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The Clinical Use of Dehydroepiandrosterone in postmenopausal women

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Walgreens
West Plains Missouri

Abstract
A basic understanding of the distinct metabolism, mechanism of action, and clinical use of dehydroepiandrosterone and its metabolites is critical to balancing the hormone milieu in postmenopausal women. To date, studies of dehydroepiandrosterone therapy in women with adrenal insufficiency suggest that they are the most likely group to gain health benefits from dehydroepiandrosterone replacement therapy. Our understanding of the potential long-term health benefits of replacing dehydroepiandrosterone along with other deficient hormones is still only in its infancy. With the evidence currently available, however, one can reasonably suggest that dehydroepiandrosterone offers the promise of a safe and efficient replacement therapy for specific symptoms common to postmenopausal women. This article reviews the metabolism, physiology, and clinical use of dehydroepiandrosterone in postmenopausal women. The clinical effectiveness of dehydroepiandrosterone for vulvovaginal atrophy, sexual dysfunction, osteoporosis, adrenal and immunological function, cardiovascular disease, and, in combination, hormone replacement therapy is reviewed. In addition, the use of the dehydroepiandrosterone metabolite 7-keto-dehydroepiandrosterone for weight loss is discussed.

The medical and nonmedical use of prohormones is not new; for decades bodybuilders and athletes have understood the benefits and risks associated with the supplementation of steroid hormone precursors. There is increasing popular and scientific interest in supplementation with the prohormones dehydroepiandrosterone (DHEA), 7-Keto-DHEA, and 7-alpha-hydroxy-DHEA for a myriad of uses ranging from Alzheimer’s, to weight loss, to HIV/AIDS. A solid understanding of the distinct metabolism, mechanism of action, and clinical use of each of these prohormones is vital to the practitioner tasked in balancing the
hormone milieu in postmenopausal women, as well as managing various androgen deficiency-related disease states.

Despite the identification of DHEA and its sulfate metabolite DHEAS more than 80 years ago, there is still considerable speculation as to the extent of their physiological role and controversy as to their therapeutic significance. While first isolated in 1934 by German Dr. Adolf Butenandt,¹ work on DHEA in the 1960s by French Dr. Etienne-Emile Baulieu² brought significant attention to DHEA as an endogenous adrenal and neurohormone. In 1996, DHEA was skyrocketed to “the superstar of superhormones” by the popularity of Dr. William Regelson’s book titled *The Superhormone Promise.*

**Physiology**

DHEA, also known as prasterone, and its sulfated metabolite DHEAS are the most abundant circulating steroid hormones in women.³ DHEA is an endogenous prohormone produced in the adrenal glands, the liver, in minute amounts in the neurons and glial cells in the brain, and, in men, is secreted by the testes.⁴ Humans, along with other primates, are unique in their adrenal production of copious amounts of DHEA,⁵ and no nuclear or membrane receptors specific for DHEA or DHEAS have been identified to date.⁶ Instead, they act as a reservoir of precursors for the intracellular production of both androgens and estrogens in nonreproductive tissues. It is estimated that before menopause 75% and after menopause 100% of total estrogens in women are synthesized in peripheral intracrine tissues from inactive adrenal precursors.⁷ Most of DHEA’s actions are via its activity at the androgen receptor (AR) or estrogen receptor (ER) after its conversion to androgen or estrogen. However, direct effects of DHEA at the AR and ER have been identified. DHEA also increases bioavailable insulin-like growth factor 1 and directly affects neurotransmitter receptors.⁸ DHEA levels generally peak around age 20 and begin a rapid descent after age 25.⁹ By the time a woman reaches menopause, her DHEA secretion has decreased by an average of 60%. Unlike the majority of men, with a lifetime of testicular activity, DHEA becomes the exclusive source for sex steroids in women after menopause. And, because there is no feedback mechanism controlling DHEA secretion, women who are deficient will remain so without clinical intervention.¹⁰

Metabolism of DHEA differs according to gender as well as varies in individual cells and tissues, which increases the difficulty in understanding the steroid hormone cascade. In addition, distinct species-specific metabolic routes and cellular interconversions of DHEA and its metabolites prevent traditional extrapolation of animal models to human physiology. DHEA is an intermediate in the production of testosterones and estrogens. In the liver, DHEA is converted to 7α-hydroxy-DHEA which is then oxidized to 7-oxo-DHEA (also known as 7-keto-DHEA) in both liver and kidney.¹¹ All androgen-and estrogen-sensitive peripheral tissues have the necessary enzymes to convert DHEA, allowing local synthesis and control of the intracellular levels of sex hormones according to local needs.¹² Humans hydroxylate DHEA at several positions, as well as interconvert 7α-hydroxy-DHEA, 7β-hydroxy-DHEA, and 7-oxo-DHEA. The 7-oxo derivatives are more active than the parent DHEA, and they do not appear to convert to either androgens or estrogens.¹² DHEA supplementation changes the circulating androgen/estrogen ratio in a gender-specific fashion. Interestingly, women tend to convert more DHEA to testosterone, whereas men convert more to estradiol.

DHEA protects the body from the effects of physical stress and inflammation, decreases pain, and improves immune system function.¹³ DHEA administration increases all of the steroid hormones, except cortisol, which decreases.¹⁴ DHEA also increases libido and sexual responsiveness; improves motivation, sense of well-being, and rapid-eye movement (REM) phase sleep; and enhances memory.¹⁵,¹⁶

Because DHEA promotes the formation of other hormones, it can help alleviate menopausal symptoms and/or decrease the amount of other hormones required in replacement therapies. DHEA also protects against autoimmune diseases like lupus erythematosus and rheumatoid arthritis.¹⁷

DHEA levels are often low in patients with cardiovascular disease (CVD), fibromyalgia, HIV/AIDS, and certain cancers. However, studies conflict on whether or not supplementation improves disease progression and quality of life in these patients. In evaluating the evidence for the clinical use of DHEA, more than mere association between high or low levels of DHEA and a disease risk should be considered; we should also require data that demonstrates the outcomes associated with direct intervention.

**Effects of DHEA on Hormonal Milieu**

In women, DHEA levels are directly related to well-being, cognitive function, and functional status.⁸ Regarding the clinical use of DHEA in women whose saliva level indicates low DHEAS, Dr. Kenna Stephenson writes in her book *Awakening Athena:* “DHEA enhances libido, helps build bone mass, lowers the levels of cholesterol and triglycerides, improves the sense of well-being and increases alertness.”¹⁸

DHEA supplementation increases the levels of all sex hormones, while decreasing cortisol levels. Consequently, the appropriate dose of DHEA to add to estrogen and progesterone replacement therapy in androgen deficient postmenopausal women is debated by practitioners. In postmenopausal women (1 to 6 years since menopause) the addition of 10 mg/day oral DHEA added to 50 mcg transdermal estradiol and 100 mg/day oral micronized progesterone results in a significantly higher increase in testosterone and estradiol and a significantly lower decrease in cortisol level than without DHEA.¹⁹ Evidence suggests that 10 mg/day of oral DHEA may be the proper dose to replace androgen deficiencies. However, the number of years since menopause, the adrenal function of the individual, and the extent of androgen deficiency need to be considered when replacing DHEA along with estrogens and progesterone.

**Cardiovascular Disease**

Research to date has not demonstrated consistent effects of DHEA on cardiovascular risk. In postmenopausal women, DHEAS is associated with a less atherogenic lipid profile and low DHEAS levels are
associated with increased CVD risk and all-cause mortality. Although declines in androgens are associated with cardiovascular risk, it remains to be seen whether replacement therapy will improve the risk factors.

Preliminary studies report possible benefits of DHEA supplementation in patients with atherosclerotic plaques. There is conflicting evidence regarding the use of DHEA in patients with heart failure or diminished ejection fraction.

Oral DHEA supplementation (50 mg/day) seems to reduce triglycerides, low-density lipoprotein (LDL), and total cholesterol, but also decreases high-density lipoprotein (HDL). Most studies conclude that oral DHEA supplementation results in an unfavorable lipoprotein profile. Lowering of the large HDL particles and the resulting potential adverse clinical implications are cited as concerns for the impact of DHEA supplementation on cardiovascular risk factors. Long-term, lower-dose studies are warranted.

**Aging Skin**

Oral DHEA supplementation increases epidermal thickness, sebum production (a desirable effect for most postmenopausal women), skin hydration, and decreases facial skin pigmentation in elderly women. Topical DHEA exerts an anti-aging effect in the skin through

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### FORMULAS USED IN THE TREATMENT OF VARIOUS HEALTH ISSUES OF POSTMENOPAUSAL WOMEN

#### 7-KETO-DHEA 5-MG SLOW-RELEASE CAPSULES

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-keto-DHEA</td>
<td>0.5 g</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>13.8 g</td>
</tr>
<tr>
<td>Methocel E4M Premium</td>
<td>10 g</td>
</tr>
<tr>
<td>Size #1 capsules</td>
<td>100 Each</td>
</tr>
</tbody>
</table>

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Blend the DHEA powder with the microcrystalline cellulose geometrically, followed by the Methocel E4M Premium, and mix well.
4. Encapsulate into 100 size #1 capsules.
5. Package and label.

**STABILITY**

A beyond-use date of up to 6 months can be used for this preparation.

DHEA = dehydroepiandrosterone

#### DHEA 10-MG SLOW-RELEASE CAPSULES

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA</td>
<td>1 g</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>13.5 g</td>
</tr>
<tr>
<td>Methocel E4M Premium</td>
<td>10 g</td>
</tr>
<tr>
<td>Size #1 capsules</td>
<td>100 Each</td>
</tr>
</tbody>
</table>

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Blend the DHEA powder with the microcrystalline cellulose geometrically, followed by the Methocel E4M Premium, and mix well.
4. Encapsulate into 100 size #1 capsules.
5. Package and label.

**STABILITY**

A beyond-use date of up to 6 months can be used for this preparation.

DHEA = dehydroepiandrosterone

#### DHEA 13-MG VAGINAL SUPPOSITORY

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA</td>
<td>0.39 g</td>
</tr>
<tr>
<td>Witepsol H-15</td>
<td>54.9 g</td>
</tr>
<tr>
<td>2-mL suppository molds</td>
<td>30 Each</td>
</tr>
</tbody>
</table>

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
4. Incorporate the DHEA and mix until uniform.
5. Pour into molds, cool, and trim if necessary.
6. Package and label.

**STABILITY**

A beyond-use date of up to 6 months can be used for this preparation.

DHEA = dehydroepiandrosterone

#### DHEA 10-MG/ML VAGINAL CREAM

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA</td>
<td>0.3 g</td>
</tr>
<tr>
<td>Ethoxydiglycol</td>
<td>0.3 mL</td>
</tr>
<tr>
<td>BHRT cream base of choice</td>
<td>qs 30 mL</td>
</tr>
</tbody>
</table>

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Mix the DHEA with the ethoxydiglycol to form a smooth paste.
4. Incorporate the BHRT cream geometrically into the mixture and mix until uniform.
5. Package and label.

**STABILITY**

A beyond-use date of up to 30 days can be used for this preparation.

BHRT = bioidentical hormone replacement therapy

DHEA = dehydroepiandrosterone
DHEA treatment in women results in increased bone formation and higher bone mineral density (BMD) along with elevated levels of osteocalcin, an indicator of bone formation and a decrease in bone resorption. Oral DHEA (50 mg to 100 mg/day) seems to improve BMD after six weeks of DHEA monotherapy, dysthymic patients note improvement may improve symptoms of depression and dysthymia. After DHEA levels and mood, clinical research indicates oral DHEA supplements the pathophysiology of depression. In addition to a correlation between depression and osteoporosis, DHEA can be a highly efficient treatment for reversing the signs and symptoms of vaginal atrophy, presumably through local androgen and estrogen formation. Daily intravaginal application of DHEA in concentrations ranging from 0.25% to 1% can decrease the percentage of parabasal cells, increase superficial cells, and decrease vaginal pH. After one week of DHEA treatment, the maturation value of the vaginal epithelial cells increases significantly. Improvements are also seen in vaginal secretions, epithelial surface thickness, and epithelial integrity. Minimal changes in serum DHEA levels are seen with doses up to 23.4 mg daily over one week. Intravaginal doses of DHEA up to 13 mg/day result in minimal or no changes in serum sex hormone levels after 12 weeks of treatment. No effects on the endometrium have been observed.

**Vulvovaginal Atrophy**

DHEA can be a highly efficient treatment for reversing the signs and symptoms of vaginal atrophy, presumably through local androgen formation and estrogen formation. Daily intravaginal application of DHEA in concentrations ranging from 0.25% to 1% can decrease the percentage of parabasal cells, increase superficial cells, and decrease vaginal pH. After one week of DHEA treatment, the maturation value of the vaginal epithelial cells increases significantly. Improvements are also seen in vaginal secretions, epithelial surface thickness, and epithelial integrity. Minimal changes in serum DHEA levels are seen with doses up to 23.4 mg daily over one week. Intravaginal doses of DHEA up to 13 mg/day result in minimal or no changes in serum sex hormone levels after 12 weeks of treatment. No effects on the endometrium have been observed.

**Libido and Sexual Dysfunction**

Metabolism of DHEA into both androgens and estrogens locally in the cells of the vaginal lining improves sexual function in postmenopausal women with vaginal atrophy. DHEA 1% applied intravaginally daily results in increased sexual desire, arousal, sensation, orgasm, and improves dryness during intercourse. A single 300-mg dose of DHEA has also been shown to improve response to sexual stimuli in postmenopausal women.

**Adrenal Response and Immune System Function**

DHEA induces a change in adrenal enzymatic activity and can modify circulating levels of androgens and progestins in both early and late menopausal women, presumably by modulating the age-related changes in adrenal gland function. DHEA supplementation results in significant increases in all steroids except for cortisol, which decreases significantly, after three to six months of therapy. Several factors are involved in the age-related decline in immune system function, but the hypothalamus-pituitary-adrenal axis plays an important role. The imbalance between cortisol and DHEA, with their opposing actions on immune function, emphasizes the importance of DHEA supplementation in aging women. The cortisol/DHEA ratio is a major determinant of age-related immunological changes. Administration of DHEA can improve cellular immune function during systemic inflammation, and DHEA and DHEAS have regulatory effects in immune homeostasis and are regulated by the nervous system, and it is seems that they may be an integral element of neuroimmunomodulation. It is unclear whether the low DHEAS levels seen in autoimmune

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**DHEA 2% FACIAL NIGHT CREAM**

**For 30 g**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA</td>
<td>0.6 g</td>
</tr>
<tr>
<td>Glycerin</td>
<td>0.6 mL</td>
</tr>
<tr>
<td>Cosmetic night cream of choice</td>
<td>qs 30 g</td>
</tr>
</tbody>
</table>

**METHOD OF PREPARATION**

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Weigh and/or measure each ingredient accurately.
3. Mix the DHEA powder with the glycerin to form a smooth paste.
4. Incorporate the mixture geometrically into the cream base and mix until uniform.
5. Package and label.

**STABILITY**

A beyond-use date of up to 30 days can be used for this preparation.

DHEA = dehydroepiandrosterone

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stimulation of collagen biosynthesis, improved structural organization of the dermis, and modulation of keratinocyte metabolism. DHEA topical cream in concentrations ranging from 0.1% to 2% applied to the face, arms, backs of hands, and upper chest results in significant increases in dermal AR expression. Also, the expression of procollagen 1 and 2 mRNAs increases, as well as proteins affecting procollagen synthesis, especially at the 1% and 2% concentrations. DHEA cream also results in dose-dependent expression of collagen and genes required for the maturation and deposition of collagen in the skin. Topical DHEA also reduces the expression of genes associated with cornification of keratinocytes. Overall, topical DHEA improves skin brightness, decreases the papery appearance of aging skin, and counteracts epidermal atrophy.
conditions, chronic fatigue syndrome, fibromyalgia, CVD, and certain cancers is a causative or resulting factor.

Of potential clinical importance, the DHEA metabolite 7-keto-DHEA has also been shown to modulate immune system function via stimulation of interleukin-2 production by lymphocytes.4

**Obesity**

In postmenopausal women, endogenous androgens play an important role in the maintenance of beneficial patterns of metabolic and morphometric parameters.5 The metabolic effects of DHEA seem to contribute to its antiobesity action, and the majority of studies evaluating the effect of DHEA on weight loss support its use for this purpose. DHEA blocks glucose-6-phosphate-dehydrogenase (G6PD), an enzyme essential for adipose tissue production, and decreases fatty acid synthetase activity,6 resulting in a decrease in fat mass and an increase in lean mass.7 Higher doses of DHEA (50 mg/day for six months) may reduce the risk factors for metabolic syndrome in overweight elderly patients. DHEA supplementation decreases insulin resistance and levels of sex hormone binding globulin (SHBG) significantly in obese late postmenopausal women. Replacement therapy with 50 mg of oral DHEA over 12 weeks can significantly increase insulin sensitivity in hypoadrenal women, suggesting DHEA could play a role in preventing type 2 diabetes.

Citing increases in metabolism and thermogenesis, the DHEA metabolite, 7-keto-DHEA, has been promoted for weight loss. Popular claims made regarding 7-keto-DHEA include increases in lean body mass and muscle mass, stimulated thyroid activity, improvements in immune system function, boosting memory, and slowing the aging process.

Proponents of 7-keto-DHEA claim the benefits of its parent DHEA, without the adverse effects. Neither oral nor topical 7-keto-DHEA has been shown to convert to testosterone or estradiol, nor does it have a clinically significant effect on serum steroid hormone levels, nor does it activate AR.8 In obese patients, 7-keto-DHEA stimulates production of thermogenic enzymes in the liver resulting in increased basal metabolic rate and increased triiodothyronine (T3) levels, and it promotes thermogenesis at about 2.5 times the rate of its parent DHEA, presumably through the stimulation of hepatic thermogenic enzymes. Significant increases in T3 have been seen with the use of 7-keto-DHEA in obese patients when used over 4 weeks.9

Early evidence indicates that 7-keto-DHEA may decrease body weight and body fat percentage in obese females, possibly by increasing resting metabolic rate (RMR) above basal levels.4 A decline in RMR, while frustrating for the patient, is normal, with restricted-calorie dieting. In preliminary studies, 7-keto-DHEA has been shown to reverse the normal decline in RMR seen in patients on a calorie-restricted diet.7 RMR comparison in patients receiving 7-keto-DHEA supplementation and placebo shows that during placebo treatment, RMR decreases by 3.9%, while RMR increases by 1.4% in the 7-keto group. Compared to exercise and diet alone, 100 mg of 7-keto-DHEA administered twice daily combined with moderate exercise and a reduced-calorie diet significantly reduces body weight and body fat composition. While no changes in serum testosterone, estradiol, TSH, or T4 are seen, significant increases in T3 are noted in patients supplemented with 7-keto-DHEA.

**Conclusion**

A basic understanding of the distinct metabolism, mechanism of action, and clinical use of DHEA and its metabolites is critical to balancing the hormone milieu in postmenopausal women. To date, studies of DHEA therapy in women with adrenal insufficiency suggest that these are the most likely to gain health benefits from DHEA replacement therapy. Our understanding of the potential long-term health benefits of replacing DHEA along with other deficient hormones is still only in its infancy. With the evidence currently available, however, one can reasonably suggest that DHEA offers the promise of a safe and efficient replacement therapy for specific symptoms common to postmenopausal women.

**References**


9. Labrie F, Martel C, Balsier J. Wide distribution of the serum dehydroepiandrosterone and sex steroid levels in postmenopausal women: Role of the ovary? Menopause 2010; 28: [In print].


