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REPORT

Why DHEA May Be the Best-Validated Anti-Aging Supplement

By Julius Goepf, MD



A review of the published scientific literature reveals that DHEA (dehydroepiandrosterone) may be the best-validated anti-aging supplement currently available. Brand-new studies indicate that DHEA is even more effective than previously demonstrated.

DHEA was introduced to Americans by the Life Extension Foundation in 1981. For nearly two decades, a battle raged between health freedom activists who wanted free access to DHEA and government bureaucrats who wanted to ban it.

The tide turned in 1996, after two Life Extension members were arrested for importing DHEA for personal use. Attorneys hired by the Life Extension Foundation proved that DHEA was not a controlled substance and was indeed perfectly legal to buy and sell.

The last two years have produced a torrent of positive research findings concerning DHEA. As most members know, DHEA is abundantly produced in healthy young adults, but its levels decline dramatically with advancing age,^{1,2} coinciding with the onset of numerous diseases of aging.²⁻⁷

While DHEA's demonstrated anti-aging benefits have made it a popular supplement, powerful new evidence supports DHEA's critical role in alleviating depression,^{8,9} enhancing endothelial function,¹⁰⁻¹² preventing atherosclerosis,¹³⁻¹⁵ increasing bone mass,¹⁶⁻¹⁸ slowing osteoporosis,¹⁶⁻¹⁸ improving insulin resistance,^{19,20} and even hastening wound healing.^{21,22}

Despite its ever-growing list of health benefits, however, DHEA remains under political attack. Its frequent mischaracterization as an "anabolic steroid" has led some in Congress to call for outlawing DHEA.

Fortunately, thanks to the concerted efforts of key lawmakers and champions of health freedom, DHEA remains readily available to all health-conscious adults who seek to reap its far-ranging, multifaceted benefits.

DHEA SUPPORTS MOOD AND SEXUAL FUNCTION

In just the last two years, researchers have published exciting new findings that underscore DHEA's value in alleviating depression, improving sexual function, and managing the symptoms of schizophrenia.

Building on earlier results pointing to DHEA's promise in treating major depression,⁹ in 2005 researchers conducted a double-blind, placebo-controlled trial of 46 men and women with major or minor depression.⁸ The subjects received 90 mg of DHEA per day for three weeks and 450 mg per day for an additional three weeks. Treatment with DHEA produced dramatic gains on standard depression rating scales, with half the subjects showing a 50% or greater improvement. The DHEA-supplemented subjects also recorded significant improvements on a score of sexual function. The researchers concluded that DHEA is effective in treating depression when used in the absence of prescription antidepressants.⁸

DHEA's effects in combating depression were further confirmed in a study published in early 2006. Scientists treated 145 HIV-positive patients showing signs of depression with either DHEA at a dose of 100-400 mg per day or a placebo.²³ Outcomes were measured using standard depression rating scales. DHEA proved superior to placebo in alleviating depression, with 56% of the DHEA-treated patients showing improvement compared to 31% in the placebo group.



DHEA is the most abundant steroid in the human body.³¹ Although primarily produced in the endocrine glands, DHEA technically is not a hormone, but rather a “prohormone,” or hormone precursor.³² In many organ systems, it is converted to the so-called “sex hormones”—the androgens and estrogens—by enzymes located in the tissues.³³ DHEA is synthesized from cholesterol in a series of enzymatic reactions that occur in the adrenal glands, liver, and small intestine. Most DHEA in the body is bound to a sulfate molecule, and thus referred to in this form as dehydroepiandrosterone-sulfate, or DHEA-S. When a person orally ingests DHEA supplements, a sulfate molecule is added as it passes through the liver. The sulfate attachment appears to be necessary to keep the entire molecule inactive until it reaches its target tissues. Both DHEA and DHEA-S were used in studies cited in this article.

Unfortunately, DHEA levels decline with advancing age,^{1,2} and this falloff is more pronounced in men than in women.¹ Some scientists believe that the drop in levels of DHEA and DHEA-S—and the consequent decline in levels of testosterone and estrogen—may be related to many common age-related conditions, including diseases of the nervous, cardiovascular, and immune systems.²⁻⁴ Other conditions now believed to be related to diminished levels of DHEA and its end products include cancer, osteoporosis, and type II diabetes.^{2,5-7}

A common thread running through some of these various conditions is the so-called “metabolic syndrome,” which appears to underlie deleterious alterations to the blood vessel linings and the way in which the body metabolizes many vital nutrients, including glucose and calcium.⁵⁻⁷

Sexual function is closely linked with emotional health and well-being, and scientists now know that DHEA levels are strongly associated with healthy sexual function. Two notable studies from 2005 found that sexual function²⁴ and overall self-reported health and functional status²⁵ were better among women with relatively high levels of DHEA-sulfate (DHEA-S). Even low-dose DHEA supplementation may be effective in providing these benefits. For example, in a group of women with systemic lupus erythematosus, daily doses of DHEA as low as 20-30 mg improved health-related quality of life and sexual interest and activity compared to placebo.²⁶ Other researchers have reported notable improvements in libido and mood in women who supplemented with DHEA.^{27,28}

Even more promising are several recent studies from 2005 suggesting that, in addition to its positive impact on depression and sexual function, DHEA may help to manage symptoms of schizophrenia. Based on their preliminary findings demonstrating DHEA’s efficacy in reducing symptoms of schizophrenia,²⁹ researchers further noted improvement in illness severity and anxiety in a group of schizophrenic patients who received DHEA in addition to their anti-psychotic medications.³⁰ The study authors attributed this specific anxiety-reducing effect to DHEA’s influence on the brain’s GABA receptors, which are central to regulating mood.³⁰

DHEA PROTECTS ARTERIES, PROMOTES CARDIOVASCULAR HEALTH

Extremely positive findings about the cardiovascular benefits of DHEA were reported in the Massachusetts Male Aging study. Researchers confirmed that men with higher DHEA-S levels were less likely to have heart disease,¹³ suggesting a valuable role for DHEA in averting the nation’s leading cause of death.

Additionally, higher DHEA levels seem to positively affect endothelial cell signaling, which could have important implications for avoiding heart disease. In a subset of men from the Baltimore Longitudinal Study of Aging,¹⁴ levels of hormones (including DHEA-S) were measured and correlated with arterial stiffness, as measured using ultrasound imaging of the carotid arteries. Men with higher levels of total and free testosterone and DHEA-S had less stiffness of the arteries, indicating a decreased risk of cardiovascular events such as heart attacks.

A similar link between low serum DHEA-S levels and greater risk for carotid artery disease was demonstrated last year in a study of young women with polycystic ovary syndrome, a condition associated with an increased risk of cardiovascular disease and metabolic syndrome.¹⁵



A study in animals in 2006 shed further light on how DHEA promotes cardiovascular health.³⁴ Researchers fed young and old female mice a daily DHEA-S supplement. After 60 days of treatment, the investigators measured the stiffness of the test animals’ left ventricle, the heart’s major pumping chamber. The DHEA-S-supplemented older mice had decreased left ventricular stiffness compared to the non-supplemented older animals. The scientists concluded that DHEA-S supplementation is capable of reversing the left ventricular stiffness that accompanies aging, thus promoting youthful structure and function in the heart’s tissues.

Another animal study simulated the depressed cardiovascular function (shock) that follows major trauma.³⁵ Researchers gave male rats doses of a DHEA metabolite. This treatment reversed the depression of cardiovascular function and organ blood flow induced by shock. Scientists were able to measure that plasma levels of the inflammatory cytokine interleukin-6, which had been elevated in the state of simulated shock, were promptly

reduced by treatment with the DHEA metabolite. The investigators concluded that treatment with a DHEA metabolite could be valuable in restoring cardiovascular function and correcting abnormal cytokine levels.

Furthermore, investigators determined that DHEA-S injected directly into the coronary arteries of pigs produced acute dilation of the blood vessels, with associated increases in coronary blood flow.³⁶

DHEA IMPROVES BLOOD FLOW AND ENDOTHELIAL FUNCTION

Strong new evidence indicates that DHEA and DHEA-S help protect aging adults against atherosclerosis and its life-threatening consequences such as coronary artery disease.^{10,11,37} Several mechanisms of action may account for these benefits.

In one blind, placebo-controlled trial, 24 older men orally ingested 50 mg of DHEA or a placebo at bedtime for two months. The researchers then measured arterial dilation and increased blood flow. While the placebo-treated subjects had no changes in any of the parameters measured, the DHEA-treated men experienced increased levels of a substance that helps blood vessels to dilate, as well as decreasing levels of a marker for blood clotting. They also had lower levels of artery-clogging low-density lipoprotein (LDL) after treatment than did the controls. The researchers concluded, based on the beneficial effects of short-term DHEA treatment, that long-term DHEA supplementation may prevent atherosclerotic changes caused by falling levels of vessel-dilating biochemicals.³⁷

HIGHER DHEA-S LEVELS TIED TO LOWER MORTALITY RISK

Of the many tactics that can be deployed to increase one's life span, supplementing with DHEA seems to be one of the most beneficial, as new findings imply that higher levels of DHEA are associated with a longer life span.³⁸

Scientists recently examined data on nearly 1,000 older Taiwanese adults to determine the relationship between DHEAS levels and three-year mortality risk.

At the study's end three years later, the data analysis revealed that participants with lower DHEA-S levels had a 64% greater risk of death than did individuals with higher DHEA-S levels. The study authors concluded that lower levels of DHEA-S have a notable effect in increasing mortality risk, and that optimal DHEA-S levels may help to promote longevity.³⁸

Previous studies have shown that platelet levels of an important vasodilating agent decrease with age, apparently due to the diminished efficiency of enzyme systems that are involved in their production.¹⁰ These changes may also influence platelet "stickiness," which tends to increase with age. These tendencies toward decreased vasodilation and increased platelet aggregation over time may be defining features of the relationship between impaired endothelial function and atherosclerosis.¹²

A study in 2003 investigated the effect of DHEA supplementation (25 mg per day) on endothelial function, an instigating factor in the development of atherosclerosis.¹¹ The investigators examined how the diameter of the large artery in the upper arm known as the brachial artery responded to blood-flow demands in DHEA-treated and placebo-treated men. Significantly, researchers found increases in blood vessel dilation—and therefore increased blood flow—in the DHEA-supplemented group. As in the study just described, investigators also found decreased plasma levels of a clotting agent in the treatment group. Finally, plasma glucose levels decreased significantly and safely in the treated group compared to controls. According to the authors, low-dose DHEA supplementation improved endothelial function, increased insulin sensitivity, and decreased blood-clotting tendency¹¹—all factors that may slow the development of numerous age-related disorders, including heart disease and metabolic syndrome.

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DHEA HELPS PREVENT AGE-RELATED BONE LOSS AND OSTEOPOROSIS

Recently, new side effects were announced for the popular osteoporosis drug known as Fosamax®. Apparently, many Fosamax® users find themselves with the troubling condition known as osteonecrosis of the jaw, in which the jaw bone essentially dies.³⁹ Unfortunately, those experiencing osteoporosis are presented with little choice other than to take the drug and hope for the best. Now, strong evidence suggests that ensuring optimal levels of DHEA may help to slow bone loss and guard against the crippling effects of osteoporosis.

Studies of both men and women have demonstrated that low levels of DHEA are associated with bone loss through mechanisms related to altered mineral absorption and metabolism, as well as through inflammatory processes.⁴⁰⁻⁴² In younger people, normal DHEA levels stimulate adequate production of a substance called insulin-like growth factor 1, which maintains new bone formation. Healthy DHEA levels also suppress production of interleukin-6, an inflammatory cytokine that causes bone breakdown (resorption), thus preventing bone loss. Decreasing DHEA levels are associated with diminished levels of insulin-like growth factor 1 and higher levels of interleukin-6, creating a situation in which bone loss exceeds new bone formation.⁴⁰



For nearly a decade, researchers have known that DHEA supplementation can slow bone loss associated with osteoporosis, while increasing bone mass.¹⁶⁻¹⁸ Although scientists knew that this effect is the result of both suppressing bone loss and enhancing formation of new bone,⁴³ DHEA's precise mechanism of action was unclear.

In the past year, science has provided powerful new evidence of just how these bone-protective effects occur. In 2006, investigators found that bone-forming cells survived longer in the presence of DHEA. This effect is explained by DHEA's ability to suppress the inflammatory agent known as nuclear factor-kappa beta, a contributor to bone loss.⁴⁴

Earlier this year, researchers also discovered that the DHEA-mediated increase in bone formation was the result of DHEA's conversion to estrogen at the local tissue level in postmenopausal women.⁴⁵

These studies demonstrate that DHEA works via several mechanisms to increase bone mass and density, thus promoting bone health and guarding against the perilous consequences of age-related bone deterioration.

DHEA IMPROVES INSULIN SENSITIVITY, MAY PREVENT METABOLIC SYNDROME

With advancing age comes progressive resistance to the glucose-controlling effects of insulin—another condition that is strongly associated with declining DHEA levels.^{46,47} Recent studies provide ample support for DHEA's beneficial effects in improving insulin resistance, which is associated with the development of metabolic syndrome and type II diabetes.⁴⁸ Both of these conditions can lead to atherosclerosis.⁵



The mechanisms by which DHEA beneficially influences blood glucose levels and insulin sensitivity are becoming increasingly clear. In a study earlier this year, DHEA supplementation increased the number and size of insulin-secreting beta cells of the pancreas.¹⁹ In short, DHEA supplementation in these animals increased their ability to manage a glucose load, as occurs when consuming meals. The study authors concluded that DHEA may be a promising agent in preventing diabetes during aging.

Fortunately, two recent human trials lend additional support to these findings. In 2005, investigators studied the effects of DHEA replacement on insulin sensitivity in women with known adrenal insufficiency (whose natural levels of DHEA were well below normal). In this 12-week, randomized, controlled trial, subjects received either 50 mg per day of DHEA or a placebo. Insulin sensitivity was then measured. The DHEA-treated subjects required significantly higher amounts of glucose to raise their blood sugar levels, demonstrating markedly improved insulin sensitivity. These subjects also demonstrated lower levels of total cholesterol and LDL. The investigators concluded that DHEA replacement increases insulin sensitivity and may prevent type II diabetes.²⁰

In another recent study, daily DHEA supplementation of 50 mg per day for six months produced notable reductions in the size of fat stores in the abdominal wall and cavity among study subjects compared to controls.⁷ The DHEA-supplemented subjects also showed greater sensitivity to insulin, maintaining their blood sugar well within limits during an oral glucose tolerance test. These researchers similarly concluded that DHEA replacement may play an important role in preventing and managing metabolic syndrome.

MAINTAINING OPTIMAL DHEA LEVELS

Since a wealth of evidence links optimal DHEA levels with protection against the diseases of aging, the Life Extension Foundation recommends that all adults monitor their levels through regular blood testing. Normal laboratory reference ranges and optimal ranges for DHEA-S are shown below.

	Normal	Optimal
Men	280-640 µg/dL	500-640 µg/dL
Women	65-380 µg/dL	250-380 µg/dL

If DHEA-S levels are below the optimal range, healthy adults may wish to begin supplementing with 15-75 mg of DHEA daily. After three to six weeks of DHEA supplementation, another blood test is suggested to assess DHEA levels and adjust dosage. Individuals with hormone-sensitive cancers should not use DHEA. Speak with your doctor to determine if DHEA supplementation is appropriate for you.



DHEA PROMOTES FASTER WOUND HEALING

The body's ability to heal wounds is key to recovering from minor injuries as well as major surgery. Recent evidence indicates that DHEA supplementation may have the beneficial effect of accelerating wound healing.

In humans and other mammals, wound healing is increasingly impaired with advancing age.⁴⁹ Given the increased rate of injury, reduced mobility, and relatively frequent need for surgery in older adults, this impairment entails substantial costs, in medical expenditures as well as pain and suffering. By one estimate, age-related impaired wound healing in the US alone carries an annual price tag of more than \$9 billion.⁴⁹

Because wound healing is positively associated with levels of estrogen and testosterone, it makes sense that their precursor, DHEA, might have a beneficial effect as well. A study from 2005 provides important evidence to support this notion.²¹ Researchers reported that DHEA levels in humans are strongly associated with protection against chronic venous ulcers, which often appear on the legs of older people with decreased mobility. The authors also demonstrated that injecting DHEA at the wound site accelerated healing in an animal model of age-related healing impairment. This important paper concluded that DHEA supplementation may be useful in both preventing and treating impaired wound healing in older adults.

Nerve tissue heals at an extremely slow rate. In a recent experiment, DHEA was shown to improve the rate of healing in nerve tissue.²² Rats were injected with DHEA or placebo at the site of damage to the sciatic nerve (the major nerve of the leg), and the size and bulk of nerves and muscles were then measured 12 weeks after the injury. Compared with placebo-treated controls, the DHEA-treated animals had heavier lower leg muscles, more myelinated (insulated) nerve fibers, and larger average nerve fibers. This study demonstrated that DHEA prevented the loss of muscle and nerve mass that so commonly follows injury to the extremities.

SUMMARY

The recent surge in research concerning DHEA is impressive. These studies dramatically underscore both the extent and variety of health benefits conferred by DHEA, which range from supporting psychological health and safeguarding cardiovascular function to improving insulin sensitivity and sustaining bone health.

Thanks to the efforts of congressional champions of health freedom such as Sens. Orrin Hatch (R-UT) and Tom Harkin (D-IA), aging Americans' access to DHEA has been preserved. Their efforts have enabled millions of Americans to continue to benefit from the neurological, cardiovascular, and other benefits associated with this health-sustaining hormone.

SEN. ORRIN HATCH ON DHEA AND BANNED SUBSTANCES

"We determined that DHEA was not in the same class as the other products listed because it is a naturally produced supplement that has been marketed for nearly 50 years, and it has a strong history of beneficial use and lack of any evidence of abuse. DHEA is an anti-aging supplement that millions of older Americans have used for years to improve their vigor

The nineteenth century American abolitionist Wendell Phillips is said to have remarked, “Eternal vigilance is the price of liberty.” While it is unclear whether federal lawmakers or bureaucrats will make further attempts to limit DHEA’s availability, the Life Extension Foundation will continue to monitor any relevant developments in Congress and will alert and mobilize members accordingly.

and health. So, after much debate, we determined that at the time the bill was passed we should not take this option away from consumers.”⁵⁰

DHEA is not for everyone—people with hormone-dependent cancers such as breast, uterine, and prostate cancers should avoid its use. However, an abundance of new studies suggests that ensuring optimal levels of this vital “prohormone” can help aging adults guard against endothelial dysfunction, vascular disease, metabolic syndrome, bone loss, and other debilitating conditions once thought to be the “inevitable” consequences of aging.

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