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DHEA Therapy: Hope or Hype?

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DEHYDROEPIANDROSTERONE (DHEA), FIRST DISCOVERED IN 1934, IS a dietary supplement widely available in pharmacies, health food stores, and via the internet. DHEA is often promoted as a panacea for aging.

Its anti-aging properties are purported to prevent cancer, heart disease, diabetes, and Alzheimer's disease in the elderly, while increasing muscle mass and strength, libido, and mood, and slowing down the aging process. Other perceived benefits include decreased insulin resistance,[1] weight loss,[2] improved immunomodulatory effects, and possibly beneficial skeletal effects.

Physiology of DHEA and DHEA-S

Circulating DHEA in both men and women is primarily produced by the zona reticularis of the adrenal cortex. In women, 90% of DHEA is adrenal in origin and 10% is from the ovaries. Almost all the DHEA is converted to the sulfated pro-hormone, DHEA-S, in the adrenal gland and the liver, both of which contain sulfotransferase. DHEA-S has a longer half-life and hence degrades more slowly than DHEA, does not bind to protein or albumin, and circulates in the blood in its free form.

DHEA and DHEA-S are converted into active androgens and estrogens in peripheral tissues (hair follicles, prostate, external genitalia, and adipose tissue). DHEA-S is converted in the genital skin in both men and women, to Δ^5-androstenediol, testosterone, androstenedione, and dihydrotestosterone. The conversion is far greater in male genital skin.[3]

DHEA-S may be directly excreted in the urine, or its sulfate group may be hydrolyzed to yield free DHEA, which is then metabolized to androstenedione. DHEA-S can also undergo hydroxylation or reversible 17-β reduction. DHEA-S and its metabolites are cleared more slowly from the serum by the kidney than its

non-sulfated analogues. A fraction of DHEA and DHEA-S and their metabolites are excreted in the feces via the biliary tract.[4]

DHEA levels are low in childhood, increase just prior to and during puberty, peak during the reproductive years, and thereafter gradually decline with age, independent of the cortisol secretion.

In women, DHEA levels peak at age 25, with levels declining steadily after age 30 by about 5% each year. DHEA levels are on average 10-30% less in young women than men and this gender difference declines with age. By age 50 years, women have approximately 50% of their peak DHEA levels,[5] becoming almost undetectable by age 70. The fall in secretion of DHEA and DHEA-S by the adrenal gland parallels the decline in formation of androgen and estrogen by steroidogenic enzymes in specific target peripheral tissues.[6]

In addition to androgen and estrogen receptors, possible sites of action of DHEA and DHEA-S include the GABA-A/benzodiazepine receptor complex (acts as an antagonist); N-methyl aspartate excitatory amino acid receptors (potentiate effects of glutamate); CAR, a novel nuclear hormone-type receptor; a cell surface receptor in vascular endothelial cells that is functionally coupled to G-proteins; and a sigma-1 receptor that binds neurosteroids and has antidepressant-like effects.[7]

The DHEA products currently marketed are synthesized in the laboratory by conversion of dioscorea from wild yam, thereby maintaining its classification as a dietary supplement. Dioscorea, a precursor of DHEA production, is also available over the counter, but is not readily bio-converted to DHEA in vivo in humans. DHEA in supplements can be converted to testosterone and estrogen in the body.

Mechanism of Action

The mode of action of DHEA is not very well understood; it perhaps acts as an androgen, estrogen, an antiglucocortiocoid, or all of these. Compared to other hormones, its circulating levels are quite high and it very likely serves as a pro-hormone or reservoir.

Clinical Trials

Although DHEA therapy has been shown to be beneficial in certain medical conditions in several studies, the existing data are confusing, contradicting, and inconsistent. This is likely due to the wide variation of formulations, doses, and duration of therapies studied, and the different standards used to assess their efficacy. In addition, animals exhibit dramatic effects with DHEA supplementation because they have little to no circulating DHEA; however, animal data cannot and should not be extrapolated to humans.

Adrenal insufficiency. DHEA and DHEA-S production is reduced in patients with primary or secondary adrenal insufficiency, with consequent decreases in circulating androgen levels, particularly in women. DHEA supplementation appears efficacious in women with adrenal insufficiency.[8-10]

In a study of 24 women with primary adrenal insufficiency receiving adequate glucocorticoid and mineralocorticoid replacement, administration of DHEA 50 mg daily for four months resulted in increased serum androgen concentrations and improved general and psychological well-being and sexuality when compared with placebo.[11] In the same study, DHEA replacement had no effect on carbohydrate metabolism, body composition, or exercise capability. Androgenic side effects in most women were mild and transient.

Another study of 50 mg DHEA daily in men and women with adrenal insufficiency reported improved self-esteem and overall sense of well-being with less fatigue and improved mood scores.[12]

Higher doses of 200 mg daily do not appear to provide additional clinical benefit. Daily doses less than 50 mg are not effective in primary adrenal insufficiency, but appear to be beneficial in secondary adrenal insufficiency.[7]

Systemic lupus erythematosus. Women with systemic lupus erythematosus (SLE) have low serum levels

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of DHEA and DHEA-S even prior to replacement with glucocorticoids.[13] In patients with SLE, DHEA replacement appears to have a beneficial effect on the overall health-related quality of life,[14] bone density,[15] cognition,[16] disease activity,[17,18] and prednisone dosage.[19]

Depression. Two small series showed some improvement in depression scores in individuals who received DHEA. In the first, 46 patients received 90 mg/d for three weeks followed by 450 mg/d vs. placebo for a further three weeks;[20] the other case series included 22 patients with major depression who were given up to 90 mg DHEA daily for six weeks.[21] Larger trials with longer duration of therapy are required to corroborate these findings.

Fibromyalgia. Clinical observations reveal abnormal responses of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis with adrenal hyporesponsiveness and low DHEA/DHEA-S levels in individuals with fibromyalgia. Forty-seven postmenopausal women with fibromyalgia received 50 mg/d of DHEA for three months to restore normal serum levels. No changes were demonstrated in well-being, pain, fatigue, cognition, functional impairment, depression, or anxiety compared to the placebo group, but subjects did report androgenic side effects from therapy.[22]

Hypopituitarism. Patients with panhypopituitarism and growth hormone (GH) deficiency are profoundly androgen-deficient and have an impaired quality of life. Administration of DHEA 50 mg/d in addition to GH therapy for six months to 51 individuals with hypopituitarism resulted in modest improvement in psychological well-being, more so in female than male patients, when compared to the placebo group.[23]

Cardiovascular disease. DHEA has been shown to act as a survival factor for vascular endothelial cells and may have beneficial effects on the vascular system. Observational studies of DHEA levels in cardiovascular disease (CVD) in humans are inconsistent; high levels may be associated with lowered CVD risk in men, but may exert the opposite effect in women.

Several epidemiologic studies have shown that there is an inverse correlation between plasma concentrations of DHEA/DHEA-S and CVD mortality in both young and older males and females.[24-28] More recent evidence from prospective studies has also shown higher CVD mortality in males with lower DHEA-S levels.[29,30]

DHEA in physiologic doses of 25-50 mg/d or a slightly higher dose of 100 mg/d resulted in a significant decrease in apolipoprotein A1 and HDL-cholesterol in women, but not in men, possibly a result of increased circulating androgen levels in women but not men.[31]

Administration of DHEA to women results in a slight decrease in HDL-cholesterol, but its effect on CVD risk is unknown.[32,33] Long-term studies are needed to elucidate the role of DHEA in altering the risk of CVD in menopausal women.

Insulin resistance. Some clinical data support the contention that DHEA supplementation improves lean body mass and glucose tolerance. In 112 elderly men and women with relative DHEA deficiency, two years of DHEA replacement did not improve insulin secretion or action, nor did it improve the pattern of postprandial glucose metabolism.[34]

DHEA use in postmenopausal women. In postmenopausal women, evidence to support the use of DHEA to improve libido and well-being is sparse and inconclusive, with a dearth of safety data.

DHEA in postmenopausal women may be useful in the prevention and treatment of osteoporosis and osteopenia. In women 60-70 years of age, DHEA administered percutaneously (to avoid hepatic first-pass effect) for 12 months resulted in an increase in bone mineral density (BMD) at the hip and lumbar spine, with a favorable impact on urinary and serum bone markers.[35]

In a recent review of randomized controlled trials of DHEA and DHEA-S use for decreased libido and well-being in postmenopausal women, the authors concluded that data are limited by inadequate sample size and short duration of treatment.[36]

Some CAM clinicians recommend a daily oral intake of 5-20 mg of DHEA to postmenopausal women with a loss of vitality and/or low libido. It is believed that at this level DHEA is converted to more potent androgens, including testosterone. At pharmacologic levels of 1,600 mg daily, DHEA will be converted to estrone and estradiol. Few adverse effects have been reported at lower doses, although in some women, androgenic side effects (e.g., facial hair growth and acne) can occur with low doses. Clinical trials are needed to support these efficacy and safety observations.

Oral DHEA given to 60 symptomatic perimenopausal women in the dose of 50 mg daily for six months resulted in little improvement of perimenopausal symptoms or well-being when compared to placebo.[37] Improvement of behavioral symptoms in postmenopausal women is believed to be mediated by neuroendocrine effects of DHEA-S or its active metabolites on pituitary beta-endorphin secretion.[38] DHEA supplementation in early and late postmenopausal women is also associated with an increase in GH and IGF-1 levels.[39] Increases in hip BMD was noted in a small group (n = 14) of women aged 60-70 years who used topical 10% DHEA cream,[35] but the results could not be replicated in a six-month trial of 100 mg DHEA daily.[40]

Topical application of DHEA for two weeks to postmenopausal women resulted in a significant increase in serum testosterone levels with little change in estradiol and estrone levels.[41] Interestingly, oral administration of DHEA to postmenopausal women was associated with an increase in estradiol and estrone levels in addition to an increase in testosterone levels, likely due to the hepatic first pass effect.[42]

Anti-aging therapy. In a two-year randomized placebo-controlled double-blind trial of individuals age 60 years of age and older with low androgen levels, neither DHEA nor testosterone replacement was effective in treating age-related changes. Likewise, there was no effect of DHEA on either muscle size or strength.[43]

DHEA was reported to improve insulin sensitivity in one small trail,[44] but a larger, long-term study did not report the same effect.[43]

Cognition and dementia. The Baltimore Longitudinal Study of Aging did not detect any relationship between cognitive status and DHEA levels. Existing data do not support any improvement in memory or other aspects of cognitive function following DHEA treatment in healthy older people.[45]

In patients with Alzheimer's disease, DHEA replacement for six months did not result in cognitive improvement or influence the severity of disease.[46]

Safety

Lower doses of DHEA (25-50 mg/d) appear to be efficacious, well tolerated, and safe in the elderly population.[47,48] Some women experience androgenic side effects such as oily skin, acne, excess facial hair, and hirsutism, but these are less common with lower doses. Long-term metabolic consequences of increased serum androgens in women are a concern, since DHEA is converted to androgens in vivo.

With high doses of DHEA, side effects reported by women include jaundice, elevated liver function tests, virilization, adverse effect on lipids and the breast, depressed mood, and, possibly, hepatocarcinogenicity. Nausea, vomiting, seborrheic dermatitis, and jaundice have been noted with low-dose chronic use.[49]

DHEA is contraindicated in women of reproductive age, especially if they are at any risk of pregnancy, because of possible masculinization of a female fetus. DHEA is also contraindicated in women who have hormone-responsive tumors.

The consistency of the amounts of DHEA in available formulations is questionable. An analysis of 16 DHEA-containing dietary supplements revealed that only seven contained DHEA within 90%-110% of the specifications on the product label.[50]

Conclusion

It is a popular notion that DHEA is beneficial, more so in older individuals and the elderly; however, the available clinical data do not support this idea. This is likely due to the wide variation in formulations, doses, and duration of therapy studied and the different standards used to assess efficacy. The ease of obtaining DHEA over the counter and the lack of regulation and quality control in the United States are major causes for concern and have been heavily criticized. Ongoing research is crucial and may serve to elucidate the potential benefits and risks of DHEA for both women and men as they age. ❖

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Relax ... with Progressive Muscle Relaxation or Yoga

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Source: Smith C, et al. A randomised comparative trial of yoga and relaxation to reduce stress and anxiety. *Complement Ther Med* 2007;15:77-83. Epub 2006 Jun 21.

Abstract: The purpose of this trial was to compare yoga and relaxation as treatment modalities at 10 and 16 weeks from study baseline to determine if either modality reduces subject stress, anxiety, or blood pressure, or improves quality of life. A randomized comparative trial was undertaken comparing yoga with relaxation in 131 subjects from South Australia who had mild-to-moderate levels of stress. Subjects received 10 weekly one-hour sessions of relaxation or hatha yoga. Outcome measures were changes in the State Trait Personality Inventory subscale anxiety, General Health Questionnaire, and the Short Form-36. Following the 10-week intervention, stress, anxiety, and quality-of-life scores improved over time. Yoga was found to be as effective as relaxation in reducing stress and anxiety and improving health status on seven domains of the SF-36. Yoga was more effective than relaxation in improving mental health. At the end of the six-week follow-up period there were no differences between groups with regard to stress, anxiety, and five domains of the SF-36. Vitality, social function, and mental health scores on the SF-36 were higher in the relaxation group during the follow-up period. Yoga appears to provide a comparable improvement in stress, anxiety, and health status compared to relaxation.

Comment

Numerous strategies are used to help people reduce stress. In spite of widespread use, little research has examined effectiveness. The authors of this report found only two studies examining yoga as a method of reducing stress. While both found that people assigned to yoga benefited more than those in the control group, the studies were small and of poor quality. With relaxation training, two systematic reviews found a variety of techniques more beneficial than the control. This study compared hatha yoga with relaxation training, but did not include a non-intervention group. The authors mentioned that such a control group would be advantageous to ensure that changes are due to the interventions, not confounding factors.

The relaxation technique used was progressive muscle relaxation (PMR). The participants assumed a relaxed position and listened to instructions on tensing and relaxing various muscles. Ocean music was played in the background. During PMR, people were given 10-15 minutes for complete quiet and possible meditation. The sessions lasted one hour and were to be attended once per week; so too for the hatha yoga sessions. These were described in detail, but it was acknowledged that the procedure varied according to people's abilities and needs. The description added that: "The aim was to achieve appropriate relaxation to start and finish for the classes for 10 min." A number of unclear statements of this type interfered with comprehension of the article.

The stress, anxiety, and health status questionnaires were administered at baseline, and blood pressure was measured. The interventions were administered for 10 weeks and all outcomes measured. Six weeks later, all the outcomes were measured again. At the end of the intervention period, yoga was as effective as PMR on all questionnaire outcomes except for one: Blood pressure did not change. After the follow-up period, the groups did not differ on most outcomes, although the relaxation group had better outcomes in three of the eight domains of the SF-36.

However, during the follow-up period, significantly

more people continued to use PMR than continued with yoga. The different outcomes may reflect participants' preference for PMR rather than long-term effects of the intervention. The authors note that this is an important finding in itself that may relate to the ease of learning PMR or of incorporating it into people's routines.

All of the outcomes must be interpreted with caution for at least two reasons. Although the protocol was designed to have people come to weekly sessions for the initial 10-week period, participants in both groups attended an average of five sessions. People gave understandable reasons for not attending, but the implications of deviating from the study design were not discussed. In addition, the researchers calculated that 80% power at the 0.05 level would require 200 participants. Only 131 subjects were randomized and yet no discussion was given of the implications of this for the significance of the results.

The authors conclude that yoga and relaxation produce similar improvements in stress, anxiety, and health status. They repeatedly referred to PMR as "relaxation" (even in the title), which fails to make clear that they were comparing yoga to one specific approach to relaxation. Yoga itself it believed to be beneficial because it can induce a relaxation response. While the study was designed to focus on a comparison of the two approaches, some description of the actual outcomes compared to baseline would have been welcome. The data given in the article did not permit an examination of the clinical significance of the changes found.

The researchers are to be commended for taking important steps to improve the quality of the study. They used an intention-to-treat analysis and well-validated outcome measurement instruments. It was not possible to blind the participants to the intervention, but the study analyst was blinded. Randomization was done appropriately and carefully concealed. Drop-out rate overall was relatively low (11% at the end of 16 weeks), although attendance at the relaxation sessions was only 50%. The study design provides a good example of a comparative randomized trial of two complementary therapies. However, in carrying out the study, changes to the study design introduced significant weaknesses that impact the confidence we have in acting upon the stated conclusions. ❖

CME Objectives

After reading *Alternative Therapies in Women's Health*, the health care professional will be able to:

1. evaluate alternative medicine and complementary therapies for women's health concerns;
2. identify risks and interactions associated with alternative therapies;
3. discuss alternative medicine options with patients;
4. offer guidance to patients based on latest science and clinical studies regarding alternative and complementary therapies.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided at the end of the semester to receive a certificate of completion. Upon receipt of your evaluation, a certificate will be mailed.

CME Questions

31. DHEA is promoted to prevent which of the following diseases?

a. Heart disease
b. Cancer
c. Diabetes
d. Alzheimer's disease
e. All of the above

32. By age 50 years, women have approximately 50% of their peak DHEA levels, becoming almost undetectable by age 70.

a. True
b. False

33. Available research indicates that DHEA may be useful in which of the following situations?

a. To prevent and treat osteoporosis in postmenopausal women
b. To increase libido in postmenopausal women
c. To improve perimenopausal symptoms
d. All of the above

34. In the study by Smith et al, relaxation was more effective than yoga in improving mental health.

a. True
b. False

Answers: 31. e, 32. a, 33. a, 34. b.

News Briefs

PubMed Has Potential to Help CAM Practitioners Engage with, Understand Research

Many health professionals use PubMed, the largest bibliographic index in the life sciences, to locate, comprehend, evaluate, and use medical research. In a recent study, researchers sought to establish the potential contributions made by a range of PubMed tools and services for use by complementary and alternative medicine (CAM) practitioners. The results were published in the June issue of the *Journal of Medical Internet Research*.

For the study, the researchers took 10 chiropractors, seven registered massage therapists, and a homeopath (n = 18)—11 with prior research training and seven without—through a two-hour introductory session with PubMed. The 10 PubMed tools and services considered in this study were divided into three functions: 1) information retrieval (Boolean Search, Limits, Related Articles, Author Links, MeSH); 2) information access (Publisher Link, LinkOut, Bookshelf); and 3) information management (History, Send To, Email Alert). Participants were introduced to between six and 10 of these tools and services. The participants were asked to provide feedback on the value of each tool or service in terms of their information needs, which was ranked as positive, positive with emphasis, negative, or indifferent, the researchers say.

The participants in this study expressed an interest in the three types of PubMed tools and services (information retrieval, access, and management). Less well-regarded tools included MeSH Database and Bookshelf. The tools and services led the participants to reflect on their understanding as well as their critical reading and use of the research, the researchers say.

The participants all wanted greater access to complete articles, beyond the approximately 15% that are currently open access. They felt that the abstracts provided by PubMed were necessary in selecting literature to read but were entirely inadequate for both evaluating and learning from the research. Because of this, the participants were frustrated about the restrictions and fees required to access full-text articles.

Overall, the study found strong indications of PubMed's potential value in the professional development of these CAM practitioners in terms of engaging with and understanding research. PubMed provides support for the various initiatives intended to increase access, including a recommendation that the National Library of Medicine tap into the published research that is being archived by authors in institutional archives and through other web sites, the researchers say.

Survey Shows Health Professionals Have Limited Knowledge of CAM

A recent survey of health professionals in Canada shows that they have limited knowledge of complementary and alternative medicine (CAM) and that they rarely ask patients about CAM use.

Researchers surveyed nurses, physicians, and allied health professionals at a Canadian tertiary care, pediatric/women's care regional center that serves a population of 2.5 million. The researchers examined personal attitudes and professional practice in addressing CAM use by patients. They also examined the availability of CAM-related information to health professionals.

The findings suggest that health professionals: 1) are supportive of the use of selected CAM therapies by patients; 2) have almost no personal experience of CAM; 3) have limited knowledge about CAM and acquire that information mainly from the Internet, friends, or family rather than professional journals; 4) are uncomfortable discussing CAM with patients, and; 5) rarely or never ask patients about CAM use.

The researchers conclude that improved access to existing policies and scientific publications, and specific continuing professional development opportunities focused on speaking openly and non-judgmentally with patients would allow health professionals to more accurately guide patients in the prevalent use of CAM. For more information on this study, see the August 2007 issue of *Complementary Therapies in Clinical Practice*. This study was also published on-line in April. ❖