LifeExtension® Print This

DHEA Restoration Therapy
Hormone Replacement Therapy

It's no accident that youth is associated with high levels of hormones. Produced throughout the body, sex hormones are critical to maintaining vibrancy and good health. In recent decades, scientists have begun to understand the powerful benefits of replacing hormones lost to aging. However, there are serious questions about the safety of conventional hormone replacement therapy, which relies on hormones that are synthesized from animals (Premarin ®) or created in a lab (Provera ®). Most recently, the widespread prescribing of these two hormones among menopausal women has come under scientific scrutiny because of the increased risk of stroke and heart attack.

As an alternative, bioidentical **hormone replacement therapy** may be one of the best things aging people can do for themselves because of the wide-ranging benefits of bioidentical hormones on everything from the cardiovascular system to the aging brain and bones. What is required, however, is an approach that harnesses the wisdom of the body and relies on bioidentical hormones to replace those that decline with age.

In 1981, Life Extension introduced dehydroepiandrosterone (DHEA) in an article that described the multiple anti-aging effects of this steroid hormone. At the time, DHEA replacement therapy was almost unheard of. Today, however, DHEA replacement therapy has been studied extensively, and decreased DHEA levels have been implicated in heart disease, high cholesterol, depression, inflammation, immune disorders, schizophrenia, Alzheimer's disease, diabetes, HIV, and osteoporosis (Hauffa BP et al 1984; Valenti G 2002; Valenti G et al 2004).

But what is DHEA exactly, and how does it work? DHEA is the most common steroid hormone in the body. It is produced mainly by the adrenal glands, and to a lesser extent, elsewhere in the body (including fat cells). DHEA is metabolized from pregnenolone, the body's “master hormone,” which itself is metabolized from cholesterol. DHEA can be metabolized into other sex hormones, including testosterone and the estrogens, and up to 150 individual metabolites.

Although there are still important research questions to answer, there is no question that youthful DHEA levels are closely associated with good health, and that low levels have been connected to various diseases. Unfortunately, after about age 35, DHEA begins to decline (Pavlov EP et al 1986; Nafziger AN et al 1998). Women, who tend to have lower levels, lose DHEA much more quickly than men as they age. Concentrations remain roughly 30% higher in men (Orentreich N et al. 1984). DHEA levels also vary according to ethnicity (Orentreich N et al. 1984; LaCroix AZ et al. 1992; Hornsby PJ 1995). By age 70, DHEA may be only 20% of young-adult levels (Belanger A et al 1994).

Modern hormone replacement therapy strives to recreate the youthful balance of hormones in the body—and this is where DHEA's value really stands out. Because it is metabolized into other hormones, supplementing with DHEA may allow the body to choose which hormone is needed, then synthesize that hormone from the available DHEA. This may account for the astonishing range of benefits that many researchers attribute to this hormone. DHEA's separate metabolites, including 7-Keto DHEA, have also been shown to have individual benefits, including lowering cholesterol, burning fat, and boosting the immune system.

There are many provocative theories that may one day help explain DHEA's role in certain diseases. For instance, many elderly people suffer from high cholesterol levels, which are a risk factor for heart disease. In this age group, the rate of heart disease rises much more rapidly among women than men, partly because of the loss of hormones during menopause. Clearly, there is a link between heart disease and sex hormones, and this phenomenon raises an intriguing possibility. Because sex hormones are synthesized from cholesterol, perhaps elevated cholesterol levels represent the body's attempt to supply more of the raw materials for hormone production. Indeed, one study showed a drop in cholesterol levels after comprehensive natural hormone therapy (Dzugan SA et al 2002).

As part of a comprehensive approach to fighting the diseases of aging, Life Extension recommends that people monitor their blood levels of DHEA and strive to reproduce hormone levels of a healthy 21-year-old. Fortunately, DHEA is well tolerated as a supplement, with only minimal side effects even at relatively high doses.

What You Have Learned So Far

- DHEA is a hormone that is produced from the synthesis of pregnenolone. It may be metabolized into testosterone or estrogen. DHEA is the most prevalent steroid hormone in the body.
- Low DHEA levels are clearly associated with a range of diseases, including heart disease, diabetes, inflammation, Alzheimer's, and others.
- DHEA levels drop dramatically as people age. There are pronounced differences in the average DHEA levels of men and women, with women on average having lower DHEA levels.
- DHEA replacement therapy can restore youthful DHEA levels.

DHEA: FIGHTING INFLAMMATION

Inflammation is an insidious condition, and we are learning more every year about its association with a host of diseases.

Inflammation is caused by internal chemicals called inflammatory cytokines that are released as part of the immune system response. These chemicals, including tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), interleukin 1(beta) [IL-1(β)] and/or leukotriene, are present in greater concentrations as we age. Reducing the concentration of inflammatory cytokines to reduce the risk of serious disease is one goal of nutrient and hormone therapy.

DHEA supplementation has been shown to improve several aspects of the immune system—cytokine production and T-cell, B-cell, natural killer cell, and monocyte function—in postmenopausal women and elderly men (Khorram O et al 1997). DHEA appears to be especially valuable against IL-6 and TNF, both of which are elevated in patients with inflammatory arthritis (James K et al 1997; Straub RH et al 1998; Straub RH et al 2002a; Leowattana W 2001). Systemic lupus erythematosus is another chronic inflammatory condition, affecting approximately 1 in every 700 women, usually younger women (Sullivan KE 1999-2000). Treatment of this type of lupus with DHEA (50 to 200 mg daily) caused clinical improvement and decreased lupus flares by 16% (van Vollenhoven RF et al 1998; Chang DM et al 2002).

DHEA IN WOMEN

Throughout their reproductive lives, women experience higher levels of estrogen produced by the ovaries. This estrogen has a cardioprotective effect, which accounts for women's lower rates of heart disease. However, around age 50, women undergo menopause, or the failure of the ovaries and the cessation of menstruation. This period is distinguished by a rapid drop in the level of sex hormones, including estrogen, DHEA, testosterone, pregnenolone, and progesterone. Various diseases have been connected to this rapid loss of hormonal protection, including heart disease and osteoporosis (Lock 1994). While many of the symptoms of menopause are caused by the loss of estrogen, there are also side effects associated with the drop in DHEA and testosterone among menopausal women, including:

- Decreased libido
- Decreased strength
- Decreased muscle mass
- Decreased bone density
- Decreased energy (Braunstein G 2002)

In menopausal women, DHEA therapy is sometimes androgenic. In other words, it tends to raise the blood levels of male sex hormones such as testosterone (Belaisch J 2002), which accounts for the small risk among some women of increased hair growth (Stomati M et al 2000). However, there is growing evidence that a modest increase in testosterone benefits women. For example, it appears to improve bone metabolism and decrease menopausal symptoms (Davis S 1999), as well as increase sexual desire (Turna B et al 2005).

One analysis of existing studies found the DHEA had these benefits among postmenopausal women:

- A 30 mg to 50 mg daily dose improved mood, sense of well-being, and sexual appetite and activity among women with adrenal insufficiency (Buvat J 2003).
- A long-term trial of women over 60 reported significant increases in bone mineral density (Buvat J 2003).
- A study among women aged 70 to 79 showed improvements in sexual desire, arousal, and enjoyment (Buvat J 2003).

DHEA IN MEN

Studies of men have shown that DHEA replacement therapy is an important complement to testosterone therapy. Among aging men, the amount of “free” testosterone, or testosterone that is available to the body, falls more quickly than the level of total testosterone. Thus, it is important to design a hormone replacement program that raises the level of free testosterone. In a 1997 study, DHEA levels were shown to parallel the levels of free testosterone in the blood. The study authors suggested that DHEA might help raise free testosterone. If this conclusion is correct, then DHEA replacement therapy would not only raise the blood level of DHEA, but also the level of free testosterone (Morley JE et al 1997).

Still, other studies have shown that DHEA may be an effective therapy for erectile dysfunction. Although there are conflicting studies in this regard, a few have shown that among men without heart or vascular disease, DHEA has been able to improve erectile dysfunction (Belaisch J 2002).

CANCER: HOPE AND CAUTION

In any discussion of hormone replacement therapy, the question of cancer will naturally arise. Certain cancers, especially breast and prostate cancer, may be hormone mediated. In other words, supplementation with hormones may cause cancer cells to proliferate. For this reason, men and women with histories of hormone receptor cancers, or with existing tumors, are warned away from hormone therapy that might aggravate their conditions.

The situation, however, is not clear-cut. In numerous lab studies, DHEA has shown anti-cancer properties (Schwartz AG et al 1993; Yang S et al 2002; Yoshida S et al 2003; Jiang Y et al 2005). Similarly, low levels of DHEA are associated with cancer (Gordon GB et al 1988; Leowattana W 2001). According to studies using animal models and cell cultures (both animal and human), DHEA has been shown to inhibit cancer development in a number of tissues, including:

- Mammary gland (Schwartz AG 1993; Lubet RA et al 1998)
- Skin (Schwartz AG et al 1993)
- Colon (Nyce JW et al 1984; Osawa E et al 2002; Pelissier MA et al 2004)
- Liver and thyroid (Moore MA et al 1986)

DHEA and breast cancer. Because DHEA may be converted into estrogen, women with breast cancer are advised not to begin DHEA therapy, which may theoretically increase the severity of their cancer. To date, no large studies have been conducted on the use of DHEA in women with breast cancer. Healthy women taking DHEA should also monitor their blood levels of estrogen and free testosterone to make sure that DHEA is creating youthful hormone balance.

DHEA and prostate cancer . Men should not begin DHEA therapy before having their prostate specific antigen (PSA) levels tested and undergoing a digital rectal exam, to measure the size and consistency of the prostate. Men with prostate cancer or severe benign prostate disease are advised to avoid DHEA because it can be converted into testosterone, which may promote cell proliferation or cause an increase in DHT (dihydrotestosterone). However, among healthy men, one study showed that DHEA did not increase PSA levels (Jedrzejuk D et al 2003). To make sure DHEA is tolerated, men should consider having their DHEA bloodlevels tested every 6 or 12 months after beginning therapy, along with testing levels of free testosterone, estrogen, and DHT. The DHT form of testosterone plays an important role in the development of benign prostatic enlargement, and is believed to contribute to the progression of prostate cancer.

WHAT DO THE STUDIES SAY?

Many of the studies examining DHEA have found an overall benefit among study subjects, especially among the elderly. Nevertheless, it's helpful to understand some of DHEA's chemical interactions to gain insight into its many roles inside the body.

DHEA owes many of its beneficial properties to its ability to inhibit an enzyme called glucose-6-phosphate dehydrogenase (G6PD). DHEA's anti-cancer properties are due at least in part to its ability to inhibit G6PD (Williams JR 2000; Arlt W 2004). DHEA's cardioprotective properties may also be partly due to G6PD inhibition (Tian WN et al 1998; Schwartz AG et al 2004).

Beyond its broad benefits, however, a survey of studies on specific diseases found that DHEA was active in fighting many of the most frightening, including:

Alzheimer's Disease. Patients with Alzheimer's disease have higher levels of cortisol (the “stress” hormone) (Rasmuson S et al 2002) and imbalanced cortisol/DHEA ratios (Murialdo G et al 2000). In a group of severely afflicted Alzheimer's patients , Dehydroepiandrosterone sulfate (DHEA-S) levels were significantly lower (Murialdo G et al 2000). Other studies have examined the role of vascular endothelial growth factor (VEGF) among Alzheimer's patients. VEGF has been shown to protect the brain, and scientists now believe that low VEGF levels may be connected to the progression of Alzheimer's disease. DHEA-S was shown to significantly increase the bioavailability of VEGF in the brain, leading the study authors to conclude that it could be a valuable treatment for Alzheimer's and aging (Solerte SB et al 2005).

Cardiovascular Disease. There is a clear relationship between DHEA levels and cardiovascular disease: as DHEA decline, the incidence of cardiovascular disease rises in men (Barrett-Connor E et al 1987; Herrington DM et al 1990; Hautanen A et al 1994; Barrett-Connor E et al 1995; Feldman HA et al 1998) and in women (Johannes CB et al 1999). Diabetic men with the lowest DHEA levels have a significantly greater chance of developing coronary heart disease (Fukui M et al 2005). The risk of death is higher among those with the lowest levels of DHEA in men less than age 70 (Mazat L et al 2001).

DHEA play a protective role in the development of atherosclerosis and coronary artery disease (Gordon GB et al 1988; Eich DM et al 1993), especially among men. Several mechanisms are involved: inhibition of G6PD, which can modify the lipid spectrum; suppression of platelet aggregation; and reduced cell proliferation (Porsova-Dutoit I et al 2000). Men with lower DHEA-S are more likely to have atherosclerosis (Herrington DM et al 1990) and calcified deposits in the abdominal aorta (Hak AE et al 2002) . Because cortisol increases the risk of heart attack and the severity of atherosclerosis in men (Laughlin GA et al 2000), raising DHEA levels to increase the DHEA/cortisol ratio has promise for reducing cardiovascular risk (Barrett-Connor E et al 1995). However, the same associations are lacking in women (Barrett-Connor E et al 1987) .

- **Myocardial Infarction.** Low DHEA is related to premature heart attack in men (Mitchell LE et al 1994). Severely ill cardiac patients and those with acute heart attack have lower DHEA levels for as long as 3 to 4 months after the event (Slowinska-Srzednicka J et al 1989; Ruiz Salmeron RJ et al 1992).
- **Metabolic Syndrome.** Metabolic Syndrome is characterized by several conditions that are all associated with elevated risk for heart disease, including increased insulin resistance, obesity, and abnormal cholesterol levels. In metabolic syndrome, these individual risk factors act synergistically, raising the risk of heart disease higher than their individual risk levels alone. Although research is still continuing, scientists have linked elevated cholesterol to lower DHEA levels (Nestler JE et al 1992). Long-term DHEA supplementation improves insulin sensitivity by 30%, raises high-density lipoprotein cholesterol by 12%, and lowers low-density lipoprotein cholesterol by 11%, and triglycerides by 20% (Lasco A et al 2001). The lowering of low density lipoproteins (LDL) by DHEA has an antioxidant effect, which could have anti-atherogenic consequences (Nestler JE et al 1988; Nestler JE et al 1991; Kurzman ID et al 1990; Khalil A et al 2000). DHEA also decreases abdominal fat, an important characteristic of metabolic syndrome (Villareal DT et al 2000; Villareal DT et al 2004).

Cognitive Decline. One of the most distressing elements of aging is the loss of mental "sharpness." Once again, DHEA has been shown to improve measures of cognitive function in laboratory studies (Roberts E et al 1987; Flood JF et al 1988). Abnormal balances in the brain between DHEA-S and cortisol have been shown to decrease brain function (Kalmijn S et al 1998; Ferrari E et al 2001).

Depression. DHEA has been extensively studied in depression. DHEA levels are reduced in major depressive disorders in both adolescents and adults, and an elevated cortisol/DHEA ratio predicts a delay in recovery (Herbert J 1998; Ferrari E et al. 2004). Women lacking detectable DHEA have an increased occurrence of depression (Yaffe K et al. 1998).

DHEA has also been a useful remedy for depression (van Broekhoven F et al 2003). A well-conducted study by the National Institute of Mental Health found DHEA to be quite effective in treating midlife long-lasting, mild depression (dysthymia). The symptoms that improved most significantly were inability to gain pleasure from normally pleasurable experiences (anhedonia), loss of energy, lack of motivation, emotional “numbness,” sadness, inability to cope, and worrying (Bloch M et al 1999). In another study, 3 months of DHEA supplementation improved self-reported physical and psychological well-being in age-advanced individuals (Morales AJ et al 1994). These results were supported by a recent study that showed DHEA therapy improved depression among middle-aged people (Schmidt PJ et al 2005).

Diabetes. DHEA appears to increase insulin sensitivity. Insulin resistance is an early indicator of type 2 diabetes and is closely associated with obesity, which are both major risk factors for heart disease. A decrease in DHEA-S is associated with the development of type 2 diabetes (Kameda W et al 2005). Among women with deficient adrenal glands, DHEA supplementation was shown to significantly increase insulin sensitivity, and the study authors concluded that DHEA might be a valuable treatment for type 2 diabetes (Dhatariya K et al 2005). DHEA has also been shown to increase insulin sensitivity among obese women (Villareal DT et al 2004).

HIV/AIDS. HIV-positive men with lower DHEA levels have comparably lower CD4 cell counts (Dyner TS et al 1993) and are 2.3 times more likely to progress to AIDS (Jacobson MA et al 1991; Ferrando SJ et al 1999). HIV-positive men have a dramatically elevated cortisol/DHEA ratio that parallels their nutritional and disease status (Jacobson MA et al 1991; Christeff N et al 1997; Christeff N et al 1999; Chriseff NA et al 2000; Ferrando SJ et al 1999).

Immune system. DHEA has been shown to enhance the immune response against a wide range of viral, bacterial and parasitic pathogens. In one animal study, DHEA supplementation showed a significant reduction in the level of internal parasites (Dos Santos TD et al 2005).

Osteoporosis. Osteoporosis (bone thinning) affects millions of late-middle-aged to elderly individuals of both sexes, but is more common in women than men. In women, a major contributing factor is the loss of estrogen at menopause, which parallels the decline in DHEA. DHEA appears to exert a positive role in bone metabolism by inhibiting bone resorption and stimulating bone formation (Labrie F et al 1997; Haden ST et al 2000). It also seems to aid calcium absorption (Carlstrom K et al 1988; Taelman P et al 1989). DHEA has proved effective in clinical trials treating osteoporosis (Villareal DT et al 2000). However, a correlation between DHEA and bone mineral density appears variably in women and not at all in men (Brody S et al 1982; Nordin BE et al 1985; Deutsch S et al 1987; Wild RA et al 1987; Barrett-Connor E et al 1993).

Stress. DHEA levels are closely tied to stress. Studies have shown that traumatic events such as burns or illnesses significantly decrease DHEA, testosterone, and androstenedione levels, while increasing the level of cortisol (Parker LN et al 1985; Lephart ED et al 1987; Wade CE et al 1988). Calmness, such as seen in individuals practicing transcendental meditation, is associated with higher levels of DHEA (Glaser JL et al 1992). In one study, participants in a stress-reduction program increased DHEA by 100% and reduced stress hormone production (cortisol) by 23% (McCraty R et al 1998).

7-KETO DHEA: THE PERFECT PARTNER

Among DHEA's many metabolites, one has attracted significant attention for its unique ability to lower cholesterol, burn fat, and improve the immune system. This metabolite, known at 7-Keto DHEA, is not converted into estrogen or testosterone, so it may be safely used among people with hormone-dependent diseases, including cancer.

Scientific studies have shown that 7-Keto can help people burn fat through a process known as “thermogenesis.” This means the body's metabolic rate is accelerated, generating heat and energy that consumes calories and burns fat. 7-Keto accomplishes this by boosting the levels of three liver enzymes that stimulate fatty acid oxidation.

In one study of 30 overweight adults, study subjects either received 100 mg of 7-Keto twice daily or placebo. They also participated in a supervised exercise and diet program. At the end of the study, those taking 7-Keto had lost 6.3 pounds on average, versus 2.1 pounds for the control group (Kalman DS et al 2000).

7-Keto has also been studied for its immune-boosting and cholesterol-lowering properties. In a study on cholesterol levels, human volunteers applied a gel containing 25 mg of 7-Keto for five consecutive days. At the end of the study, the subjects taking 7-Keto had experienced a rise in good HDL cholesterol and a slight reduction in harmful LDL cholesterol (Sulcova J et al 2001).

Another study looking at immune function found that four weeks of 7-Keto supplementation improved immune function in elderly men and women. In this study, subjects over age 65 took 100 mg of 7-Keto twice daily or placebo. The subjects on 7-Keto experienced a significant decrease in immune suppressor cells and an increase in immune helper cells (Zenk JL et al 2004).

Because 7-Keto is not converted into estrogen or testosterone, it may be the perfect complement to DHEA therapy, as well as providing an option for people who have hormone dependent cancers. In some women, high doses of DHEA may cause the growth of unwanted hair or acne. By adding 7-Keto to a daily program, it may be possible to lower the dosage of DHEA.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Because of the overwhelming evidence connecting low levels of DHEA to the degenerative diseases of aging, Life Extension suggests that all people over age 40 begin DHEA therapy. For most people, 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. One recent study showed that doses under 30 mg were not enough to significantly raise blood levels of DHEA in young adults (Cameron DR et al 2005). At these levels, DHEA has shown no major side effects.

Ideally, DHEA replacement therapy should begin with blood testing to establish a base range. Since almost everyone over age 35-40 has lower than optimal levels of DHEA, most people begin supplementation and test their blood DHEA levels later to make sure they are taking the proper dose. Normal serum reference ranges and ideal ranges of DHEA-S are:

	Normal	Ideal
Men	280-640 ug/dL	500-640 ug/dL
Women	65-380 ug/dL	250-380 ug/dL

After 3 to 6 weeks, another test is recommended to measure serum DHEA. All individuals react differently to DHEA replacement therapy, so it's a good idea to closely monitor your blood levels and side effects. If side effects appear, it may be possible to add 7-Keto DHEA and reduce the dose of DHEA.

Those with liver disease should use DHEA sublingual tablets, which bypass liver metabolism. Otherwise, capsules containing the more common micronized DHEA are quite effective in restoring DHEA to youthful ranges.

DHEA SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

DHEA (DEHYDROEPIANDROSTERONE)

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.
- DHEA can cause androgenic effects in woman such as acne, deepening of the voice, facial hair growth and hair loss.

For more information see the Safety Appendix

***These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure or prevent any disease.**