Tides of Life
an international women's holistic health resource group

DHEA: Dehydroepiandrosterone

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Introduction

Dehydroepiandrosterone (DHEA) and its active metabolite, DHEA sulfate (DHEAS), are endogenous hormones synthesized and excreted primarily by the zona reticularis of the adrenal cortex in response to adrenocorticotropic hormone. The exact mechanism of action and clinical role, if any, of DHEA and DHEAS remain unclear. Epidemiological data indicate an inverse relationship between serum DHEA and DHEAS levels and the frequency of cancer, cardiovascular disease (in men only), Alzheimer's disease and other age-related disorders, immune function, and progression of HIV infection.[1] Animal (primarily rodent) studies have suggested many beneficial effects of DHEA, including improved immune function and memory and prevention of atherosclerosis, cancer, diabetes, and obesity. Many of the benefits seen in animal studies have yet to be shown in humans.[1-3]

Uses

Clinically substantiated (yet still controversial) uses of DHEA include replacement therapy in patients with low serum DHEA levels secondary to chronic disease, adrenal exhaustion, or corticosteroid therapy; treating systemic lupus erythematosus (SLE), improving bone density in postmenopausal women; improving symptoms of severe depression; improving depressed mood and fatigue in patients with HIV infection; and increasing the rate of reepithelialization in patients undergoing autologous skin grafting for burns.[1,4-8] Other possible uses (with some supporting clinical studies) include enhancing the immune response and sense of well-being in the elderly, decreasing certain cardiovascular risk factors, and treating male erectile dysfunction.[4,8-12] Use of DHEA to slow or reverse the aging process, improve cognitive function, promote weight loss, increase lean muscle mass, or slow the progression of Parkinson's disease and Alzheimer's disease is clinically unsubstantiated.[3,4,9]

Pharmacology

In women, the synthesis of DHEA and DHEAS occurs almost exclusively in the adrenal cortex, whereas in men the testes secrete approximately 5% of DHEAS and 10-25% of DHEA.[3] Minute amounts are synthesized de novo in the brain.[3,13] In young adults the adrenal cortex secretes approximately 4 mg of DHEA and 25 mg of DHEAS per day.[2] During gestation, large amounts of DHEA and DHEAS are secreted by the fetal adrenal glands. At birth, output drops to negligible amounts in both sexes and remains that way until five to seven years of age. At the onset of adrenarche, the adrenal glands gradually resume DHEA and DHEAS production, which accelerates through puberty. DHEA and DHEAS output is maximal between the ages of 20 and 30 years and then starts a decline of approximately 2% per year, leaving a residual of 10-20% of the peak production by the eighth or ninth decade of life.[2,14-16]

DHEA and DHEAS are interconvertible by sulfohydrolases in peripheral and adrenal tissues.[3] Some 64-74% of the DHEAS produced each day is converted to DHEA, but only 13% of the DHEA produced is metabolized to DHEAS.[2,17,18] In humans, the brain-to-plasma ratios for DHEA and DHEAS are 4-6.5 and 8.5, respectively, indicating a neuroendocrine role for these hormones.[2,19,20]

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.[2,16] There appears to be a sex-specific response to DHEA replacement therapy in humans. In postmenopausal women (ages 50-65), supraphysiological doses of 100 mg of DHEA per day have predominantly androgenic effects, increasing testosterone levels approximately 300% over baseline levels.[21] In older men (mean ± S.D. age, 58.8 ± 5.1 years), 100 mg/day did not affect testosterone or dihydrotestosterone levels, but 17 beta-estradiol and estrone levels were increased over baseline by 37% and 225%, respectively ($p < 0.0001$ for both).[22] It has been hypothesized that the increase in serum estrogens may provide a mechanism for beneficial cardiovascular effects in men; however, clinical studies addressing the possible cardioprotective effects of DHEA have been inconclusive.

Several mechanisms of action of DHEA and DHEAS other than their role as precursors of the sex hormones have been proposed. In the central nervous system, both DHEA and DHEAS appear to affect neurotransmitter receptors. In rodents, DHEAS binds to the γ-aminobutyric acid (GABA)/benzodiazepine-receptor complex (GABA-RC) and acts as a negative noncompetitive modulator of GABA-RC. DHEA, on the other hand, appears to have GABA-agonist effects on the GABA-RC.

DHEA selectively enhances the neuronal response to N-methyl- D-aspartate.[3,4] Also, DHEA and DHEAS appear to have neurotrophic effects, increasing the number of neurofilament-positive neurons and regulating the motility and growth of corticothalamic projections in cultured mouse embryo brain cells.[23-25]

Supraphysiological oral doses of DHEA (100-300 mg/day) in humans have been found to inhibit the synthesis of thromboxane A 2 in activated platelets, reduce plasma plasminogen activator inhibitor type 1 and tissue plasminogen activator antigen, increase serum levels of insulin-like growth factor 1 (IGF-1), and increase cyclic guanosine monophosphate and nitric oxide synthesis (either directly or via increased levels of IGF-1).[4,26-28] These effects suggest that DHEA may be beneficial in improving circulation in the microvasculature and regulating some of the risk factors of cardiovascular disease, such as platelet aggregation and ischemia. Clinical studies in this area have been equivocal, with a majority showing an inverse relationship between DHEA or DHEAS levels and cardiovascular morbidity and mortality in men but not in women.[29] However, a recently published five-year epidemiologic cohort study found no statistically significant correlation between serum DHEA or DHEAS levels and the development of atherosclerosis in men or women.[30]

DHEA may play a positive role in modulation of the immune response. Clinical studies in elderly persons have demonstrated that oral DHEA doses of 50 mg/day increase IGF-1 levels ($p < 0.01$) and cause functional activation of T cells (increases in CD8+ and CD56+ cells [natural killer cells] and enhanced cytotoxic activity).[4,9,31,32] Serum levels of interleukin- 6 (a proinflammatory cytokine involved in the pathogenesis of osteoporosis, rheumatoid arthritis, atherosclerosis, Alzheimer's disease, Parkinson's disease, and beta-cell malignancies) increase significantly with age and are inversely correlated with serum DHEA and DHEAS levels ($p < 0.001$). In addition, DHEA, DHEAS, and androstenedione inhibit the production of interleukin-6 by peripheral blood mononuclear cells in a concentration-dependent manner ($p < 0.001$).[33]

Pharmacokinetics

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 51-73% of the elimination of DHEAS and its metabolites.[2,4,34-36]

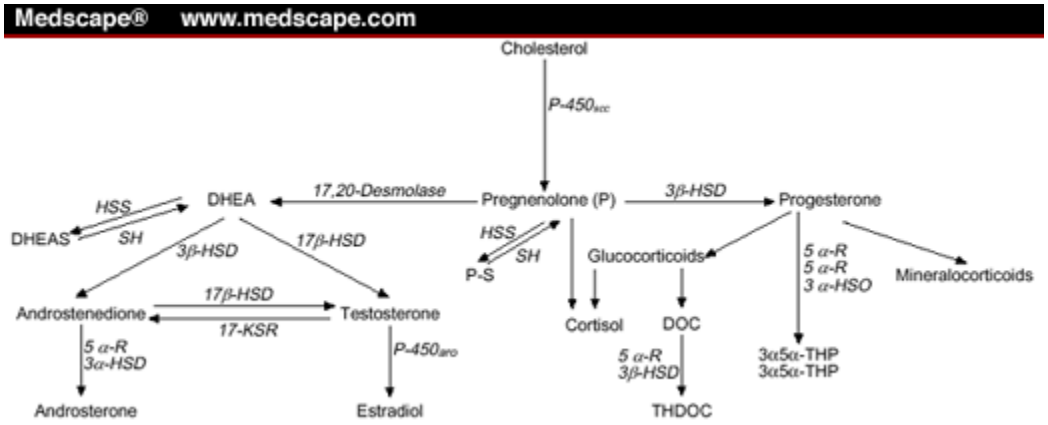

Figure 1. Synthesis of dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and other steroids. The listing of more than one enzyme indicates a multistep process. aro = aromatase, DOC = deoxycorticosterone, HSD = hydrosteroid dehydrogenase, HSO = hydrosteroid oxidoreductase, HSS = hydrosteroid sulfatase, KSR = ketosteroid reductase, R = reductase, scc = side-chain cleavage, SH = sulfohydrolase, P-S = pregnenolone sulfate, THDOC = tetrahydrodeoxycorticosterone, THP = tetrahydroprogesterone. Reprinted from reference 3, with permission.

Clinical Studies

To date, clinical studies of DHEA in patients with specific diseases have yielded generally inconclusive results. Most of the studies were open label or had very small samples. Most of the studies discussed below were randomized, double-blind, placebo-controlled trials in which the oral dosage was ≤300 mg/day. Tummala and Svec [37] demonstrated that incremental increases in serum DHEA and DHEAS levels appear to plateau at an oral DHEA dosage of 300 mg/day and inferred that doses greater than this have little additional therapeutic value.

Postmenopausal Bone Density

In a randomized, double-blind, placebo-controlled study by Baulieu et al.,[10] 280 healthy men and women ages 60-79 years were given DHEA 50 mg/day orally for 12 months. Increases in bone mineral density ($p < 0.05$) and decreases in biochemical markers of bone turnover ($p < 0.01$ for serum C-terminal peptide and $p < 0.05$ for serum bone alkaline phosphatase) were observed at 12 months in women older than 70 but not in any other subgroup.

Systemic Lupus Erythematosus

DHEA supplementation has shown promise for the treatment of SLE. In a randomized, double-blind trial,[38,39 28] women with SLE received DHEA 200 mg/day for three months. In the DHEA group, the SLE Disease Activity Index score and both the patients' and the physicians' overall assessments of disease activity decreased, whereas small increases were seen in the placebo group. However, significance was achieved only for the visual-analogue- scale component of the index (p = 0.022). Lupus flares occurred less frequently in the treatment group than in the placebo group (three versus eight flares, p = 0.053), and a nonsignificant decrease in prednisone requirements was noted in the treatment group (from a mean ± S.D. daily dose of 12.4 ± 3.2 mg to 9.1 ± 2.3 mg, compared with an increase from 5.3 ± 1.37 mg to 7.3 ± 2.9 mg in the placebo group). Serum titers of antibodies to double-stranded DNA and levels of complement components C3 and C4 did not change significantly between the groups.

Well-being and Cognition

In a randomized, placebo-controlled, crossover trial, 30 patients ages 40-70 years were given 50 mg of DHEA orally daily.9 Within two weeks, this dose restored serum DHEA levels in both men and women to those found in young adults. With DHEA treatment, 67% of the men and 84% of the women perceived an increase in physical and psychological well-being. However, the study has been criticized for its use of an open-ended questionnaire for self-assessment of well-being.[40]

At present, there are no rigorous data to support an improvement in memory or other aspects of cognitive function after DHEA replacement therapy. Low endogenous levels of DHEA and DHEAS do not appear to be associated with an increased risk of dementia.[41]

Depression

The possible relationship between depression and serum DHEA and DHEAS levels is intriguing; however, more research is needed. Some authors have suggested that abnormal diurnal variations in serum DHEA and DHEAS levels, as well as abnormally high cortisol- to-DHEA ratios, may be causative factors in depression in adults and depression with comorbid panic or phobic disorders in adolescents.[3,42-44]

In a randomized, double-blind trial by Wolkowitz et al.,[45] 22 patients who had major depression (a Hamilton Rating Scale for Depression [HAM-D] score of 16 or greater) and who were either medication free or stabilized on antidepressant regimens received DHEA (30 mg/day for weeks 1 and 2, 60 mg/day for weeks 3 and 4, and 90 mg/day for weeks 5 and 6) or placebo. At the end of the six weeks, the mean decrease in the HAM-D score was 30.5% in the treatment group and 5.3% in the placebo group ($p < 0.04$). Five of 11 patients in the treatment group were considered responders (at least a 50% decrease in HAM-D score), compared with none of the 11 patients in the placebo group.

Effects in HIV-Infected Patients

In a recent open-label trial evaluating the effect of DHEA on depressed mood and fatigue, 45 HIV-positive patients (39 men and 6 women) received oral DHEA doses of 200-500 mg/day for eight weeks.[11] Of the 32 patients who completed the trial, 23 (72%) had an improvement in mood and 26 (81%) had a reduction in fatigue. There was a significant increase in body cell mass and libido but no effect on CD4+ lymphocyte counts or testosterone levels in men. The positive effects on mood, fatigue, and body cell mass continued for an additional four weeks in a subsequent double-blind phase of the study. Christeff et al.[46] have noted an inverse relationship between serum DHEA and DHEAS levels and the immunologic deterioration in HIV patients, which suggests a role for DHEA and other androgens in the normal functioning of the immune system.

Effects on Physical Variables

A randomized, double-blind, placebo-controlled crossover trial by Morales et al.[21] looked at the effects of oral DHEA 100 mg/day in 16 subjects 50-65 years of age. Baseline levels of serum DHEA, DHEAS, androstenedione, testosterone, and dihydrotestosterone were at or below the low end of the range for young adults. In both sexes, DHEA 100 mg/day restored serum DHEAS to levels at or slightly above the upper limit of the young-adult range. In women, androstenedione, testosterone, and dihydrotestosterone were increased to three to five times baseline levels ($p < 0.001$ for each hormone), or to levels above the sex-specific ranges for young adults, whereas in men only androstenedione was significantly increased above baseline ($p < 0.05$). Serum IGF-1 levels increased by a mean ± S.D. of 16% ± 6% ($p = 0.04$) in men and 31% ± 12% in women ($p = 0.02$). In men but not women, fat body mass decreased by 6.1% ± 2.6% ($p = 0.02$), and there were

increases in knee muscle strength (15.0% ± 3.3%, p = 0.02) and lumbar back strength (13.9% ± 5.4%, p = 0.01). No changes in basal metabolic rate, bone mineral density, urinary pyridinoline cross-links, fasting insulin, glucose, cortisol, or lipids were observed in either sex.

Dosage

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.[2,4,8] These dosages are usually adequate to increase serum DH-EAS to the levels found in adults 20-30 years of age and to bestow the reported benefits of a heightened sense of well-being in both sexes, increased bone mineral density in postmenopausal women, and amelioration of erectile dysfunction in men. Higher dosages may be necessary for increasing suppressed DHEA and DHEAS levels secondary to chronic disease, adrenal exhaustion, and corticosteroid therapy. Replacement doses of DHEA are usually taken once daily in the morning.

It is imperative that serum DHEAS concentration be measured before DHEA replacement therapy is started. The serum DHEAS level should be checked at least annually to ensure that it is in the normal range. To minimize adverse effects and maximize benefits, it is suggested that replacement dosages in healthy adults be adjusted to maintain serum levels of DHEAS in the second or third quartile of sex-specific, young-adult ranges.

Pharmacologic dosages of 200 mg/day have been successfully used in patients with SLE. Dosages of 200-500 mg/day have been used in HIV-positive patients with depressed mood and fatigue. It is not known what effect long-term physiological or supraphysiological doses of DHEA may have on suppression of the zona reticularis of the adrenal cortex; however, there does not appear to be feedback inhibition of DHEA or DHEAS secretion by the hypothalamic-pituitary axis.[2]

Adverse Effects

Increased facial sebum production, acneiform dermatitis, and mild hirsutism have been reported in women taking DHEA in physiological or supraphysiological dosages (25-200 mg/ day).[4,21,38] Hepatitis was reported in a postmenopausal woman with preexisting high titers of antinuclear antibodies who received a single oral dose of 150 mg of DHEA; causality could not be established.[4,47] A supraphysiological dosage of DHEA (100 mg/day) was shown to increase androstenedione,

testosterone, and dihydrotestosterone levels threefold to fivefold in postmenopausal women.[21] The long-term effects of these increases in androgen levels in women are not known. A nested case-control study by Dorgan et al.[48] found that postmenopausal women (not taking DHEA or hormone replacement therapy) whose levels of endogenous DHEAS were in the highest quartile had a significantly higher risk of breast cancer (risk ratio, 2.8 [95% confidence interval 1.1-7.4]) than women whose levels of endogenous DHEAS were in the lowest quartile.

Drug Interactions

Calcium-channel blockers and metformin increase levels of endogenous DHEAS, whereas corticosteroids and insulin significantly decrease them.[3] Supraphysiological dosages of DHEA can increase serum triazolam levels because of an inhibition of metabolism.[8] Theoretically, aromatase inhibitors, such as chrysin (5.7-dihydroxyflavone), an extract from the plant Passiflora coerula, can increase levels of androgens, including DHEA and DHEAS, in both men and women. Kroboth et al.[3] published an excellent review of the effects of disease, diet, exercise, and medications on endogenous DHEA and DHEAS levels.

Contraindications

DHEA supplementation is contraindicated in patients with a history of sex hormone-responsive cancers, such as breast, ovarian, endometrial, and prostate cancer. Women with a family history of postmenopausal, estrogen- sensitive cancers and men with benign prostatic hypertrophy or a family history of prostate cancer should carefully weigh the risks and benefits of DHEA replacement therapy with their physician. If replacement therapy is deemed necessary, close monitoring of serum DHEAS and its androgenic and estrogenic metabolites should be performed frequently. DHEA supplementation should be avoided during pregnancy and lactation.

Conclusion

Clinical data suggest that DHEA may have a role in hormone replacement therapy in patients with low endogenous DHEA and DHEAS levels due to chronic diseases, adrenal exhaustion, corticosteroid therapy, and advancing age. However, as a potent steroid precursor, DHEA can significantly increase androgen levels in women and may enhance the

progression of estrogen and testosterone-sensitive cancers. Supplementation with DHEA should never be undertaken without direct medical supervision. The long-term effects of DHEA supplementation are unknown.

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