and six months of 100 mg oral DHEA daily. Fasting early morning blood samples were obtained. Serum DHEA, DS, sex steroids, IGF-I, IGFBP-1, IGFBP-3, growth hormone binding protein (GHBP) levels and lipid profiles as well as body composition (by DEXA) and muscle strength (by MedX testing) were measured at baseline and after each treatment.</td>
<td>A daily oral 100 mg dose of DHEA for 6 months resulted in elevation of circulating DHEA and DS concentrations and the DS/cortisol ratio. Biotransformation to potent androgens near and slightly above the range of their younger counterparts occurred in women with no detectable change in men. Given this hormonal milieu, an increase in serum IGF-1 levels was observed in both genders but dimorphic responses were evident in fat body mass and muscle strength in favour of men. These differences in response to DHEA administration may reflect a gender specific response to DHEA and/or the presence of confounding factor(s) in women such as estrogen replacement therapy.</td>
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<td>Double-blind, randomized, placebo-controlled trial. Hormone levels, bone mineral density (BMD), bone turnover markers, body composition, upper and lower extremity strength, physical performance.</td>
<td>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. 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.</td>
<td>[2]</td>
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It was performed on 280 healthy ambulatory and independent men and women aged 60 to 80 years. The study design was a double-blind placebo-controlled trial. Dehydroepiandrosterone sulfate serum concentration, handgrip strength, isometric and isokinetic knee muscle strength, and thigh (fat and muscle) cross-sectional area were analyzed before and just after 12 months of placebo or Dehydroepiandrosterone treatment. The results give evidence that Dehydroepiandrosterone administration restores Dehydroepiandrosterone sulfate serum concentrations to the normal range for young adults (aged 20-50 years). However, no positive effect inherent to Dehydroepiandrosterone treatment was observed either on muscle strength or in muscle and fat cross-sectional areas. | [3] |

This manuscript examines the relationships of total testosterone (T), bioavailable T, DHEA, and DHEA sulfate (DHEAS) to measures of physical performance in a large, population-based, random sample of men. In the most recent wave of the Massachusetts Male Aging Study, measures of strength and physical performance [seven-item physical performance test (PPT), timed chair stand test, and grip strength] were made in 684 men, aged 55–85 years. Complete hormone data were also obtained. Initial graphical exploration of performance outcomes as a function of hormone levels showed linear increases in physical performance up to certain threshold hormone concentrations, beyond which the associations were diminished. All hormones exhibited significant age-adjusted positive association with PPT score below, but not necessarily above, the thresholds. DHEA was positively associated with chair stand score below, but was not above the threshold. None of the hormones studied was significantly associated with grip strength. Up to certain critical concentrations, elevated levels of TT, total T, bioavailable T, DHEA, and DHEA sulfate are associated with increased physical performance, as indicated by the PPT. However, levels beyond those critical concentrations, as might be achieved through exogenous supplementation, do not appear to confer any additional benefit. In general, hormone concentrations do not appear to be meaningfully associated with grip strength or chair stand scores. | [24] |
A randomized, placebo-controlled, double-blind design was used to study 40 healthy, trained (>1 year weight training) male subjects (mean +/- SD: age 48.1 +/- 3.9 years; 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 weeks. All testing, including venous blood samples, body composition, and performance, was conducted at three time points: presupplementation (1 d), at 6 week, and postsupplementation (12 week).

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). The results of this study suggest that supplementation with 100 mg x 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.

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<td>[9]</td>
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**Table 2. Food additives containing Prasterone (Dehydroepiandrosterone).**

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<tr>
<td>1.</td>
<td>DHEA (Blade Nutrition Test Booster), 180 caps.</td>
<td>25 mg.</td>
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<td>2.</td>
<td>DHEA (MRM), 90 caps.</td>
<td>25 mg.</td>
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<td>3.</td>
<td>DHEA (Natrol), 300 tabl.</td>
<td>25 mg.</td>
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<td>4.</td>
<td>DHEA Fast Dissolve (Natrol), 30 tabl.</td>
<td>25 mg.</td>
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<tr>
<td>5.</td>
<td>DHEA MAX (Nutraceutics), 60 tabl.</td>
<td>25 mg.</td>
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<tr>
<td>6.</td>
<td>DHEA (Ultimate Nutrition), 100 caps.</td>
<td>25 mg.</td>
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<tr>
<td>7.</td>
<td>DHEA (Healthy ‘N Fit), 100 caps.</td>
<td>50 mg.</td>
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<tr>
<td>8.</td>
<td>DHEA (MRM), 60 caps.</td>
<td>50 mg.</td>
</tr>
<tr>
<td>9.</td>
<td>DHEA (Natrol), 60 tabl.</td>
<td>50 mg.</td>
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<tr>
<td>10.</td>
<td>DHEA (S.A.N.), 90 caps.</td>
<td>50 mg.</td>
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<tr>
<td>11.</td>
<td>DHEA (Ultimate Nutrition), 100 caps.</td>
<td>50 mg.</td>
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<tr>
<td>12.</td>
<td>DHEA (PharmaFreak), 28 caps.</td>
<td>60 mg.</td>
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<tr>
<td>13.</td>
<td>DHEA (Maximum Nutrients), 60 caps.</td>
<td>100 mg.</td>
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of 300 mg/day and inferred that doses greater than this have little additional therapeutic value. [31] Sometimes professional and nonprofessional athletes take aromatase inhibitors when they take Prasterone for increasing testosterone levels. These sportsmen take also aromatase inhibitors when they make an anabolic steroidal cycle. The function of the aromatase inhibitors is to prevent gynecomastia. Aromatase inhibitors are classified as either steroidal or nonsteroidal, or as first, second or third generation. Steroidal inhibitors such as formestane and exemestane inhibit aromatase activity by mimicking the substrate androstenedione. Nonsteroidal enzyme inhibitors such as anastrozole and letrozole inhibit enzyme activity by binding with the heme iron of the enzyme. First-generation aromatase inhibitors such as aminoglutethimide are relatively weak and nonspecific; they can also block other steroidogenic enzymes necessitating adrenal steroid supplementation.[32] Although aromatase inhibition by anastrozole and letrozole is reported to be close to 100%, administration of these inhibitors to men will not suppress plasma estradiol levels completely. In men third-generation aromatase inhibitors will decrease the mean plasma estradiol/testosterone ratio by 77%.[33,34] It is important to note that the use of the aromatase inhibitors for sport purpose is over the counter, it is not supported by the today’s medicine.

Legality

DHEA is legal to sell in the United States as a dietary supplement. DHEA is specifically exempted from the Anabolic Steroid Control Act of 1990 and 2004.[10] It is banned from use in athletic competition. In Canada, DHEA is a Controlled Drug listed under Section 23 of Schedule IV of the Controlled Drugs and Substances Act and as such is available by prescription only.[11] In Australia it is a controlled drug. Australian customs classify DHEA as an “anabolic steroid[s] or precursor[s]” and, as such, it is only possible to carry DHEA into the country through customs if one possesses an import permit which may be obtained if one has a valid prescription for the hormone.[12] DHEA is included in the “List of drugs currently controlled under the misuse of drugs legislation“ in UK. DHEA is a Class C Controlled Drug drug under the Misuse of Drugs Act. In Bulgaria Prasterone (DHEA) is legal to sell as a dietary supplement. DHEA is a prohibited substance under the World Anti-Doping Code of the World Anti-Doping Agency. [13] In January 2011, NBA player O.J. Mayo was given a 10-game suspension after testing positive for DHEA. Mayo termed his use of DHEA as “an honest mistake,” saying the DHEA was in an over-the-counter supplement and that he was unaware the supplement was banned by the NBA.[14] 2008 Olympic 400 meter champion Lashawn Merritt has also tested positive for DHEA and was banned from the sport for 21 months.[15]

Conclusion

Undoubtedly the intake of Prasterone gives benefits but to put a definitive evaluation are needed more specific studies. The researches show that Prasterone (DHEA) may have a role in hormone replacement therapy in patients with low endogenous DHEA and DHEAS. Many clinical trials suggest that doses of 30–50mg of oral DHEA may produce physiologic androgen levels. These studies report a dose-dependent effect and lack of accumulation of serum androgen levels. These studies also reveal a gender-specific response to DHEA therapy such that testosterone levels are increased in women but not in men. The trials show that supplementation with Prasterone restores Dehydroepiandrosterone sulfate serum concentrations to the normal range for young adults (aged 20-50 years). Although the DHEA supplementation is well widely practiced by athletes, the trials have consistently shown that DHEA supplementation does not increase statistically significant testosterone levels, enhance muscle mass or muscle strength. The DHEA supplementation gives improvement in short physical performances. The conditions in which Dehydroepiandrosterone could preserve or improve muscle strength and morphological features still need to be determined and more clinical studies are needed.

Acknowledgement

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References:


11. Health Canada, DHEA listing in the Ingredient Database

12. Therapeutic Goods Administration, Personal Importation Scheme

13. World Anti-Doping Agency


23. Deborah R. The Use of Dehydroepiandrosterone Therapy in Clinical Practice, Treatments in Endocrinology, April 2005, Volume 4, Issue 2, pp 95-114


25. Labrie F, Bélanger A, Van LT et al. DHEA and the intracrine formation of androgens and es-
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