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DHEA: The remedy for andropause

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Abstract

Andropause is a clinical and biochemical syndrome associated with advancing age in males and mainly characterized by a deficiency in serum (blood) androgen, mostly testosterone, levels. The condition is sometimes referred to as androgen decline in the aging male (ADAM), partial androgen deficiency in the aging male (PADAM) or aging associated androgen deficiency (AAAD). Although the term andropause is used most often in the scientific literature, it is actually something of a misnomer because androgen releases never fully stops or “pauses” in the majority of aging men. A growing body of research suggests that DHEA can prevent or reverse the diseases that anti-aging experts have identified as the most prominent markers of accelerated aging: atherosclerosis (hardening and clogging of the arteries), cancer, diabetes, and reduced immunity.

Keywords: Androgen decline, Aging associated decline, Aging associated androgen deficiency

Introduction

The word andropause is formed by combining two Greek words - andro meaning male and pauses meaning stop. Andropause is a condition that comes about when “masculinity” declines. In the first medical literature, it has been called "male menopause”. The results of a previous study reported in a 1944 issue of the Journal of the American Medical Association described the use of testosterone injections to rapidly and thoroughly relieve the symptoms of andropause

Andropause, sometimes colloquially called “man-opause” is a name that has been given to a menopause-like condition in aging men. This relates to the slow but steady reduction of the production of the hormones testosterone and dehydroepiandrosterone in middle-aged men, and the consequences of that reduction, which is associated with decreases in Leydig cells. Unlike women, middle-aged men do not experience a complete and permanent physiological shutting down of the reproductive system as a normal event. A steady decline in testosterone levels with age is well documented. "Andropause" is a term of convenience describing the stage of life when symptoms of aging appear in men. The impact of low levels of testosterone had been reported previously. The "male climacteric" including loss of libido, potency, nervousness, depression, impaired memory, the inability to concentrate, fatigue, insomnia, hot flushes, and sweating. Subjects with lower levels of testosterone than the normal level, shows the symptoms of andropause which, can be replaced by certain doses of testosterone. Andropause has been observed in association with Alzheimer's disease.

In one study, 98.0% of primary care physicians believed that andropause and osteoporosis risk were related. The term "symptomatic late onset hypogonadism" is sometimes considered to refer to the same condition as the word "andropause". Researchers prefer the term "androgen deficiency of the aging male", to more accurately reflect the fact that the loss of testosterone production is gradual and

asymptotic. Proponents of andropause as a distinct condition claim that it is a biological change experienced by men during mid-life, and often compare it to female menopause. Andropause is a decline in the male hormone testosterone. This drop in testosterone levels is considered to lead in some cases to loss of energy and concentration, depression, and mood swings. While andropause does not cause a man's reproductive system to stop working altogether, many experience bouts of impotence. Andropause is usually caused by a very gradual testosterone deficiency and an increase in sex hormone-binding globulin that occurs from age 35 onwards. Premature andropause can occur in males who experience excessive female hormone stimulation through workplace exposure to estrogen.

By their mid-50s, about 30 percent of men experience andropause. About 5 million American men do not produce adequate testosterone, which leads to early andropause. In Australia, about one in every 200 men under the age of 60 and about 1 in every ten men over 60 have low testosterone. Regardless of location, the most likely males to develop early andropause are those with diabetes, hypertension, and genetic disorders that produce hypogonadism, including Klinefelter's, Wilson-Turner, and Androgen insensitivity syndromes. Andropause is a change of life in middle-aged men, which has hormonal, physical, psychological, interpersonal, social, sexual, and spiritual aspects.

Fig.1. represents the structure of Dehydroepiandrosterone **(**DHEA**).** It has been implicated in a broad range of biological effects in humans and other mammals. It acts on the androgen receptor both directly and through its metabolites, which include androstenediol and androstenedione, which can undergo further conversion to produce the androgen testosterone and the estrogens, including estrone, estradiol, and estriol. DHEA is also a potent sigma-1 agonist. It is considered a neurosteroid.

DHEA is produced from cholesterol through two cytochrome P450 enzymes. Cholesterol is converted to pregnenolone by the enzyme P450 SCC (side chain cleavage); then another enzyme, CYP17A1, converts pregnenolone to 17α-hydroxypregnenolone and then to DHEA. As almost all DHEA is derived from the adrenal glands, blood measurements of DHEAS/DHEA are useful to detect excess adrenal activity as seen in adrenal cancer or hyperplasia, including certain forms of congenital adrenal hyperplasia. Women with polycystic ovary syndrome tend to have elevated levels of DHEAS.

Causes of andropause

The primary is that as men get older; their testes don't work as well. Something called "leydig cell" produce testosterone less frequently and in a lesser quantity. Other reasons are that the hormones that produce testosterone just are not creating as much and some of that testosterone is being converted to other hormone like estradiol and DHT.

Dehydroepiandrosterone, or DHEA as it is more often called, is a steroid hormone naturally produced in the adrenal gland. It is the most abundant steroid in the bloodstream and is present at even higher levels in brain tissue. DHEA levels are known to fall precipitously with age, falling 90% from age 20

Fig.1. Structure of Dehydroepiandrosterone (DHEA)

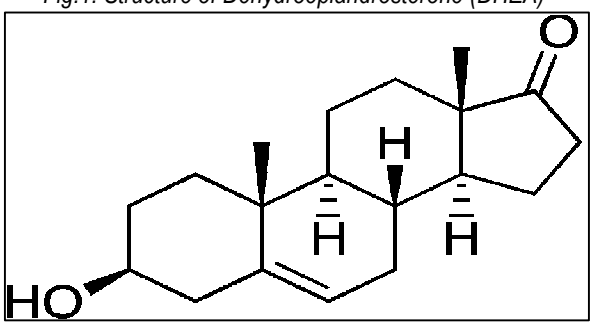
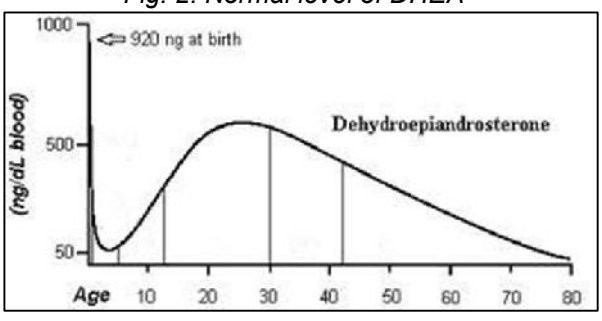


Fig. 2. Normal level of DHEA



to age 90. DHEA is known to be a precursor to the numerous steroid sex hormones (including estrogen and testosterone) which serve well-known functions (Fig.2.)

Diagnosis

You usually detect andropause by its symptoms, therefore, in order to get a full understanding as to whether you fall into this category, you'll undergo a couple of screening procedures to aid in proper diagnosis, including

- ADAM questionnaire
- Rigi scan
- Full hormonal panel
- Physical exam

Signs and symptoms of andropause

In recent times a more accurate name than "male menopause" is being used to describe this syndrome, it is androgen decline in aging males or ADAM. This name was coined because androgen deficiency in older men is generally moderate and not complete. It differs most markedly from female menopause in the speed with which the symptoms occur. In women, the menopause is a universal and comparatively sudden change. In men, the change is much more gradual and difficult to pinpoint. This difference suggests that referring to the syndrome in men as "male menopause" is not accurate.

- Erectile dysfunction
- Decreased libido
- Mood disturbances, including depression, irritability and feeling tired
- Loss of muscle size and strength
- Osteoporosis
- Increased body fat
- Difficulty with concentration and memory loss
- Sleep difficulties

Pathophysiology

The hypothalamic neurons from the fetal olfactory placode that secrete GnRH. The function of these neurons is modulated by neural input and neurotransmitters. At puberty, olfactory placode demonstrate increased perikaryon size Golgi apparatus, secretory vesicles and increase in the number of GnRH staining cells. Ultimately, they secrete GnRH in a pulsatile fashion dependent upon the presence of Ca2+, glucose, insulin, and voltage-dependent Ca++ channels. Pulsatile release of GnRH induces pituitary synthesis and secretion of LH and FSH, which induce testicular secretion of testosterone and inhibin. With age, GnRH mRNA content does not change, the number of GnRH secreting neurons decreases.

Pharmacology

In men, the synthesis of DHEA and DHEAS occurs in testes approximately 5% of DHEAS and 10-25% of DHEA. Minute amounts are synthesized de novo in the brain. In adults the adrenal cortex secretes approximately 4 mg of DHEA and 25 mg of DHEAS per day. During gestation, large amounts of DHEA and DHEAS are secreted by the fetal adrenal glands. DHEA and DHEAS are interconvertible by sulfohydrolases in peripheral and adrenal tissues. 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 and cause functional activation of T cells.

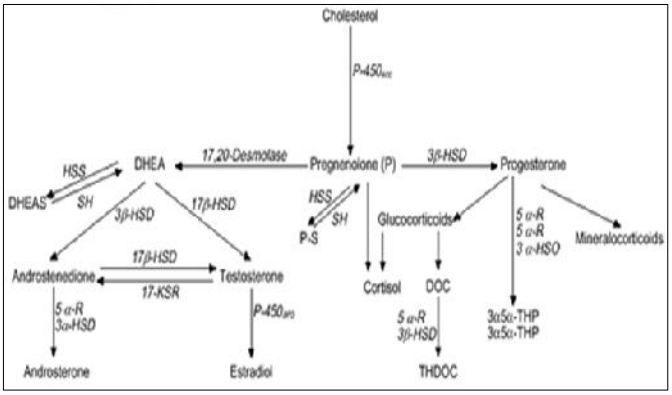
In the central nervous system, both DHEA and DHEAS appear to affect neurotransmitter receptors. DHEA which inhibit the synthesis of thromboxane A 2 in activated platelets, reduce plasma plasminogen activator inhibitor type 1 and tissue plasminogen activator antigen, increase serum levels of insulin-like growth factor 1 (IGF-1), and increase cyclic guanosine monophosphate and nitric oxide synthesis. This effect that suggest the DHEA regulating some of the risk factors of cardiovascular disease, such as platelet aggregation and ischemia

Pharmacokinetics

Oral absorption of DHEA is excellent. DHEA and DHEAS are converted into several active metabolites, including androstenedione, testosterone, estrone, estradiol, and estriol.

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 Fig.3.

Fig.3.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 (Arnlov *et al.*, 2006)

DHEA and systemic lupus erythematosus

DHEA supplementation has shown promise for the treatment of SLE. In a randomized, double-blind trial, 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. Lupus flares occurred less frequently in the treatment group than in the placebo group, and a non significant decrease in prednisone requirements was noted in the treatment group. Serum titers of antibodies to double-stranded DNA and levels of complement components C3 and C4 did not change significantly between the groups.

DHEA and 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.

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.

DHEA AND BRAIN

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.

In a randomized, double-blind trial by Wolkowitz et al. 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 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.

Schizophrenia

Initial research reports benefits of DHEA supplementation in the management of negative, depressive, and anxiety symptoms of schizophrenia. Some of the side effects from prescription drugs used for schizophrenia may also be relieved. Further study is needed to confirm these results before a firm conclusion can be drawn.

Alzheimer's disease

Initial research reports that DHEA does not significantly improve cognitive performance or change symptom severity in patients with Alzheimer's disease, but some experts disagree. Additional study is warranted in this area.

DHEA and 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 six women) received oral DHEA doses of 200-500 mg/day for eight weeks. 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. 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.

DHEA and libido

The people over the age of 40 who feel their sexual dysfunction. DHEA restoring the levels of hormones for male and female, may feel them more sexual energy and vitality, who feel their sex lives are beginning to lag. For men, increase the DHEA levels by supplements of 50mg/day for 6 months, which reduce the impotence and sexual dysfunction.

DHEA and aging

The changes felt with aging is fatigue, there is a loss of energy in the late afternoon, a decrease in work activity, an inability to exercise or a feeling of unrest after a full night sleep. In a chronic complaints of fatigue, headache, obesity, and depression show low DHEA blood levels measured as DHEAs. A biochemical explanation for the lack of efficient cellular energy production may be a cause for the vast array of chronic condition, such as many illnesses thought to be psychosomatic are by state of DHEA deficiency.

DHEA and cardiovascular disease

Initial studies report possible benefits of DHEA supplementation in patients with cholesterol plaques ("hardening") in their arteries. There is conflicting scientific evidence regarding the use of DHEA supplements in patients with heart failure or diminished ejection fraction. Other therapies are more proven in this area, and patients with heart failure or other types of heart disease should discuss treatment options with a cardiologist.

DHEA and thiredoxin

DHEA has been shown to be associated with anti-oxidant properties, but the mechanism is clearly not known. DHEA in the model of H_2O_2 induced oxidative stress in cell. The results showed that pre-treatment of DHEA protect the cell against the H_2O_2 induced toxicity as per dose. The thioredoxin mRNA transcription was inhibit by H_2O_2, the pre-administration DHEA it should reverse the process.

DHEA and cancer

In a study, nine healthy elderly men took 50 mg of DHEA for 20 weeks. Scientists found that DHEA increased the activity of lymphocytes, which are natural killer cells that find and destroy not only viruses, but also abnormal cells that may turn cancerous. Although the number of T lymphocytes was unaffected, T cell function was increased. In this way DHEA increased the quality of the body's natural defense against cancer, not necessarily the quantity of cells that do the fighting.

Conclusion

Clinical data suggested that the DHEA may have a role in horomone replacement therapy, in patients with low endogenous level on DHEA and DHEAS. It is a potent steroid precursor; DHEA can significantly increase androgen levels in women and may enhance the progression of estrogen and testosterone-sensitive cancers. DHEA should never be undertaken without direct medical supervision. The long-term effects of DHEA supplementation are unknown.

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