

DHEA - The Next Generation By James South MA

Dehydroepiandrosterone (DHEA), in its sulphated form (DHEA-S), is the most plentiful adrenal steroid circulating in the human bloodstream. Along with the major human glucocorticoid, cortisol, DHEA is produced in the adrenal cortex. DHEA circulates primarily as DHEA-S, which is generally metabolically inactive. As cells take DHEA-S from the blood, they reconvert it into DHEA, and possibly other metabolites. The pregnenolone metabolite, 17-hydroxypregnenolone, is the common parent molecule for both DHEA and cortisol.(2) Humans, along with some other primates, are unique in having adrenals which secrete large amounts of DHEA/DHEA-S.(1) "Adrenal secretion of DHEA and DHEA-S increases in children at the age of 6 - 8 yr, and maximal values of circulating DHEA-S are reached between the ages of 20-30 yr. Thereafter, serum DHEA and DHEA-S levels decrease progressively. In fact, at 70 yr of age, serum DHEA-S levels have decreased to approximately 20% of their peak values, and they further decrease to only 5% [of their peak values] by the age of 85-90 yr. It is remarkable that up to 60% of the age-related decrease in serum DHEA and DHEA-S concentration, however, takes place before the age of 50-60 yr." (1)

There have been literally thousands of scientific articles published on the metabolic and health properties of DHEA during the last 50 years, yet only in the 1990's did a reasonably clear picture of DHEA's role in human health and physiology begin to emerge. Ironically, one of the chief perplexities facing researchers has been the amazingly wide diversity of DHEA's effects. DHEA has been reported to have anti-diabetic, anti-dementia, anti-obesity, anti-carcinogenic, anti-stress, immune-enhancing, anti-viral and anti-bacterial, anti-aging and anti-heart disease effects. (3,4,5). One paper alone lists eight different possible mechanisms of DHEA's "protean physiologic activity," aside from any possible standard steroid-genetic effects. (5) In order to better understand the wide-ranging protective power of DHEA, it will be helpful to survey some recent studies which highlight DHEA's role as "molecular Superman."

IMMUNE EFFECTS

It is in the field of immunology that DHEA has perhaps shown its most broad-spectrum positive action. A recent study found a strong inverse correlation between human serum DHEA-S levels and interleukin 6 (IL-6) levels. IL-6 is one of many cytokines, or immune cell "quasi-hormones," which collectively regulate immune activity. High IL-6 levels are implicated as a causal factor in many diseases, such as rheumatoid arthritis, osteoporosis, B-cell cancers, atherosclerosis and Parkinson's disease. (7) IL-6 levels tend to dramatically increase with aging, just as DHEA-S levels decrease with aging. (6) After studying 120 healthy human subjects, 15-75 years of age, R.H. Straub and colleagues concluded: "decreased DHEA serum concentrations during aging or inflammatory diseases will be paralleled by a significant increase in IL-6 production. Thus, we conclude that the decrease in DHEA levels is a deleterious process, in particular during chronic inflammatory diseases."(7)

In a recent study with eleven postmenopausal women, P.R. Casson and co-workers administered 50 mg DHEA daily in a double-blind crossover study. They reported that "The major finding in this study was the dramatic enhancement in natural killer cell activity. This natural killer cell enhancement was seen in each of the 11 subjects. In this study DHEA appeared to suppress the unexplained increase in stimulated IL-6 production seen in the placebo group" (8) Natural killer cells are a key part of the immune system. They are (ideally) in constant surveillance mode, looking especially for viruses and cancer cells to destroy.

R.A. Daynes and B.A. Araneo have published many articles on DHEA and immunity. In a 1992 brief review paper on natural immuno-regulation, they state: "Our studies support the concept that DHEA may function as important regulators of the mammalian immune system in vivo. The effects of DHEA on T cells are to enhance their ability to produce [immune-activating] IL-2, IL-3, and γ -IFN [gamma interferon]. Such effects only occur if the cells are activated while under the influence of this hormone, and appear to be most prominent in lymphoid [immune] organs that contain the greatest ability to convert the circulating precursor DHEA sulfate to the active metabolite [DHEA]. Replacement therapy [i.e. giving DHEA] should therefore restore normal immuno-competence [that tends to be lost with aging]." (9)

O.Khorram, L.Vu and S.S.C. Yen, long-time DHEA researchers, published an important DHEA study in 1997. Nine healthy "age-advanced men" (mean age: 63) were given 50 mg DHEA daily for 20 weeks after 2 weeks' placebo treatment. They noted that "Our study demonstrates the stimulatory effects of DHEA on the immune function of age-advanced men. DHEA rejuvenated the immune system by increasing the secretion of IL-2, a potent T-cell growth factor, increasing the number of cells expressing the [IL-2 receptor], and enhancing T cell responsiveness to mitogen stimulation. All of which decline during physiologic aging. The significant increase in NK [natural killer] cell cytotoxicity in DHEA treated subjects was potentially related to the increased number of NK cells, both events being mediated by [DHEA-induced] IL-2 stimulation. There were no adverse effects noted with DHEA administration." (10)

H. Danenberg and colleagues reported the ability of DHEA to protect mice from endotoxin (LPS) shock. LPS-endotoxins are released from bacterial cell walls during gram-negative infections, and can cause a high incidence of death from "endotoxic shock." They reported that "Mortality of CD-1 mice exposed to a lethal dose of [LPS-endotoxin] was reduced from 95% to 24% by treatment with a single dose of DHEA, given 5 minutes before LPS." (11)

The preceding represents just the "tip of the iceberg" of a myriad of pro-immune DHEA studies done with humans and animals in recent years, but it should make the point: DHEA has great potential to restore age-degraded immune systems.

DHEA vs. INSULIN

In his recent book *The Anti-Aging Zone*, (12) B. Sears declared age-related increases in insulin levels/insulin resistance to be the chief "pillar of aging." Similarly, Dilman and

Dean in their masterpiece *The Neuroendocrine Theory of Aging and Degenerative Disease* also consider age-related derangements of insulin /glucose metabolism to be a chief culprit of aging and degenerative disease. (13) A growing body of evidence indicates DHEA has a significant role to play in reducing age-related increases in insulin levels, insulin resistance, and blood glucose. In 1995 Jakubowicz, Beer and Rengifo reported their results from a 30 day double blind, placebo controlled study with 22 men (mean age:57), using 100 mg DHEA nightly. Serum insulin decreased from 35.3 to 25.8 mU/ml, while serum glucose declined from 93.4 to 88.9 mg/ml. Serum insulin and glucose did not change significantly in the placebo group. (14)

The P. Diamond group of Quebec, Canada performed a 12 month study with 15 60-70 year old women, using a 10% DHEA cream applied to the skin. "É a 3.8% increase ($P < 0.05$) in femoral fat and a 3.5% increase ($P < 0.05$) in femoral muscular areas were observed at 12 months. These changes in body fat and muscular mass were associated with a 11% decrease ($P < 0.05$) in fasting plasma glucose and a 17% decrease ($P < 0.05$) in fasting insulin levels." (15)

In a 1993 case report study of a 15 year old woman with Type II diabetes, C. Buffington and co-workers reported that a 150 mg twice daily dose of DHEA led to "É a marked improvement in insulin sensitivity, as determined by a more than 30 % reduction in fasting and oral glucose tolerance test insulin levels, a threefold stimulation of the rate of glucose disappearance with intravenous insulin, and a 30% increase in insulin binding. DHEA improved insulin sensitivity and É ameliorated the diabetic state." (16)

G.W. Bates et al gave 15 postmenopausal women (mean age:62) 50 mg DHEA for 3 weeks. They concluded that DHEA supplementation in postmenopausal women may decrease age-related increases in insulin resistance. (17)

P. Casson and colleagues gave 50 mg DHEA to 11 postmenopausal women in a 3-week placebo/crossover double-blind study. They noted, "T-lymphocyte insulin binding and degradation increased with DHEAÉ. Enhancement in T-lymphocyte insulin binding and degradation [is] a previously defined marker of insulin sensitivityÉ." (18)

It should be obvious by now that supplementation of DHEA from early middle age on holds the prospect of decreased insulin levels/ resistance and decreased blood glucose - a key factor to promote healthy aging.

ENERGY AND WELL-BEING

A.J. Morales, S.S.C. Yen and co-workers published in 1994 the results of a 6 month placebo /double-blind crossover trial of 50 mg DHEA daily in 13 men and 17 women, age 40 - 70. One of their key findings was "É a remarkable increase in perceived physical and psychological well-being for both men (67%) and women (84%) É after 12 weeks of DHEA administration, whereas less than 10% reported any change after placebo É. Specific statements of well-being ranged from improved quality of sleep, more relaxed, increased energy, to better ability to handle stress. Of note, there were five subjects who self-reported marked improvements of pre-existing joint pains and mobility during DHEA replacement." (19)

F. Labrie, P. Diamond et al published a further data in 1997 from the 12 month DHEA-skin cream study previously mentioned. While focusing on the anti-osteoporosis, bone-building benefits of DHEA, they also noted: "Well-being and an increase in energy were reported in 80% of all women. Our data also confirm the beneficial effects of DHEA on well-being and energy previously reported [in the 1994 Morales/Yen study]." (1)

In 1996 a group led by C. Berr and E.E. Baulieu (the pioneer of DHEA research) published their epidemiological results from a 4 year study of 622 subjects over 65 years of age living in a small community in France. Among the 356 women assessed, lack of limitation in activities of daily living, lack of confinement to bed or home, lack of dyspnea [shortness of breath], lack of depressive symptoms, self-perceived good health, general life satisfaction and low medication use were all statistically significantly correlated with high mean levels of DHEA-S. Among men (266) only self-perceived good health and low medication use were statistically correlated with high mean DHEA-S levels. Clearly, for the elderly women of this study, high (natural) levels of DHEA-S were strongly correlated with well-being and quality of life. (20)

In a 1999 study, M. Bloch et al used a double blind crossover trial of DHEA to treat 15 patients suffering from midlife dysthymia (minor depression of middle-age onset). There was a 60% improvement during the DHEA phase, while only 20% improvement during the placebo phase. "The symptoms that improved most were anhedonia [lack of joy in daily living] loss of energy, lack of motivation, emotional 'numbness', sadness, inability to cope, and worry". (2)

The authors note that due to lack of correlation between baseline DHEA-S levels and positive therapeutic response "one cannot infer that the mood disorder in any way reflects a deficiency of DHEA." (21) Nonetheless, the study clearly showed the ability of DHEA to significantly enhance energy and well-being in people where that was seriously lacking.

DEMENTIA

Two of the most feared and debilitating impairments of old age are Alzheimer's dementia (AD), and multi-infarct dementia (MID), which is the result of numerous mini-strokes. A growing body of DHEA literature connects low DHEA levels with both AD and MID.

D.Rudman, K. Shetty and D. Mattson published a major study on DHEA and the elderly in 1990. They compared DHEA-S levels in 50 independently-living community men, age 55 - 94 with DHEA-S levels in 61 nursing home men, age 57 - 104. "DHEA was significantly lower in the nursing home men [who were generally more debilitated] than in the community men. Plasma DHEA-S was subnormal (less than 30 mcg/dL) in 40% [25] of the nursing home residents and in only 6% [3] of the community subjects. In the nursing home men plasma DHEA-S was inversely related to the presence of an organic brain syndrome [AD or MID] and to the degree of dependence in activities of daily living. Plasma DHEA-S was subnormal in 80% of the nursing home men who required total care. In total care patients with either [AD] or [MID] the prevalence of low DHEA-S was 68% and 100% respectively." (3)

B. N...sman and co-workers compared 45 AD and 41 MID patients to an elderly control group. They state: "Patients with AD and MID had significantly lower serum DHEA-S values than the control group. The ratio of plasma cortisol to serum DHEA-S was higher in AD and MID patients than in healthy controls. DHEA has been suggested to act as an antiglucocorticoid. A high cortisol/DHEA-S ratio in demented patients may thus damage hippocampal cells [these mid-brain "memory cells" die off in organic dementia] especially - as these neurons are preferentially sensitive to the toxic effects of [cortico]steroids." (22)

T. Yanase and colleagues also found low DHEA-S levels in AD and CVD (cerebrovascular dementia). "We also determined the serum concentrations of DHEA-S in 19 patients with AD, 21 patients with CVD and 45 age and gender matched elderly control individuals. The patients with AD and the patients with CVD were found to have lower concentrations of serum DHEA-S. Interestingly, one preliminary clinical trial based on an intravenous administration of 200 mg a day of DHEA-S for 8 weeks suggested slight and modest improvements in cognition and behavior in patients with AD and CVD, respectively." (2)

H.D Danenberg et al reported findings in 1996 that may help explain a key aspect of DHEA's anti-dementia neuroprotection. "Amyloid b protein (Ab) is the major component of senile plaques, a distinct lesion in brain tissue of AD patients." These toxic amyloid deposits which gradually kill AD brain cells are produced from amyloid precursor protein (APP) by a specific enzymatic pathway - the "amyloidogenic pathway." "DHEA treatment increases APP processing via the nonamyloidogenic pathway and may reverse the [gradual accumulation of toxic Ab proteins] observed in the elderly. The increase in APP production in DHEA-treated cells is accompanied by increased secretion of the nonamyloidogenic [non-toxic protein forms]. These [non-toxic] isoforms demonstrate neuroprotective properties, and participate in neurite outgrowth. Thus, not only is increased production of APP not ultimately [harmful], it may be beneficial when followed by [nonamyloidogenic processing]. It is possible that the age-associated decline in DHEA levels may contribute to the pathological APP processing and eventually to the development of AD." (24)

Thus, there is hope for protecting the structure and function of aging brains through long-term DHEA supplementation.

IGF-1

One of the most exciting results of 1990's DHEA research has been the discovery that it may enhance insulin-like growth factor -1 (IGF-1) release. IGF-1 (formerly called "Somatomedin C") is the "hidden anabolic power behind the throne" of growth hormone (GH). GH stimulates the liver to produce and release IGF-1. It is the IGF-1 that then circulates through the bloodstream and leads to the anabolic (tissue-building) actions GH gets credit for. (19)

The Morales/Yen study previously referred to under ENERGY & WELL-BEING also found significant increases in both men and women in IGF-1 status. "DHEA replacement

induced an approximately 10% rise in serum IGF-1 levels and an approximately 19% decline in IGFBP-1 [IGF-1 binding protein] levels, resulting in an IGF-1/IGFBP-1 ratio by 50% in both men and women." (19) The authors also remark that the increased IGF-1/IGFBP-1 ratios suggest "an increased bioavailability of IGF-1 to target tissues." (19)

Yen, Morales and Khorram conducted a one year double-blind placebo-controlled crossover experiment with 100 mg DHEA with 16 men and women, age 50-65 years. A significant increase in IGF-1 levels occurred in both men and women after 6 months' DHEA treatment, while IGF-1 levels dropped below baseline levels during placebo. Men gained approximately 20% in IGF-1, while women gained about 30% in serum IGF-1. The relative increase in IGF-1 was greater in those with low DHEA-S levels at baseline. (31)

The Jakubowicz study previously mentioned under INSULIN also found a significant increase in IGF-1 from 100 mg DHEA nightly for 30 days. "Serum IGF-1 increased from 96.7É to 183Éng/ml ($p < 0.001$)É. Serum concentration of É IGF-1 did not change in the placebo group." (14)

In the Khorram study previously mentioned under IMMUNE ASPECTS, 50 mg DHEA daily for 20 weeks also led to increased IGF-1. Khorram et al note that "DHEA administration resulted in a 20% increase ($p < 0.01$) in serum IGF-1m a decreasing trend in IGFBP-1, and a 32% increase in the ratio of IGF-1 /IGFBP-1 ($p < 0.01$)." (10) The authors also report a 4-fold increase in the DHEA-S/cortisol ratio. (10) As will become evident shortly, this major increase in DHEA-S/cortisol ratio may hold the key to many of DHEA's diverse benefits.

In 1995 E. Bernton and colleagues reported their results from testing U.S. Army Ranger School trainees during their gruelling training, which included a loss of 8-15% of bodyweight over 8 weeks from intentional caloric deprivation and continuous physical work, limitation of sleep to 4 hours per night, and long exposures to extreme environments.

They reported a decrease in mean salivary DHEA/cortisol ratio from 0.076 to 0.041 ($p < 0.001$), and a mean decrease of serum IGF-1 of 60% during Ranger training, while GH increased 4-fold, "reflecting a dissociation of growth hormone from IGF-1 secretion, attributable in part to negative [food] energy balance and high cortisol levels É. In vivo, IGF-1 levels are therefore increased by glucocorticoids [i.e. cortisol] and increased by É DHEA É. We hypothesize that tissue ratios of DHEA to cortisol may regulate IGF-1 secretion in stressed individuals such as ranger trainees." (25)

DHEA: NATURAL COUNTER-REGULATOR OF CORTISOL

The emphasis on the DHEA/cortisol ratio as a key health determinant is hardly unique to the Army Ranger and Khorram studies just described. Most of the papers I reviewed to prepare this article specifically mention DHEA's anti-glucocorticoid (i.e. anti-cortisol) action and/or the DHEA/cortisol ratio as key factors in DHEA's benefits. The following assessment by Regelson and Kalimi, veteran DHEA researchers, is somewhat typical of

the DHEA literature: "Among the myriad of biological actions, the anti-glucocorticoid properties of DHEA are now clearly emerging. In fact the anti-glucocorticoid action of DHEA may explain many of the seemingly diverse biological activities of DHEA, such as its effects on stress, obesity, diabetes, immune response and protection against acute lethal viral infections."

In fact, even Regelson and Kalimi's enumeration of areas of biological effect of the antagonistic action of DHEA and cortisol does not go far enough. I listed 14 of the key properties of cortisol (excess) action - i.e. its "dark side." [Refer to Table 1.] As can be seen from Table 1, DHEA has actions opposite to cortisol in all 14 areas listed. It thus becomes obvious that one of the key functions of DHEA is to serve as a counter-regulator to cortisol - to "put the brakes on the cortisol gas pedal," as it were - so that cortisol's catabolic (tissue-destroying) actions do not get out of control. And since cortisol tends to remain constant or increase with age (cortisol also increases dramatically with severe/prolonged stress), while DHEA drops dramatically with age/stress, it is obvious that there is a general life-long, progressively worsening failure of DHEA to oppose the catabolic excesses of cortisol.

B. Sears calls excess cortisol the "second pillar of aging", (12) while Dilman and Dean also focus on the general age-related failure of human physiology to control cortisol levels. (13)

Thus, it should be clear that maintaining a lifelong high DHEA /low cortisol ratio is a key anti-aging strategy. And the simplest way to maintain high blood levels of DHEA from the 30's onwards is through DHEA supplementation.

DHEA SUPPLEMENTATION: POSSIBLE CONCERNS

The biggest concern over DHEA supplementation repeatedly raised in the DHEA scientific literature is the issue of androgen/estrogen production from DHEA. Various tissues can locally convert DHEA to either androgens (testosterone, dihydrotestosterone, androstenedione) or estrogens (estrone, estradiol). Many DHEA studies report significant androgen increases in women, even at the relatively low dose of 50 mg. (1, 8, 18, 19, 21) Increased androgen levels in women may relate not only to the mild effects of excess facial hair and acne, but to the more serious issues of abdominal obesity, hyper-glycemia and insulin resistance. (26) And one report found a decreased testosterone level in men, combined with an increase in estradiol, hardly ideal for a man's health. (21) Fortunately, a natural metabolite of DHEA, normally found in the human body, and which cannot be bio-transformed into androgens or estrogens, (28) is now available. And preliminary evidence indicates this "new" DHEA metabolite may be even more potent than DHEA.

7-KETO - DHEA TO THE RESCUE!

7 - keto - DHEA (7KD) (also called "7 -oxo-DHEA,") is almost identical in structure to DHEA (see Diagram 1). Human skin (and other tissues) contain enzymes that convert DHEA to 7KD in a two-stage process. (27) (Interestingly, many animal experiments with DHEA get best results if the DHEA is given subcutaneously, hinting at skin DHEA bio-processing.) Research into 7KD has been conducted primarily by Dr. Henry Lardy and

associates at the University of Wisconsin. (28, 29, 30) Based on his research, Lardy has been granted various patents on the use of 7KD, including immune enhancement/modulation, Alzheimer's treatment and weight loss.

"7-keto-DHEA has been evaluated in both preclinical studies and human clinical trials for safety. These studies show no mutagenic activity and no adverse effects for 7-keto-DHEA up to doses of 2000 mg /kg in rats and 500 mg /kg in primates. It should be noted that 500 mg /kg is É 3.5 grams in a normal 70 kg human." (30) Zenk notes that a clinical trial conducted to measure the effects of 7KD on several endocrine and safety parameters in healthy adult men found 7KD to be safe and well-tolerated at doses up to 200 mg/day of a 28-day period. (30) Zenk also reports that laboratory safety tests also showed 7KD does not affect haematology, serum chemistry, or urine chemistry differently than healthy subjects taking placebo. (30)

Lardy has found that 7KD (7-oxo-DHEA) is a potent increaser of liver thermogenic enzymes. He reports that "The 7-oxo-derivatives of both DHEA [i.e. 7KD] and androstenediol are the most active compounds tested. over the range of 0.01 to 0.1% of the diet, 7-oxo-DHEA was 2.5 times as active as DHEA." (28) Research at the University of Wisconsin found 7KD helpful in treating primates infected with Simian Immunodeficiency Virus (SIV). CD-4 (T helper) cell counts, CD-8 cell counts, and total white blood cells increased. The SIV-infected primates also showed improvements in their physical state, increased weight, and overall improvement in behavior and clinical condition. (30)

7KD was also shown to increase IL-2 production better than DHEA, in human lymphocytes. IL-2 is the key cytokine regulator of T-helper cells, along with interferon-gamma, which activates the immune system to "go into battle" against invading pathogens. (30) Lardy and colleagues also found 7KD to enhance memory in 2-year old mice. "The mice were trained to negotiate a water maze and then were given DHEA or 7-keto DHEA É. They were retested after two weeks. The control mice took 34 seconds [to negotiate the maze]; those on DHEA took 22 seconds; and those on 7-keto-DHEA took only 7.6 seconds.

Dr. Lardy found similar results in mice using scopolamine to abolish memory. When protected with 7-keto DHEA [and given anti-memory scopolamine] the mice were able to negotiate the water maze in 6.5 seconds, compared to 11.5 with DHEA treatment and 22 seconds with scopolamine treatment only." (30)

7-KETO DHEA: A PERSONAL COMMENT

I have been interested in DHEA since 1984. However, my personal experience with DHEA was disappointing. I found DHEA to induce a severe depression after only 1 - 3 doses. I retried DHEA about a dozen times between 1984 to 1996, always getting the same rapid-onset depression. I talked to a doctor colleague, who reported that she had the same response to DHEA, and that some 5-10% of her patients who tried DHEA also experienced a relatively rapid onset of depression (1 - 10 days). I began taking 7KD in the fall of 1998, hoping for a different response. Much to my surprise, I found 7KD

experientially very different from DHEA. I have been taking 7KD for about 18 months now, gradually reducing my dose from 25 mg/day to 10-15 mg/day. I have found 7KD to be an energy enhancer, anti-cortisol stress reducer, and general revitalizing agent. I have gradually dropped 20 pounds of weight, have experienced a significant thinning of my face away from the classic cortisol "moon face" I was developing in recent years. I consider 7KD one of my core anti-aging supplements. I have also used 7KD to quickly revive 2 cats traumatized from combined surgical/anaesthesia/vaccine stress. My wife finds 7KD to be the single most energizing supplement she's ever taken.

DHEA/ 7-KETO DHEA: DOSAGES

For those wishing to get the potential androgenic benefits of DHEA, extremely low doses are advised. 10-25 mg /day for women, 20-40 mg/day for men. Anyone suffering any serious disease or hormonal condition should only use DHEA under competent medical supervision. 7KD may be effective at doses as low as 5-10 mg/day, with 25-50 mg/day being probably adequate for all but medical use in disease treatment under medical supervision.

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