

DHEA AND ANTI-AGING MEDICINE

The aging process is inextricably tied to a decrease in beneficial hormones, such as growth hormone, thyroid and DHEA, and an increase in hormones whose elevated levels are clearly harmful, such as insulin and cortisol.

The dramatic drop in DHEA levels observed during aging parallels the development of degenerative syndromes such as immunosenescence, atherosclerosis, osteoporosis, cognitive decline, depressed mood and increased risk of cancer. The elderly suffer from a decline in DHEA secretion and a rise in cortisol. Those with very low levels of DHEA and higher levels of cortisol are most likely to suffer from dementia. The neuroprotective effects of DHEA replacement may be the most important anti-aging benefit, since ultimately there is nothing as important as slowing down the aging of the brain.



-by Ivy Greenwell

Can replacing DHEA through oral, sublingual or transdermal route help prevent the degenerative disorders of aging? Is it safe? Research keeps answering these questions in the affirmative. At the same time, the picture is complex. DHEA appears to be metabolized differently in men than in women, and consequently have somewhat different effects. It may be more crucial to men for cardiovascular protection, yet the antidepressant effect may be stronger for women, who are also more likely to report an increase in libido, and show improvement in skin thickness and bone mass. Interestingly, the rise in serum estradiol and testosterone is more commonly seen in women (Legrain 2000; Baulieu 2000). At this point, the majority of studies point to anti-aging benefits of DHEA replacement that simply cannot be ignored.

Hormone replacement for older men and postmenopausal women

"Andropause," also referred to as "partial androgen deficiency in the aging male," is characterized by symptoms such as decline in muscle mass and strength, increase in body fat, especially around the abdomen, dry skin, reduction in libido, fatigue, loss of bone mass and mood disorders such as depression and apathy. The simple answer seems to be testosterone and DHEA replacement. Mainstream physicians are slowly beginning to accept the need for testosterone replacement, but most are still unaware of the need to replace DHEA as well.

One of the most exciting studies on the importance of DHEA for older men was published by Morley (1997). Morley found that bioavailable testosterone (also known as "free testosterone," meaning testosterone not bound to sex hormone binding-globulin [SHBG]), correlated best with various markers of physical and cognitive function. DHEA, in turn, correlated well with the levels of bioavailable testosterone. It is well known that both free testosterone and DHEA dramatically decline with aging. It is also known that DHEA can be easily converted to testosterone, and in that sense DHEA and its sulfated form serve as precursors for testosterone. But the values obtained in this study indicated a larger involvement of DHEA in the regulation of the levels of free testosterone. As Morley puts it, "The rate of decrease in bioavailable testosterone paralleled almost exactly that of DHEA." Free



testosterone travels in the bloodstream bound to albumin, a protein in the serum that can serve as a carrier for various substances needed by the tissues. Morley suggests that DHEA facilitates the binding of testosterone to albumin. If this hypothesis is correct, then DHEA would be a very welcome addition to testosterone replacement. Total testosterone does not decline as rapidly with aging in men; it is the loss of free testosterone that is crucial. The right dose of DHEA would presumably increase both DHEA and the delivery of free testosterone to tissue receptors.

Several other studies have confirmed the benefits of DHEA replacement. For instance, a Czech study investigated the effects of transdermal DHEA (50 mg in gel) on men of various ages (mean age 52). The authors found that dermal DHEA was well absorbed and quickly converted to DHEA-S, androstenedione, and then the estrogenic and androgenic metabolites, including estradiol and testosterone. Negative correlations were found between DHEA and lipoprotein (a), DHEA-S and cholesterol, and DHEA, DHEA-S, testosterone and triglycerides. In other words, as DHEA levels rose, the levels of various serum lipids went down in a way that indicated cardioprotective benefits. There was, however, a decrease in endogenous DHEA. Because of the brief duration of the study, the main conclusion that can be drawn is that the transdermal route of DHEA application (gel) does significantly increase the levels of those steroids that are the metabolites of DHEA.

DHEA supplementation may be of most help to both men and women over 70, since their natural production has usually suffered a profound decline by that age. A recent study investigated the effects of 50 mg oral DHEA per day for six months on men and women between the ages of 72 and 74. In response to DHEA replacement, both sexes showed an increase in bone mineral density, both total and in lumbar spine, and an overall increase in lean body mass combined with a decrease in fat mass. DHEA replacement also resulted in increased IGF-1 and total testosterone. At the same time, a small placebo-controlled pilot study at a University of Vienna impotence clinic found that supplementation with 50 mg DHEA resulted in an improvement in erectile function without an increase in PSA or prostate volume. Such findings indicate that DHEA replacement can at least partly reverse aging-related changes in the elderly, increasing the sense of well-being and sexual function.

Speaking of the prostate, the fear that is often raised when it comes to any androgen replacement is the possibility of increased risk of prostate cancer. Some unexpected findings in animal studies suggest that starting DHEA treatment early may in fact help prevent prostate cancer. In a study by McCormick and Rao (1999), rats treated with DHEA prior to exposure to carcinogen appeared to be resistant to developing prostate cancer. As the authors state, "DHEA inhibits prostate cancer induction both when chronic administration is begun prior to carcinogen exposure, and when administration is delayed until preneoplastic prostate lesions are present." While retinoic acid turned out to be the most potent inhibitor of prostate cancer induction, DHEA produced sufficiently dramatic results to make the authors name both retinoic acid and DHEA as "the most active agents" for the chemoprevention of prostate cancer.

Another study by Rao confirmed that, "nontoxic doses of DHEA confer significant protection against prostate carcinogenesis in rats." Furthermore, the findings indicate that DHEA is effective also in later stages of induction and can inhibit the progression of precancerous lesions to invasive cancer. We do know that DHEA may help prevent certain kinds of cancer. Likewise, some holistic physicians believe that if androgen replacement is started early enough, both DHEA and testosterone actually help prevent prostate cancer (although as a precaution, holistic physicians also recommend supplements such as zinc, saw-palmetto, omega-3 fatty acids, lycopene and flavonoids [green tea, soy], as well as regular exercise). More research is obviously needed. For now, we have the findings of one in-vitro study using culture prostate cancer cells, showing that while the so-called "strong form" of testosterone, dihydrotestosterone (DHT) stimulated cell growth, DHEA had no effect. Likewise, patients with prostate cancer do not appear to have higher DHEA levels than healthy controls, as confirmed by a recent study done at the University of Vienna (Schatzl 2000). Nevertheless, it is too early to make any firm statements about DHEA and the risk of prostate cancer. (Note of caution: Our knowledge is incomplete, and it is better to err on the side of caution. Men diagnosed with prostate cancer should not take DHEA.)



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taking 50 mg of DHEA sulfate with women using the low-dose (50 micrograms) estradiol patch, and women taking both DHEA sulfate and using the low-dose estradiol patch. All three groups showed a similar improvement in the levels of beta endorphins and a decrease in menopausal symptoms. The group receiving DHEA or DHEA plus the estradiol patch also showed higher levels of DHEA, DHEA-S, androstenedione and testosterone. In addition, the group receiving either estradiol alone or the combined therapy also showed increased levels of estradiol, estrone and growth hormone. The ability of DHEA supplementation to increase the levels of androgens argues for the desirability of the combined therapy, since it restores a more balanced endocrine profile.

Another Italian study investigated the effects of 50 mg DHEA on postmenopausal women according to their age (50 to 55 for early postmenopause versus 60 to 65 for late postmenopause) and weight (normal versus overweight, BMI 26 to 30). The study found an increase in DHEA, DHEA-S, androstenedione, testosterone and dihydrotestosterone in all women. The levels of sex hormone-binding globulin decreased only in women who were older and overweight. All groups showed a three-fold rise in beta endorphins, together with an increase in allopregnanolone (a neurosteroid with a calming effect). In addition, all groups showed a drop in cortisol and gonadotropins. Younger women experienced an improvement in menopausal symptoms. There was no effect on uterine endometrium, which is good news for those women who are bothered by breakthrough bleeding when using mainstream-type hormone replacement therapy.

The antidepressant effect may be the best news of all. A separate study by the same team of investigators found a significant increase in plasma beta-endorphin levels in women using 100 mg of oral DHEA. The authors hypothesize that DHEA could enhance the sense of well-being by restoring neuroendocrine control of beta-endorphin secretion by the pituitary.

Because of the risks involved in the mainstream hormone replacement therapy for postmenopausal women, scientists have turned their attention to DHEA as a possible alternative. Several studies have explored the effects of short-term treatment with DHEA on postmenopausal women. It is worth noting that while in men the levels of DHEA decline in a linear fashion, in women there is a dramatic 40% fall during the sixth decade, reflecting menopause. This is due to the fact that a portion of women's DHEA is produced by the ovaries. After menopause the ovarian production of androgens normally diminishes or even ceases with ovarian atrophy. Recent findings from the Rancho Bernardo Study indicate that women in the 50 to 89 age range have lower levels of DHEA than men and, what is potentially more worrisome, a higher cortisol/DHEA-S ratio. The latter may be related to women's higher risk for osteoporosis and decline in brain function, including greater susceptibility to depression and Alzheimer's disease.

There is a special interest in the ability of DHEA to improve the sense of well-being in postmenopausal women. This effect appears to correlate with the rise in the levels of circulating beta endorphins, known to decline with menopause. One recent Italian study compared women

A German study, likewise using 50 mg oral DHEA, found similar effects in women with initial DHEA deficiency due to adrenal hypofunction. The serum levels of DHEA, androstenedione and testosterone rose into the normal range; sex hormone-binding globulin decreased. The women reported improved overall sense of well-being, less anxiety and depression, less obsessive-compulsive behavior, stronger libido and more sexual satisfaction. One negative effect was a lowering of HDL cholesterol. Minor side effects included increased oiliness of the skin and scalp hair, acne, more sweating, and increased growth of facial and body hair (on the forearms, for instance), the coarsening and darkening of facial and body hair, and deepening of the voice. These side effects are androgenic in nature, that is, related to male hormones, especially dihydrotestosterone (DHT). The most prevalent side effect of DHEA replacement in women is simply acne, which some women find mild enough to control with a topical lotion.



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Unfortunately, it is very difficult to control the way the body chooses to convert DHEA. In women (but not in men), both testosterone and its stronger form, DHT, usually go up considerably when DHEA is taken; in fact, DHT levels can triple. One solution is to lower the dose. Women naturally produce less DHEA than men, and their replacement dose should be lower than for men. Some holistic physicians recommend no more than 25 mg of DHEA every other day. Men do not seem to have any side effects when taking even large doses of DHEA, although there have been some anecdotal reports of elderly, testosterone-deficient men developing acne. One theory is that in women (i.e. in predominantly estrogenic milieu), the conversion of DHEA is mainly androgenic, while in men (i.e. in predominantly androgenic milieu), it's mainly estrogenic. More research on the metabolism of DHEA is needed before the question of sex differences can be settled.

The repeated finding of improved well-being in women on DHEA replacement is especially interesting in light of the Rancho Bernardo Study findings that low DHEA, but not the deficiency of other sex hormones, correlates with depression in older women. A Japanese study similarly found a significant inverse correlation between mood and DHEA levels, but not between mood and other steroids.

Bone building effects and other benefits

The role of DHEA in helping fight osteoporosis in both men and women deserves special discussion. The bone-density increasing action of DHEA has been explained in terms of its two-fold mechanism: anabolic and anti-osteolytic.

For anabolic (tissue-building) purposes, the bone tissue uses the enzyme aromatase to convert DHEA to estrone. Estrone in turn stimulates osteoblasts, or bone-building cells, to produce more bone tissue. Estrone promotes bone formation in both men and women; testosterone can also be easily converted to estradiol, which is then turned into estrone. The current thinking about sex steroids and bone formation emphasizes the importance of estrogens for both sexes. Ravaglia and Forti, for instance, state, "In contrast to traditional belief, estrogens may be more important than androgens and IGF-1 in male bone metabolism." DHEA is a significant source of estrogens for both men and women. Women in the lowest quartile of estradiol or DHEA-S have been found to have twice the risk of fractures. A French study found that low levels of DHEA-S in women were also related to low muscle strength, independent of age.

IGF-1 is also involved in bone building, and some studies have found a significant positive correlation between the levels of DHEA-S and IGF-1, as well as an increase in IGF-1 with DHEA use. Finally, some studies have shown that DHEA can lower sex hormone-binding globulin, which leads to higher levels of "free" or bioavailable sex hormones.

The anti-osteolytic mechanism derives from the ability of DHEA to inhibit pro-inflammatory cytokines such as TNF and IL-6. The levels of these cytokines increase with age. Pro-inflammatory cytokines cause a release of free radicals, which in turn stimulate osteoclasts (bone-destroying cells) to step up the dissolution of existing bone. By inhibiting cytokines such as IL-6, DHEA is able to slow the process of bone breakdown.

Another established benefit of DHEA is its ability to maintain youthfulness of skin cells. A recent *in vitro* study confirmed that DHEA can increase collagen production while inhibiting its breakdown by the enzyme collagenase. Increased collagen production benefits all connective tissue, including blood vessels and joints. A French study using 50 mg of oral DHEA/day for a year found an improvement in skin thickness, hydration, pigmentation and sebum production, especially in older women.

Overall, the best argument for inclusion of DHEA in hormone replacement regimens stems from its role as a precursor for both androgen and estrogen production in various kinds of tissue, including bone. Primates, including humans, are unique in producing large quantities of adrenal DHEA and DHEA-S. These are converted to androstenedione, and then into other sex steroids according to local need. Postmenopausal women are particularly dependent on the peripheral conversion of precursor hormones for their supply of essential sex steroids. Because DHEA production dramatically drops with age, with a profound drop in women at menopause, women's peripheral tissue may suffer the effects of hormone deficiency especially acutely, unless replacement is provided. Even more important, there is a significant drop in beta endorphins after menopause, with consequent decrease in the sense of well-being. Sufficient DHEA increases beta endorphins and improves mood.

There are even those who favor replacement with DHEA alone (or with DHEA and pregnenolone), arguing that providing hormone precursors is best, and that conversion into estrogens and androgens as needed should be left to the wisdom of the body. A practical advantage of using DHEA (or DHEA combined with pregnenolone) instead of typical hormone replacement for women is that, according to repeated studies, there is no effect on the endometrium-even if the dose of DHEA is large enough to cause changes in the lining of the vagina. Thus, the woman who uses only DHEA need not worry about balancing her estrogen dose with just the right dose of progesterone. Sore breasts are also unlikely. The most typical side effects are androgenic rather than estrogenic: acne and more abundant facial and body hair. Women who are sensitive to the effects of a dramatic rise in androgen levels (chiefly DHT) often drop DHEA after a few months, chiefly due to acne. Many other women, however, find that they have no side effects, and are satisfied with the increased energy, improved sense of physical and mental well-being, and other benefits of DHEA as a postmenopausal hormone replacement. For those women who benefit from DHEA, but produce too much DHT, taking the prescription drug Proscar every other day might be advisable. Proscar inhibits an enzyme (5-alpha reductase) that converts testosterone into excess DHT.

A note of caution should be sounded here: those postmenopausal women who are abdominally obese ("apple-shaped") may be hyperandrogenic and already have high levels of DHEA. High natural levels of DHEA in premenopausal women are not associated with higher risk of breast cancer. High natural DHEA levels in postmenopausal women, however, have been found to raise breast cancer risk (Stoll 1999). Abdominally obese postmenopausal women are known to be at a higher risk of breast cancer, and should not take DHEA supplements unless a blood test indicates a deficiency.

The precautions regarding DHEA and breast cancer risk may be surprising and confusing to those women who remember the first enthusiastic reports about DHEA several years ago. Both *in-vitro* and animal studies appeared to indicate that DHEA actually inhibited the growth of breast tumor cells. Such growth inhibition does take place, but only in the presence of high concentrations of estrogens. When the levels of estrogens are low, DHEA has been found to stimulate tumor growth, possibly through tissue conversion to estradiol and estrone, and possibly also by raising IGF-1, a known promoter of tissue proliferation. Thus, postmenopausal women who wish to take DHEA (or DHEA and pregnenolone) as their sole hormone

replacement are also urged to protect themselves by taking melatonin, palm-oil tocotrienols, indole-3-carbinol (I3C) and vitamin D3.

Women diagnosed with breast cancer and men with prostate cancer should not take DHEA, unless under strict medical supervision.

DHEA may help reduce diabetes damage

Kidneys are one of the organs severely damaged by the high serum glucose characteristic of diabetes. DHEA has been shown to have antioxidant activity that is also protective against lipid peroxidation caused by excess glucose. A recent in-vitro study found that DHEA could reverse glucose-induced impairment of growth in kidney cells, as well as reduce the lipid peroxidation and preserve the cellular reduced glutathione. An animal study done at the University of Louisiana found that DHEA protected the kidneys of diabetic rats against the development of fibrosis in a way that resembled the benefits of calorie restriction.

Essentially the same protective effects were observed in neural tissue, including also the restoration of normal alpha-tocopherol levels and healthy levels of unsaturated fatty acids in cell membranes. Another study found an increase in the antioxidant enzyme catalase in brain tissue treated with DHEA. In liver and kidney tissue, DHEA also raised the levels of reduced glutathione, and enhanced the activity of superoxide dismutase, glutathione-peroxidase and catalase, reducing free radical levels. DHEA was also protective in an animal model of diabetes and stroke: the multi-targeted antioxidant action of DHEA significantly reduced free radical concentrations in the neural tissue. Because DHEA can enhance glucose disposal, it is regarded as a fat-reducing hormone. It is also known to increase resting metabolic rate and lipid oxidation. While not as powerful as growth hormone and testosterone in preventing obesity, DHEA also plays a role. Unfortunately, it seems that it takes pharmacological doses of DHEA to make it work for significant body fat loss in humans.

Cancer prevention

A prospective nested case-control study using serum samples from blood donors in Washington County, Maryland, compared serum DHEA and DHEA-S between 117 cases and controls matched for age, sex and race. The authors found that men in the highest quartile of DHEA-S levels had only about one-fourth (.26) the risk of developing colon cancer compared to men in the lowest quartile. The mean serum DHEA-S concentration of cases (before the cancer diagnosis) was 13% lower than in healthy controls. Statistical significance was not reached, however. Before we can conclude that DHEA-S may protect against colon cancer in men, a larger study needs to be done.

Summary

Overall, previous findings about DHEA continue to be upheld, with more knowledge being gained on various aspects of its benefits. Study after study has found that DHEA can lower levels of tumor necrosis factor alpha (TNF-alpha), thus reducing the damage produced by excess inflammation. It has also been confirmed that DHEA has immunoenhancing properties, and is a promising adjunct therapy not only in chronic inflammatory diseases, but also during various acute bacterial and viral infections, including those that often accompany traumatic injury. The cardioprotective effects of DHEA in males also appear to be reasonably well-established, although we do not fully understand their mechanism.

Maintaining a youthful hormonal balance is an essential part of an anti-aging regimen. This includes trying to maintain youthful levels of DHEA. Unless supplemented, DHEA levels decrease dramatically due to the aging process, with harmful consequences.



DHEA is an important neurosteroid, protecting the neural tissue against various kinds of damage. Nothing is so important in anti-aging medicine as protecting the brain against the ravages of aging. Maintaining the correct ratio of DHEA-S to cortisol appears to be crucial to this protection. It seems to be especially important for diabetics, since DHEA replacement appears to be able to counteract the damage arising from high blood sugar in critical organs such as the brain and the kidneys. But past a certain age, essentially everyone could use more DHEA as protection against Alzheimer's disease and other degenerative brain diseases.

Maintaining a youthful hormonal balance is an essential part of an anti-aging regimen. This includes trying to maintain youthful levels of DHEA. Unless supplemented, DHEA levels decrease dramatically due to the aging process, with harmful consequences such as impaired immune function and more chronic inflammation. DHEA users generally report more energy and an improved state of well-being, as well as greater ability to cope with stress.

Last but not least, stress of all types (emotional, physical, infection-induced, etc.) remains our great enemy, an accelerator of aging. DHEA has been shown to be a versatile anti-stress hormone, an antiglucocorticoid-an antagonist of cortisol, our main "stress hormone." In many ways the action of DHEA is the opposite to that of cortisol. While cortisol is catabolic, causing loss of muscle and bone, DHEA is an anabolic hormone: it helps the body build new tissue. DHEA also protects us against the immune failure due to aging. In particular, maintaining a normal DHEA/cortisol ratio appears to be critical in trying to prevent the degenerative changes of aging.

Some questions about DHEA remain to be elucidated. Large-scale, long-term human studies are needed. Because DHEA is an over-the-counter supplement rather than a drug such as Premarin, getting funding for such studies would be enormously difficult. Nevertheless, evidence from short-term studies has been accumulating. DHEA's anti-stress, immunoenhancing and neuroprotective benefits are not in doubt. In men, the cardiovascular benefits of DHEA also appear to be well established. Due to its multiple benefits, DHEA has a firm place in any anti-aging protocol.