Dhea Restoration

The natural steroid hormone dehydroepiandrosterone (DHEA) was first introduced to Life Extension supporters four decades ago at a time when the medical community was largely unaware of the scientific data supporting this hormone's multifaceted benefits. Fast forward to today, when more than 3700 papers have evaluated the scientific effects of DHEA upon many different cells and tissues of the body. This multifunctional hormone and its metabolite dehydroepiandrosterone sulfate (DHEA-S) provide critical hormonal benefits in both men and women (Traish 2011; Savineau 2013). As a precursor to androgens (male hormones) and estrogens (female hormones), DHEA plays a fundamental role in the maintenance of hormonal balance and youthful vitality. It also modulates a variety of pathways throughout the body involved in various aspects of health and disease via direct actions independent of its role as a precursor to androgens and estrogens (Samaras 2013; Traish 2011; Savineau 2013).

Aging disrupts hormonal balance, with the levels of several critical hormones dramatically reduced in comparison with youthful levels, and DHEA is no exception. By age 80, levels of DHEA fall by as much as 80%–90% compared to what they were during young adulthood (Samaras 2013). The gravity of this becomes clear after understanding the roles DHEA plays in supporting healthy, youthful physiology across several body systems. Studies have shown that reduced levels of DHEA-S are linked with the pathophysiology underlying numerous age-associated disease states, including cognitive decline, cardiovascular disease, bone loss, cancer, depression, sexual dysfunction, and various inflammatory disorders (Samaras 2013; Traish 2011; Savineau 2013; Dong 2012; Zaluska 2009; Labrie 2009; Straub 2000; Krysiak 2008; Lopez-Marure 2011).

Restoring youthful DHEA levels provides a unique opportunity to mitigate the consequences of dwindling hormones. Unlike direct administration of androgens (ie, testosterone replacement therapy) or estrogens (ie, estrogen replacement therapy), bolstering DHEA levels provides a "reservoir" of this hormone precursor that various tissues can convert into androgens and estrogens (Traish 2011; Arlt 1998; Morales 1994; Aldred 2010; Samaras 2013; Panjari 2007). However, DHEA administration cannot supplant the need to measure and restore other hormones because the rate at which it is converted to androgens and estrogens varies among individuals and with gender (Samaras 2013; Arlt 1999; Schulze 2013; Fitzpatrick 2001; Miller 2004). Therefore, restoring DHEA levels should be viewed as an integral part of a comprehensive hormone restoration regimen rather than an alternative to testosterone replacement in men and estrogen replacement in women.

In addition to its role as a hormone precursor, DHEA also modulates inflammation, which is a driving force in many diseases. This multifunctional hormone also promotes the production of the cell-signaling molecule nitric oxide within the delicate lining of blood vessels by activating an enzyme called endothelial nitric oxide synthase (eNOS). Nitric oxide is a pivotal regulator of blood flow via its ability to stimulate blood vessel dilation. Thus, it is not surprising that low DHEA levels have been linked to cardiovascular disease in the medical literature (Samaras 2013; Traish 2011).

Upon oral administration, DHEA is mostly converted to DHEA-S, which circulates in the blood far longer than DHEA. Circulating DHEA-S acts as a reserve upon which tissues can draw. Once taken up by tissues, DHEA-S is converted back to DHEA, which can then be locally converted to androgens and estrogens or exert direct action (Samaras 2013; Traish 2011).

Since DHEA-S is more abundant in the bloodstream than DHEA (Traish 2011; Savineau 2013), simple blood tests to measure DHEA-S concentrations can be integrated into any healthy aging strategy for both men and women. With regular monitoring of blood levels of DHEA-S and other hormones, individuals are provided with specific feedback about the state of their hormonal milieu (Traish 2011). This allows for development, implementation, and optimization of individualized regimens that can help maturing individuals lead full, active, healthy lives (Samaras 2013).

Bioidentical hormone replacement therapy is a method of administering hormones that are structurally identical to those

produced by the human body. Treatment with DHEA, which is also bioidentical, is an integral component of any comprehensive hormone restoration regimen. On the other hand, some forms of conventional hormone replacement therapy utilize hormones that are not identical to those produced by humans and are either derived from animals or synthesized. Evidence suggests that bioidentical hormone replacement therapy may be safer and associated with greater patient satisfaction than conventional hormone replacement therapy (Holtorf 2009). Life Extension's Male Hormone Restoration and Female Hormone Restoration protocols provide a thorough overview of bioidentical hormone replacement therapy and should be referred to in conjunction with this protocol.

DHEA: Background and Biology

The human body derives DHEA from cholesterol via two enzymatic reactions. First, cholesterol is converted into pregnenolone, which is sometimes referred to as "the master hormone" due to its role as a precursor to the hormonal cascade that eventually gives rise to the primary sex hormones testosterone and estrogen. Next, pregnenolone is converted into DHEA (Traish 2011; Samaras 2013; Savineau 2013).

The primary location for DHEA production is the outer layer of the adrenal glands, called the adrenal cortex; some other tissues such as the testes in men and ovaries in premenopausal women also produce DHEA, but to a much lesser extent. Production of DHEA peaks in the 2nd to 3rd decade of life. Thereafter, levels decline steadily with age (Traish 2011; Samaras 2013).

Up to the early 2000s, much of the research on DHEA focused on its role as a precursor to androgens and estrogens. However, more recent investigations revealed several biological actions mediated directly by DHEA. Studies have shown that specialized receptors on cellular membranes in the blood vessel lining (endothelium), heart, kidney, and liver interact directly with DHEA (Samaras 2013; Traish 2011). For example, one significant androgen- and estrogen-independent action of DHEA is the activation of an enzyme in blood vessels called endothelial nitric oxide synthase (eNOS), which produces the potent vasodilator nitric oxide (NO) that is important for healthy vascular function (Samaras 2013; Traish 2011; Liu 2002; Liu 2004; Simoncini 2003).

Effects of DHEA

DHEA in Mood and Brain Health

Although adrenal glands produce the majority of DHEA, it can also be produced by the brain (Lazaridis 2011). Moreover, levels of DHEA in the central nervous system (CNS) are 6–8 times higher than in the blood (Traish 2011). This has led several researchers to classify DHEA as a "neurosteroid" (Lazaridis 2011; Baulieu 1998). DHEA has been shown to modulate the release and signaling of neurotransmitters in various brain regions. It is therefore not surprising that DHEA has garnered interest for certain health conditions involving the brain, such as depression and anxiety (Traish 2011; Samaras 2013; Dong 2012).

As humans age, cognitive function and memory typically become impaired. This corresponds with an age-related reduction in levels of brain neurosteroids. Likewise, some neurodegenerative diseases such as Alzheimer's disease have been linked to declining neurosteroid levels (Aldred 2010; Charalampopoulos 2008). It is thought that age-related decline in DHEA may compromise neuronal function and integrity (Charalampopoulos 2008).

Several studies have revealed a relationship between DHEA and cognitive function in a variety of settings. A study that followed 755 older individuals for 3 years found that DHEA-S levels declined in tandem with cognitive function as measured by the Mini Mental State Examination (MMSE), a standardized assessment of cognition. Moreover, subjects who scored better on their baseline MMSE were more likely to have higher DHEA-S levels than their counterparts who scored more poorly, and having a lower DHEA-S level at baseline was predictive of larger declines in cognitive function over the study

period (Valenti 2009). In another study on 24 healthy young men, DHEA dosed at 150 mg twice daily for 7 days resulted in an improvement in mood and memory. This study also found that DHEA supplementation reduced evening levels of cortisol, which is a hormone released in response to stress (Alhaj 2006). A separate double-blind, placebo-controlled study that enrolled 24 postmenopausal women found that 50 mg of DHEA daily led to improved visual-spatial performance as measured by several standardized tests. The researchers also found that higher levels of DHEA and its metabolites correlated with better performance on visual-spatial tasks (Stangl 2011). A study conducted on 27 women aged 65–90 living at an assisted-care facility in Japan found that supplementation with 25 mg of DHEA daily for 6 months led to improved cognitive scores in the subjects allocated to active treatment, whereas cognitive function deteriorated in those who received a placebo (Yamada 2010).

One way DHEA may modulate cognitive function in certain populations is by preserving the production of several neuroprotective factors such as IGF-1 (insulin-like growth factor-1), VEGF (vascular endothelial growth factor), and TGF-β (transforming growth factor-beta). A laboratory study measured levels of these neuroprotective factors produced by cells taken from subjects with mild to moderate Alzheimer's disease and compared the results to samples taken from healthy, age-matched controls. The scientists found that Alzheimer's patients' cells produced significantly diminished amounts of these neuroprotective growth factors compared to healthy cells. However, when the Alzheimer's patients' cells were incubated with DHEA-S, the production of growth factors returned to levels similar to those seen in healthy control cells. The authors remarked *"These data suggested that DHEA-S is able to increase the … production of neuroprotective growth factors … suggesting a new approach in the treatment of dementia*" (Luppi 2009).

In addition, DHEA may exert neuroprotective action by countering the deleterious effects of glucocorticoids (eg, cortisol) in neurons. This is an important consideration in the context of mood disorders since elevated glucocorticoids are associated with psychiatric conditions such as social anxiety and depression (Herbert 1998). Indeed, research has linked depression with a low serum DHEA concentration in adult, senior, and adolescent populations (Wong 2011; Herbert 1998; Yaffe 2008; Zaluska 2009). DHEA supplementation is also associated with reduced anxiety and improved response to anti-psychotic medications in schizophrenics (Ritsner 2011; Strous 2005). In middle-aged adults, DHEA (90 mg daily for 3 weeks and then 450 mg daily for 3 weeks) improved dysthymia, a chronic, low-grade depressed mood (Bloch 1999). Supplementation with 50 mg of DHEA daily for 6 months in advanced-aged men and women improved psychological well-being (Morales 1994). Another study found that DHEA, dosed at 100–400 mg daily for 8 weeks, alleviated non-major, persistent depression in HIV/AIDS patients (Rabkin 2006). Restoration of DHEA levels may also support mood when pituitary function is suboptimal. DHEA replacement at 50 mg daily led to long-term improvements in psychological well-being in both male and female hypopituitary patients on growth hormone replacement therapy (Brooke 2006).

DHEA and Bone Health

Although often thought of as only affecting women, osteoporosis affects the lives of men. Millions of men in the United States are affected by osteoporosis or low bone mass, and that number is likely to grow as the population ages (Cawthon 2011; Kawate 2010; Nuti 2010). In addition, evidence suggests that postmenopausal women with low bone-mineral density have lower DHEA-S levels compared to postmenopausal women with normal DHEA-S levels. In fact, a Czech study found low bone-mineral density to be present in 86% of women whose DHEA-S levels fell into the lower quarter of distribution, whereas a rate of about 30% was predicted for healthy postmenopausal women (Fingerova 1998). Bone-mineral density is largely regulated by 2 cell types: osteoblasts, which build bone, and osteoclasts, which break down or resorb bone. DHEA promotes osteoblast activity and suppresses osteoclast-mediated bone breakdown. It appears to accomplish this both by being converted into estrogen, which stimulates osteoblastic activity, and via androgen- and estrogen-independent mechanisms (Adachi 2006; Wang 2012).

Bone tissue is especially responsive to hormonal modulation. Therefore, age-related decline in hormone levels, including DHEA, has considerable implications for both men and women with regard to bone health (Corina 2012; Weiss 2009). DHEA and other androgen hormones play a pivotal role in the bone building process; thus, declining DHEA levels may compromise bone metabolism and promote osteoporosis (Adachi 2006; Samaras 2013). DHEA has been shown effective for

treating osteoporosis at a dose of 50 mg daily over the course of 1 year in otherwise healthy older women by increasing bone mineral density of the lumbar spine. DHEA was also shown to decrease serum C-terminal telopeptide of type-1 collagen, a marker for bone turnover (Okuno 2005; von Mühlen 2008). In another study, women aged 65–75 who were given 50 mg of DHEA daily along with 650 IU of vitamin D and 700 mg of calcium displayed a 3.6% increase in spinal bone-mineral density after 2 years of treatment (Weiss 2009).

Refer to the Life Extension protocol on Osteoporosis for a comprehensive overview of strategies to support bone health.

DHEA and Cardiovascular Health

The decline of DHEA-S associated with aging may contribute to vascular disease and the risk of cardiac events, especially among post-menopausal women (Shufelt 2010). In men, decreased DHEA-S levels appear to be associated with a higher risk of diabetes and coronary heart disease (Ponholzer 2009). Observational studies have also shown that as DHEA-S levels decline, cardiovascular disease rates rise (Mitchell 1994).

DHEA supplementation has been shown to improve cardiovascular health. Short-term treatment with DHEA in healthy elderly subjects appears to increase the production of NO, decrease low-density lipoprotein (LDL) cholesterol, and increase testosterone levels (Martina 2006). DHEA was also found to inhibit the inflammatory process in the innermost cell layer of blood vessels (the endothelium) (Li 2009). Obese women given 100 mg of DHEA-S over 3 months saw a shift in fatty acid balance whereby saturated fats in their blood were decreased, thus indicating a healthier metabolic profile (Gómez-Santos 2012; Gómez-Santos 2011).

Additionally, DHEA may support the healthy remodeling of vascular tissue following injury (Ii 2006). Among women undergoing a cardiovascular procedure (ie, coronary angiography), those whose DHEA-S levels fell into the bottom one-third of distribution were more likely to die from any cause than women whose DHEA-S levels were in the upper two-thirds of the distribution over 6-years of follow up time. Specifically, while 21% of the women whose DHEA-S levels were in the bottom one-third of distribution died during follow up, only 10% of women in the top two-thirds of the distribution for DHEA-S levels died. This evidence suggests a further protective role of DHEA in heart disease (Schufelt 2010). Animal studies further suggest that DHEA exerts a favorable effect on vascular remodeling (Dumas de la Roque 2010).

DHEA and Blood Sugar Regulation

DHEA appears to increase insulin sensitivity and combat insulin resistance. Insulin resistance is an early indicator of type-2 diabetes and is closely linked with obesity, both of which are major risk factors for heart disease (Basat 2006; Steinberger 2003). DHEA has been shown to have a protective role against diabetes (Heurta-Garcia 2011). In fact, one study showed that taking 50 mg of DHEA for 1 year improved insulin response, as seen by the oral glucose tolerance test, with further improvement after 2 years among participants whose glucose tolerance was impaired at the beginning of the study (Weiss 2011). Another study showed that 50 mg of DHEA daily taken over 6 months led to a trend toward reduced insulin resistance (Talaei 2010). The combined results of these studies may suggest that longer-term administration may be required to see significant changes in insulin resistance.

Another group of researchers found that women with potentially impaired adrenal function exhibited improved insulin sensitivity after daily supplementation with 50 mg of DHEA over 12 weeks (Dhatariya 2005). A separate study found low DHEA-S levels in 77% of type-2 diabetic men with coronary artery disease. When low DHEA-S were combined with three other risk factors (testosterone deficiency, elevated high-sensitivity C-reactive protein [hs-CRP], and high plasma N-terminal pro-B-type natriuretic peptide [NTproB]), the risk for cardiovascular mortality jumped a staggering 63-fold above healthy control subjects (Ponikowska 2009). Other evidence suggests that DHEA protects against blood vessel damage induced by high concentrations of glucose (Huerta-Garcia 2011). Elevated blood sugar can cause damage by driving oxidative stress and the formation of dysfunctional proteins via a process called glycation. As shown by a study conducted on 20 subjects with type-2 diabetes, supplementation with 50 mg of DHEA daily for 12 weeks improved the oxidative imbalance induced by

high blood sugar levels and prevented advanced glycation end-product (AGE) formation. These findings indicate that DHEA may exert a beneficial effect on the onset and/or progression of chronic complications in type-2 diabetic patients (Brignardello 2007).

See the Life Extension Weight Loss protocol for further discussion.

DHEA and Immune Function

Another important role of DHEA is to counter the actions of cortisol (the “stress hormone”) in the context of the immune system. While DHEA enhances immunity, cortisol suppresses it (Butcher 2005; Buford 2008). This is particularly significant for aging individuals, since advancing age is associated with a decrease in the DHEA:cortisol ratio (Buford 2008). In other words, aging individuals are exposed to more unopposed immunosuppression by cortisol than younger individuals, potentially increasing their risk of infection (Butcher 2005).

In fact, it is thought that age-associated DHEA deficiency, resulting in an imbalance between DHEA and cortisol, may be partially responsible for the decline in immune function common among the elderly (Butcher 2005; Buford 2008; Roxas 2007). In general, the immune system decreases in function as we age. This is known as immunosenescence. Similarly, the decline of hormone production due to the loss of function of multiple glands (including the adrenal cortex) is known as endocrinosenescence (Buford 2008). In the elderly, 50 mg of DHEA daily may enhance the immune system and potentially prevent some common infections (Roxas 2007).

DHEA and Skin

DHEA has been shown to function as an antioxidant and anti-inflammatory agent in skin (Puizina-Ivic 2010; Chan 2013), and decreases in DHEA have been linked to skin atrophy and increased skin aging (El-Alfy 2010; Labrie 2010). Topically administered DHEA could exert an anti-aging effect in the skin through stimulation of collagen biosynthesis and improved structural organization of the dermis, the layer of tissue directly under the surface of the skin (El-Alfy 2010; Calvo 2008). Through topical administration of a 1% formula of DHEA to postmenopausal women over 4 months, study participants experienced increased sebum production, which contributes to the suppleness of skin (Noveau 2008).

DHEA and Sexual Function in Men and Women

A considerable body of research has examined the relationship between DHEA and sexual health, especially among women. Aside from the increased risk of osteoporosis and heart disease as women age, sexual function and interest tends to decline as well (Yasui 2012). DHEA has been shown to improve virtually all aspects of sexual function including desire, arousal, activity, interest, and drive (Traish 2011). One study found that DHEA administered vaginally in postmenopausal women with moderate-to-severe symptoms of vaginal atrophy exerts beneficial effects on several important aspects of sexual function including arousal/sensation, lubrication, and orgasm (Labrie 2009). Another study found that daily oral DHEA therapy at the dose of 10 mg led to a significant improvement in sexual function and frequency of sexual intercourse in healthy postmenopausal women (Genazzani 2011). DHEA has been shown to benefit men’s sexual health as well (Traish 2011). Impotent men given 50 mg of DHEA daily for 6 months experienced improved sexual function, but not increased PSA, testosterone, prolactin, or prostate volume (Reiter 1999).

DHEA and Weight Loss – Focus on 7-Keto® DHEA

7-Keto® DHEA is a metabolite of DHEA that is not converted into testosterone or estrogen but does possess prohormonal properties (Worrel 2011; Amato 2012). 7-Keto® DHEA appears to increase basal metabolic rate and thermogenesis (ie, the conversion of stored energy into heat in the body) (Bobyleva 1997; Ihler 2003; Hampl, Starka 2006). Greater basal metabolic rate and thermogenesis lead to reduction in energy stores (ie, body fat). In one study, resting metabolic rates were increased

3.4% in overweight adults using a combination formula containing 50 mg of 7-Keto® DHEA along with calcium citrate, green tea extract, vitamin C, chromium, and vitamin D3 (Zenk 2007). Moreover, DHEA and its metabolites counteract the actions of cortisol, a catabolic stress hormone associated with greater fat accumulation (Moyer 1994; Abraham 2013; Muller 2006; Hennebert 2007; Marin 1992; Buoso 2011). In healthy men, 7-Keto® DHEA has been shown to be safe at doses of up to 200 mg/day for 4 weeks (Davidson 2000).

DHEA in Inflammation and Autoimmunity

As humans age, the immune system weakens. One of the possible consequences of this progressive aging of the immune system is an increased incidence of certain cancers and predisposition to infections (Ramos-Casals 2003). DHEA modulates several aspects of the immune system. In elderly men, cytokine production and the function of T-cells, B-cells, NK cells, and monocytes appear to be improved by DHEA (Khorram 1997). The inflammatory markers interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), both of which are elevated in patients with chronic inflammation or inflammatory diseases, appear to be positively influenced by DHEA (James 1997; Straub 1998; Straub 2002; Leowattana 2001). In an experimental study, immune cells were taken from asthmatic patients and treated with DHEA. The scientists found that DHEA suppressed the release of inflammatory mediators by these cells and reduced their hyperreactivity (Choi 2008).

In addition, research suggests restoring optimal DHEA levels may act as an immunomodulator in certain situations (Hazeldine 2010). One study revealed that DHEA and certain metabolites were decreased in female subjects with autoimmune hypothyroidism (Drbalová 2008). Another study found that DHEA-S was decreased in a group of female type-1 diabetics (Simunkova 2010). In systemic lupus erythematosus, DHEA led to a clinically significant improvement in quality of life according to a comprehensive review of several studies (Crosbie 2007). In adult women, treatment of lupus with DHEA (200 mg daily) caused a 16% decrease in the number of patients with flares, and daily doses of 50-200 mg DHEA were clinically beneficial (van Vollenhoven 1998; Chang 2002).

DHEA and Frailty Prevention

Some studies have looked at the decline in DHEA in the elderly as a primary marker of aging. One such study found that declines in DHEA were consistent with declines in quality of life markers, such as gait speed, mental status, and neuropsychological scores in women. Fundamentally, aging women with the highest levels of DHEA-S performed best on these tests. Thus, measuring DHEA-S blood levels may represent a simple way to help determine an individual's rate of aging (Sanders 2010).

Falling and bone fractures are a significant concern for the aging population. DHEA may be able to help in this regard. In a 6-month trial, women with low DHEA-S, low bone mineral density, and frailty were given 50 mg/day of DHEA (along with vitamin D and calcium) and performed 2 gentle exercise routines per week. At the end of the trial, lower extremity muscle strength and function were improved (Kenny 2010). In March of 2010, William Davis, MD wrote an article in Life Extension Magazine titled *Don't Fall Victim to Frailty: Evidenced-based strategies for lifelong power in aging individuals*. In the article, Dr. Davis brought to light several pieces of evidence including the use of DHEA in improving aspects of physical function and well-being (Davis 2010; Morales 1994).

DHEA and Longevity

Numerous scientific studies have found that declining DHEA levels are associated with greater likelihood of death due to a variety of causes:

- In a study on 270 women suspected of having reduced blood flow to cardiac muscles, subjects whose DHEA-S levels fell within the bottom one-third of distribution were 11% more likely to die from any cause over a 9-year follow-up period compared to women whose DHEA levels fell into the upper two-thirds of distribution (Shufelt 2010).

- In another study in which 242 men aged 50 to 79 were followed for 12 years, having a DHEA-S level below 140 µg/dL was associated with a 3.3 fold risk of death from cardiovascular disease compared to higher levels. Moreover, an increase of 100 µg/dL in DHEA-S was associated with a 36% reduction in risk of death from any cause, even after adjustments were made for a number of confounding factors (Barrett-Connor 1986).
- Researchers from the University of Cambridge followed 963 men for up to 9 years and found that as circulating DHEA-S levels increased above the lower one-fourth of distribution, the risk of death from any cause decreased by about 30% (Trivedi 2001).
- In a study on men undergoing dialysis for chronic kidney disease, low plasma DHEA-S levels were associated with a roughly 2.9-fold risk of death due to any cause compared to higher levels after adjustment for potential confounding factors (Hsu 2012).
- A similar study on 313 men undergoing dialysis corroborates the finding that lower DHEA-S levels predict increased mortality in this population (Kakiya 2012).
- In a study that followed 2644 men from Sweden for an average of 4.5 years, men whose DHEA-S levels fell within the lower one-fourth of the distribution were 54% more likely to die during follow up compared to men with higher DHEA-S levels, even after the researches adjusted the findings to account for variables that could influence the results (Ohlsson 2010).
- An analysis of 4255 Vietnam-era U.S. army veterans revealed that higher DHEA-S levels were associated with a 49% reduced likelihood of death over a 15-year follow-up period (Phillips 2010).
- A long-term study that followed 940 subjects for 27 years found that men whose DHEA-S levels were greater than 200 µg/dL had were significantly less likely to die during the study period than men whose levels were lower (Enomoto 2008).
- A 3-year study among 963 older Taiwanese individuals revealed that having a DHEA-S level less than 54.5 µg/dL was linked to a 64% greater risk of death during the study period than having higher levels (Glei 2006).
- French researchers studied 290 subjects over a 10-year period and found that risk of death increased 1.9 fold among men with low DHEA-S level compared to those with high levels; this was especially true among men 65 – 69 years of age, where the magnitude of the risk was 6.5 fold (Mazat 2001).
- In another study in which 123 heart-attack survivors were followed for up to 10-years, low DHEA-S levels were found to be predictive of death due to cardiovascular disease (Jansson 1998).
- In a group of 622 individuals older than 65 who participated in a French community-based study, low DHEA-S levels were strongly linked to greater risk of death over 2 and 4 years in men (Berr 1996).
- In another study, when low DHEA-S were combined with three other risk factors (testosterone deficiency, elevated high-sensitivity C-reactive protein [hs-CRP], and high plasma N-terminal pro-B-type natriuretic peptide [NTproB]), the risk for cardiovascular mortality jumped a staggering 63-fold above healthy control subjects (Ponikowska 2009).

Interestingly, in addition to the overall level of DHEA-S, some evidence suggests that the rate at which it declines with age may independently influence longevity. In one study on 950 individuals 65 or older, those whose DHEA-S levels declined on a steeper trajectory were 75% more likely to die during the study period than subjects whose DHEA-S level declined more slowly. These findings were in spite of the fact that baseline DHEA-S were not associated with mortality in this study (Cappola 2009).

DHEA and Cancer Risk

Because DHEA may increase sex hormone levels, concerns have been raised about its use in people who have or had hormone-related cancers. To date, no study has convincingly shown an increase in human hormone-dependent cancer risk as a result of DHEA or pregnenolone supplementation (Trevano 2011; Krysiak 2008; Traish 2011). In July 2011, Life Extension Magazine addressed this issue in the article *State of California Decrees Strong Warning Labels on DHEA and Pregnenolone* as follows.

> Both pregnenolone and DHEA are “parent” hormones of the sex hormones estrogen, progesterone, and

testosterone. Taking pregnenolone or DHEA supplements, therefore, may indeed raise levels of those sex hormones; in fact, that is considered one of the desired effects. Mainstream physicians, however, continue to express concern about boosting sex hormone levels late in life, citing the theoretical risk of hormone-dependent malignancies such as breast and prostate cancers (Trevano 2011).

The truth, as always, is more nuanced. Important work by Harvard urologist Abraham Morgentaler and others has revealed that low testosterone levels may increase prostate cancer risk, although this is a controversial concept. Morgentaler himself has become a strong proponent of supplementation with testosterone in older men. He was also the lead researcher on a study demonstrating that DHEA supplementation in rats enhanced total testosterone levels without producing any deleterious changes in prostate tissue (Trevano 2011; Rhoden 2003).

Similar theoretical risks apply for breast cancer. But no increased risk of breast cancer has been demonstrated in large studies of combinations of natural estradiol and progesterone (the natural products of DHEA and/or pregnenolone). Furthermore, natural progesterone alone may reduce cancer risk, again suggesting that boosting sex hormone levels with precursors such as DHEA and pregnenolone is safe. One recent animal study demonstrates a direct anti-cancer effect of DHEA in obese rats (Trevano 2011; Hakkak 2010).

Any individual who is known to have cancer of any kind should consult with his/her physician when using any new supplement or medication (Trevano 2011).

Life Extension Suggestions

Optimizing DHEA Blood Levels

Because of the overwhelming evidence connecting low levels of DHEA to the degenerative diseases of aging, Life Extension suggests that most people over age 40 begin DHEA therapy. For most individuals, the starting dose of DHEA is between 15–75 mg, taken in one daily dose. Many studies have used a daily dose of 50 mg (Stangl 2011; Morales 1994; Brooke 2006; von Mühlen 2008; Weiss 2009; Weiss 2011; Talaei 2010; Dhatariya 2005; Brignardello 2007; Roxas 2007; Kenny 2010; Reiter 1999).

Ideally, DHEA replacement therapy should begin with blood testing to establish a base range. Since almost everyone over age 40 has lower-than-optimal levels of DHEA, most people begin supplementation and test their blood DHEA-S levels later to make sure they are taking the proper dose (Hinson 1999).

After 3–6 weeks of supplementation, a DHEA-S test is recommended. Individuals react differently to DHEA replacement therapy, so it is a good idea to closely monitor your blood levels and note any side effects.

Standard and Optimal DHEA-S Blood Levels

Blood Test	**Standard Reference Range (20-24 yo)** (Labcorp 2013)	**Optimal Levels**
DHEA-S	Men: 211–492 µg/dL	Men: 350–500 µg/dL
	Women: 148–407 µg/dL	Women 275–400 µg/dL

As DHEA can be converted in the body to testosterone and estrogen, individuals with hormone-sensitive cancers (such as breast, uterine, or prostate cancer) should not take DHEA. Some side effects that have been reported with DHEA include liver problems, masculinization (in women), breast enlargement (in men), hair loss, aggression, acne, and insomnia; although these are relatively uncommon (UMMC 2013; Mayo Clinic 2012). Since DHEA supplementation can influence levels of

other hormones, individuals on a DHEA regimen should regularly monitor their hormone levels via blood testing. More information about comprehensive hormone balance and using blood testing to monitor hormone levels is available in the Male Hormone Restoration and Female Hormone Restoration protocols.

Disclaimer and Safety Information

This information (and any accompanying material) is not intended to replace the attention or advice of a physician or other qualified health care professional. Anyone who wishes to embark on any dietary, drug, exercise, or other lifestyle change intended to prevent or treat a specific disease or condition should first consult with and seek clearance from a physician or other qualified health care professional. Pregnant women in particular should seek the advice of a physician before using any protocol listed on this website. The protocols described on this website are for adults only, unless otherwise specified. Product labels may contain important safety information and the most recent product information provided by the product manufacturers should be carefully reviewed prior to use to verify the dose, administration, and contraindications. National, state, and local laws may vary regarding the use and application of many of the treatments discussed. The reader assumes the risk of any injuries. The authors and publishers, their affiliates and assigns are not liable for any injury and/or damage to persons arising from this protocol and expressly disclaim responsibility for any adverse effects resulting from the use of the information contained herein.

The protocols raise many issues that are subject to change as new data emerge. None of our suggested protocol regimens can guarantee health benefits. The publisher has not performed independent verification of the data contained herein, and expressly disclaim responsibility for any error in literature.

DHEA Restoration Therapy

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