

Dehydroepiandrosterone: a springboard hormone for female sexuality

Richard F. Spark, M.D., F.A.C.E.

Department of Endocrinology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Objective: To determine the role of adrenal androgenic hormone precursors in female sexual function.

Design: A review of current literature on sexual function and the androgen precursor hormone dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS).

Result(s): The C₁₉ steroid DHEA is both an ovarian and adrenal androgen precursor hormone, whereas DHEAS is only synthesized in the adrenal cortex. Dehydroepiandrosterone sulfate secretion begins at age 10, peaks at age 20, and then wanes. Low DHEAS levels occur in men and women with adrenal insufficiency and in the elderly. Dehydroepiandrosterone, 50 mg/d, increases DHEAS levels. In women but not men, the increased DHEAS levels facilitate additional production of downstream androgens, testosterone, dihydrotestosterone, androstenedione, and androstenediol glucuronide. With the improved female androgenic profile women with adrenal insufficiency have increased sexual thoughts and fantasies as well as an enhancement in mood and well-being. In the elderly >age 65 — DHEAS levels increase in both men and women with DHEA 50 mg/d but only in women were the higher DHEAS levels accompanied by a surge in testosterone levels and in women >age 70 increased libido and enhanced sexual satisfaction as well as a 26% diminution in bone resorption, and a 10% decrease in skin pigmentation.

Conclusion(s): The female adrenal androgen deficiency syndrome, characterized low serum DHEAS levels may be corrected by DHEA supplements that increase levels of DHEAS and downstream androgens of importance to female sexuality. (Fertil Steril® 2002;77(Suppl 4):S19–25. ©2002 by American Society for Reproductive Medicine.)

Key Words: Female sexuality, androgens, DHEA, DHEA sulfate

Dehydroepiandrosterone (DHEA) and its sulfate, DHEAS, are among the most plentiful circulating adrenal hormones. Yet both the regulatory control and true physiologic role of these adrenal androgens remain shrouded in mystery. Egregious claims that DHEA offered elders a “fountain of youth” have, until recently, stifled serious scientific inquiry into the physiologic role of DHEA. Now new evidence has emerged indicating that DHEA is of greater importance to health and well-being than previously believed (1).

Placebo-controlled studies have demonstrated that DHEA has functions as diverse as the capacity to bolster bone density in postmenopausal women (2) and attenuate the disabling symptoms of systemic lupus erythematosus (SLE) (3). This article focuses on new evidence indicating that DHEA may also function as an important springboard hormone for human sexuality of greater importance to women than men.

DHEA AND DHEAS AS UNIQUE ADRENAL ANDROGEN PRECURSOR HORMONES

Androgen production roles in men and women are relegated to the adrenal glands and gonads. The gonads are the site of testosterone production and secretion in men throughout life; testicular testosterone output persists albeit in an attenuated fashion in most aging men. But, at menopause, the ovary ceases to become a source of androgens for women (4).

The persistence of testosterone in the blood stream of a menopausal woman is largely due to peripheral conversion of adrenal androgen precursors such as dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) to testosterone (5–7). Although the ovary may secrete some DHEA, the sulfated form of this hormone, DHEAS, is primarily an adrenal cortical androgen that differs in many respects from the more commonly recognized adrenal steroids.

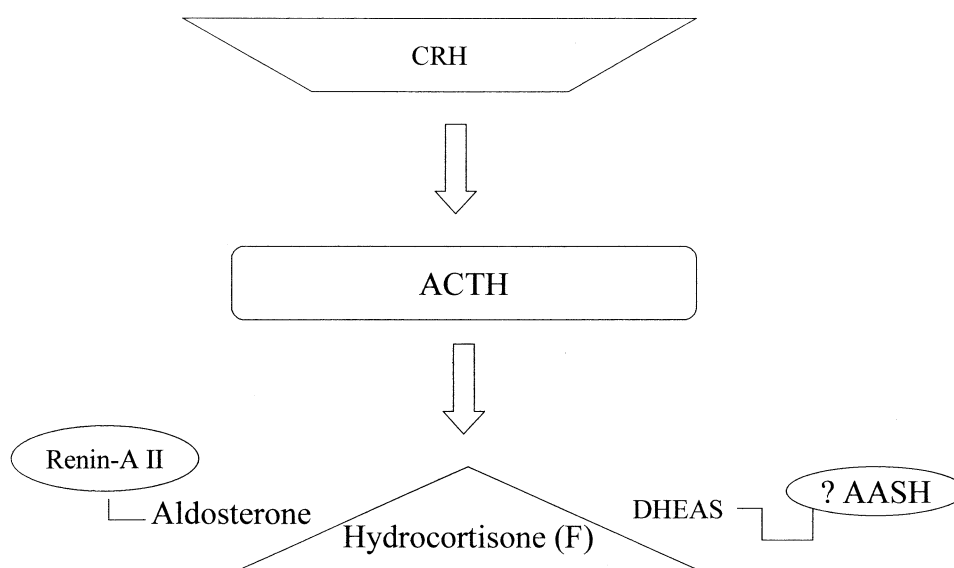
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Reprint requests: Richard F. Spark, M.D., Department of Medicine, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, Massachusetts 02115 (FAX: 617-667-1036; E-mail: rspark@caregroup.harvard.edu).

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FIGURE 1

Control of adrenal steroid production. Pituitary ACTH secretion regulates adrenal cortical hydrocortisone secretion and the renin-angiotensin system modulates aldosterone secretion. A separate adrenal androgen-secreting hormone has been postulated as the stimulus to adrenal androgen secretion.



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The other major adrenal cortex hormones, cortisol and aldosterone, oscillate in response to well-defined patterns of stimulation and suppression. Diurnal variations in pituitary adrenocorticotropic hormone (ACTH) levels govern the moment-to-moment ebb and flow of cortisol secretion from the adrenal gland's zona fasciculata, whereas plasma volume mediated fluxes in the renin-angiotensin system serve to modulate adrenal aldosterone secretion from the cells in the outer adrenal zona glomerulosa.

Adrenal DHEA and DHEAS are products of the adrenal gland's zona reticularis and are synthesized occasionally in response to, but more often than not, independent of the ambient ACTH level. Dehydroepiandrosterone sulfate levels vary widely throughout fetal and adult life without any readily defined stimulatory or inhibitory influences. At one time, a separate adrenal androgen-secreting hormone (AASH) was believed to be responsible for the apparently capricious meanderings of DHEA and DHEAS throughout a person's lifetime (Fig. 1), but a tropic hormonal influence has only been identified to explain the surge in DHEA and DHEAS production occurring during pregnancy.

Placental corticotropin-releasing hormone (CRH) is the adrenal androgen-stimulating hormone in utero (8), which activates fetal adrenal DHEA and DHEAS production. During pregnancy, these adrenal androgens provide the vital hormonal substrates used by the placenta to aromatize to estradiol and estriol that are needed to support the ongoing

pregnancy. Dehydroepiandrosterone and DHEAS levels decline immediately after parturition (9) and are held in check throughout the early childhood years.

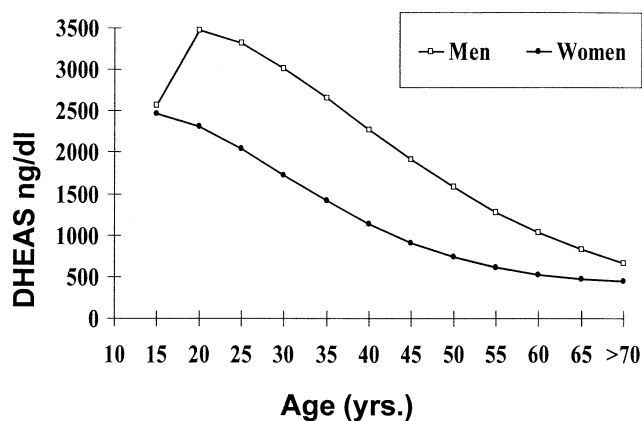
Vigorous DHEA and DHEAS secretion resumes in both prepubertal boys and girls at about age 8–10 to facilitate the growth of sexual hair in the youngsters' genital areas and axillae. This sudden surge in adrenal androgen secretion is referred to as *adrenarche* (10). Ibanez has presented evidence to implicate a sudden surge in hypothalamic CRH as the trigger to adrenarche in both boys and girls, but even here a gender disparity exists regarding evidence for the role of CRH in activating adrenal androgen secretion; it has only been demonstrated in young girls whose lives have been disrupted by the onset of precocious puberty (11).

Adrenarche, the onset of DHEAS (i.e., adrenal androgen secretion), is the obligate precursor of *gonadarche*, the gateway to sexuality and reproductive competence in both sexes. Events of gonadarche are responsible for ovulatory menses in girls as well as spermatogenesis and testosterone secretion in boys.

Curiously, DHEAS levels peak briefly then exhibit a steady *decline* in both sexes. Women still maintain their DHEAS levels within what has been considered to be a normal young adult female range of 1,100–2,470 ng/mL until age 40–44. Thereafter, DHEAS levels decline steadily at a rate of 5% per year. A 70-year-old woman's DHEAS

FIGURE 2

Change in serum DHEAS levels over time in men and women. From Orentreich N et al. (12). Reprinted by permission of the publisher.



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level is only 20% of her normal young adult value (12) (Fig. 2).

The age-related decline in adrenal androgen secretion has been referred to as the *andropause* (13). The forces behind the onset of adrenal androgen production (adrenarche) as well as those factors responsible for andropause, which is the age-related decline in adrenal androgen (DHEAS secretion), involve both hormonal and nonhormonal influences but have not yet been fully defined (14).

CLINICAL CONSEQUENCES OF THE ANDROPAUSE

The apparently inevitable DHEAS decline is more pronounced in some individuals than in others. For men, disproportionately low DHEAS levels have been identified as a risk factor for death from premature cardiovascular disease (15). Men and women choosing to reside in Rancho Bernardo, a California retirement community, agreed to have baseline blood tests to measure a variety of known as well as some suspected health risk factors. Twelve years later, investigators returned to Rancho Bernardo to see how the residents had fared. As expected, DHEAS values declined progressively in all men, but for some men, at each 5-year interval, the decrement in DHEAS levels was greater than in others (15). Those men with the lowest baseline DHEAS levels had died from cardiovascular disease in the interval from initial blood sampling to follow-up evaluation (Table 1).

This observation led to the widespread but still unproven belief that use of DHEA supplements to maintain youthful DHEAS levels could both stifle the aging process and ward

TABLE 1

Baseline DHEAS level and 12-year mortality in men age 50–79.

Age group	Alive n = 166	Deceased n = 76
50–54	277 ± 146	102 ± 0
55–59	213 ± 112	129 ± 7
60–64	157 ± 79	136 ± 44
65–69	156 ± 78	114 ± 48
70–74	136 ± 94	120 ± 62
75–79	100 ± 54	79 ± 43

Note: From Barrett-Connor E, et al. (15). Reprinted by permission of the publisher.

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off death from premature heart disease. No placebo-controlled trial has yet proven this to be true.

PLACEBO-CONTROLLED TRIALS WITH DHEA

The resurgence of interest in DHEA has allowed investigators to identify specific clinical conditions where DHEA supplements have proven to be useful. Because DHEAS is an adrenal based steroid, it is not secreted in patients with adrenal insufficiency. Until recently, conventional treatment of adrenal insufficiency called for replacement therapy with hydrocortisone and the aldosterone surrogate fludrocortisone (Florinef, Apothecon). Dehydroepiandrosterone supplements have not been routinely offered to men and women with adrenal insufficiency. When daily oral 50 mg DHEA supplements are added to conventional hydrocortisone and fludrocortisone therapy, however, substantial benefits accrue to men and women with adrenal insufficiency. In both sexes, the addition of DHEA to conventional adrenal hormone replacement therapy improves well-being and alleviates fatigue.

Furthermore, in women but not in men with adrenal insufficiency, DHEA treatment dramatically improves libido and sexual responsiveness. In separate studies of older men and women with normal adrenal function but low serum DHEAS levels, comparable DHEA doses had a positive beneficial effect on bone turnover and skin hydration, as well as libido in women only.

DHEA VS. PLACEBO IN ADRENAL INSUFFICIENCY

Twenty-four young women (mean age 42 years), 14 with primary and 10 with secondary adrenal insufficiency, who were receiving conventional adrenal hormone replacement with glucocorticoid and, when necessary, mineralocorticoid supplements were treated with either 4 months of DHEA 50

mg/d or placebo. Then, at the conclusion of the treatment period, all these women had a 1-month washout before receiving the treatment they had not received during the first 4 months.

Prior to and during placebo treatment phase, serum DHEA, DHEAS, androstenedione, testosterone, androstenediol glucuronide, and dihydrotestosterone (DHT) were all subnormal. With DHEA 50 mg/d levels of serum DHEAS increased into the normal young female range ng/mL as did levels of downstream androgenic steroids androstenedione, testosterone, and androstenediol glucuronide.

Serum androstenedione increased from 0.05–1.2 ng/mL; testosterone improved from 0.02–0.24 ng/mL; androstenediol glucuronide rose from 0.02–5.0 ng/mL; and dihydrotestosterone (DHT) levels increased from barely detectable to 0.08 ng/mL. In all cases, the DHEA-induced increases for each downstream steroid was significant at the $P < .001$ level. With DHEA treatment, serum DHEAS and androstenedione levels normalized, and serum testosterone and dihydrotestosterone were in the low normal female range. For androstenediol glucuronide, the increase was into the high normal young adult female range.

Coincident with the increase in these downstream steroids, DHEA-treated but not placebo-treated women reported improvement in the frequency of sexual thoughts or fantasies (baseline scores of 29 ± 14 increased to 41 ± 23 , $P < .001$), more sexual interest (baseline scores of 31 ± 15 increased to 45 ± 22 , $P < .001$), as well as measurable improvements in both mental and physical satisfaction with sex baseline scores of 34 ± 25 increased to 55 ± 24 ($P < .04$).

Compared with placebo, DHEA treated women with adrenal insufficiency also experienced an increased sense of well-being. Scores on multidimensional mood questionnaires in the restless—calm domain increased in 4 months from 30 ± 6 to 33 ± 6 ($P < .05$). Increased sexual thoughts and fantasies, however, were apparent within 1 month of starting DHEA (16).

In a separate study restricted to men and women with primary adrenal insufficiency (Addison's Disease), a similar beneficial effect on mood and well-being was observed in both men and women. In that study, mood was assessed by a General Health Questionnaire (GHQ) that assessed anxiety, depression, self-esteem, coping, and social dysfunction individually as well as an overall score. The higher scores indicated that more symptoms are present (17).

A control population of men and women had a GHQ total score of 55.1 ± 10.6 and Addisonian patients had a baseline score of 56.74 ± 8.12 before and 52.59 ± 9.25 ($P < .08$) after DHEA. On a separate mood and fatigue questionnaire scores were unchanged with placebo, but were significantly better after DHEA treatment with the greatest benefit in mood and fatigue evident in the evening hours. The improvement in female sexuality apparent in the Arlt study was not evident

in this series. The authors noted that with DHEA therapy male testosterone levels were unchanged and the percentage increase in female testosterone levels above baseline was not quite as significant as it was in the earlier study (18).

DHEA TREATMENT OF OLDER MEN AND WOMEN WITH NORMAL ADRENAL FUNCTION

In older men and women (>age 65) with normal adrenal function but low serum DHEAS levels (19), the beneficial effects of DHEA were evident once again only in women. As in the studies of men and women with adrenal insufficiency, DHEA 50 mg/d or placebo was administered. Compared with baseline placebo-treated men and women, DHEA-treated men had no improvement in bone density, skin hydration, or sexual function after 12 months.

Bone Density

In DHEA treated women age 60–69, significant increases in bone density at the femoral neck and Ward's triangle were evident. Radius bone density increased for 70–79-year-old women. The biologic index of bone resorption (Ctx) decreased by 11% at month 6 and 26% at month 12.

Skin Hydration

Skin surface hydration improved in DHEA treated men and women $P < .01$ at month 12 of DHEA treatment as did age-related skin pigmentation; but the changes were more dramatic in women with a 7% and 10% reduction in pigmentation, respectively, in women under and over age 70. Compared to pretreatment measurements after 12 months of DHEA therapy skin surface hydration increased in both men and women $P < .01$ whereas the decline in facial skin pigmentation was more pronounced in women $P < .03$.

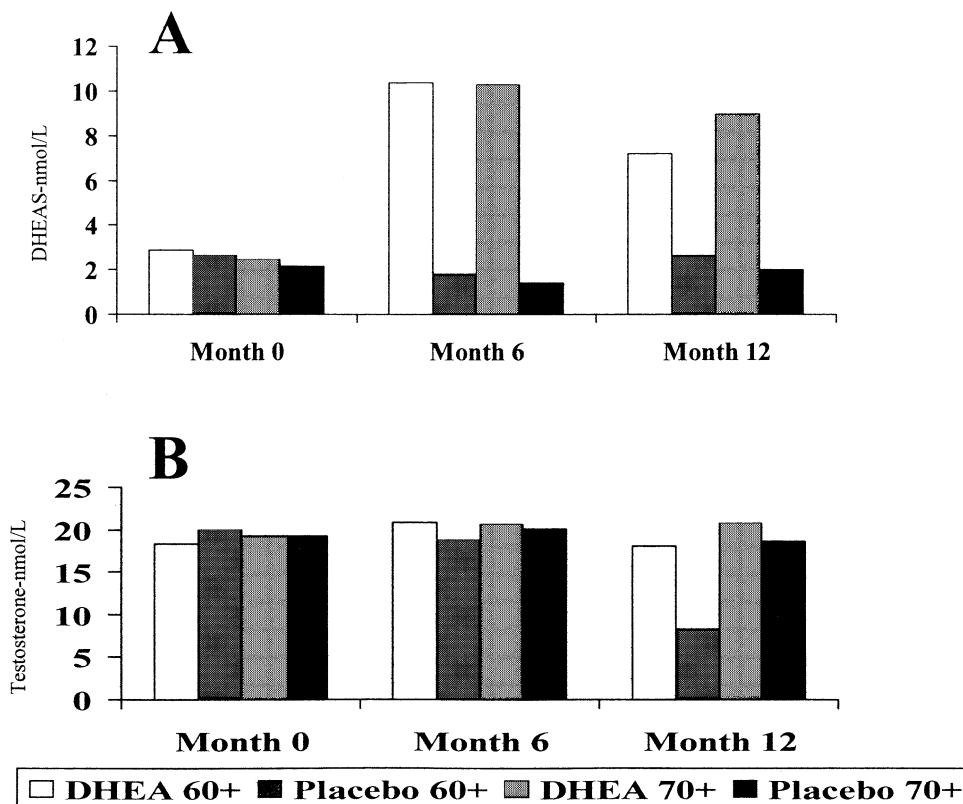
Androgen Levels and Sexual Function

During DHEA treatment, prompt increases in serum DHEAS levels were apparent in both sexes. In men, however, the increase in serum DHEAS level was not accompanied by any change in serum testosterone level (Fig. 3A, B), whereas in women, DHEA treatment was associated with a twofold increase in serum testosterone levels above baseline (Fig. 4A, B). Dehydroepiandrosterone-treated women responded to questions similar to those used to evaluate sexual function in women with adrenal insufficiency.

Coincident with the increase in their serum testosterone level, sexual function improved. Compared with their baseline responses, women over age 70 had both an increase in sexual excitation and libido at 6 months ($P < .05$), and at 12 months had statistically significant improvements in intercourse or masturbation frequency and quantitative sexual satisfaction ($P < .01$).

FIGURE 3

(A and B), Serum DHEAS and testosterone levels in men >age 60 after placebo or DHEA 50 mg/d. Adapted from Baulieu EE et al. (19).



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VARIABLE POTENCY OF DHEA PREPARATIONS

Not everyone who takes DHEA experiences the same beneficial response. In order to understand why, Parrisrampurria and Schwartz obtained 17 DHEA-labeled bottles from various sources, analyzed each tablet for actual DHEA content, and then reported their findings in the *Journal of the American Medical Association (JAMA)*. Tablets from three vendors contained no DHEA at all. Most had 59%–82% of the expected amount whereas one tablet had significantly more — actually 149% — of the amount of DHEA stated on the label (20).

DISCUSSION

Dehydroepiandrosterone has had a murky history and now appears to be poised to make the transition from trendy health food supplement to an androgenic hormone worthy of study. Lacking a pharmaceutical sponsor to usher it through the arduous process of Federal Drug Administration (FDA)

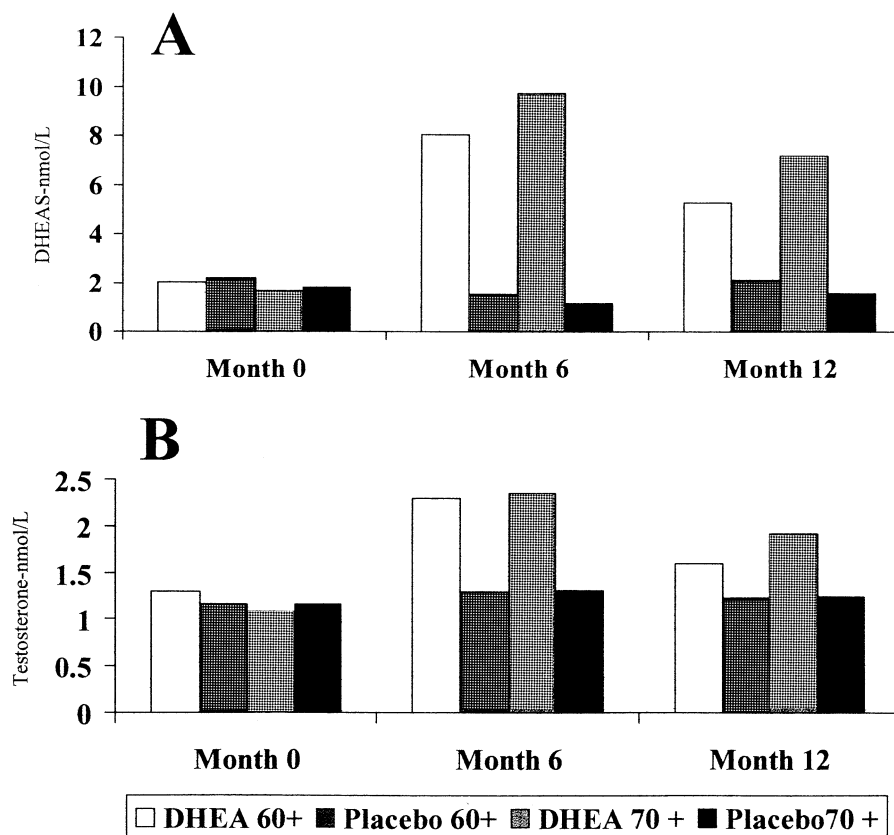
approval, DHEA drifted for years in the netherworld of health care products.

Two events of note changed the destiny of DHEA. The first was the 1986 Rancho Bernardo report noting that men with a DHEAS level lower than their age-matched controls were more likely to experience a premature cardiovascular death. The second event was the passage of the 1994 Dietary Supplement and Health Education Act (DSHEA), which resulted in the classification of this natural adrenal androgenic hormone as a “dietary supplement” to be sold as an over-the-counter health care product. The ready availability of DHEA coupled with a public eager to believe that DHEA offered a veritable fountain of youth resulted in the promotion of this hormone by the anti-aging community where it continues to flourish.

Serious scientists shunned what appeared to be a cult androgen until the latter part of the 20th century when independent placebo-controlled studies demonstrated that DHEA supplements improved well-being in men and women with adrenal insufficiency and improved sexual

FIGURE 4

(A and B), Serum DHEAS and testosterone levels in women >age 60 after placebo or DHEA 50 mg/d. Adapted from Baulieu EE et al. (19).



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function in women with adrenal insufficiency. Similarly, in men and women over age 60, DHEA proved more useful to women than men.

How do androgens in general and DHEA in particular improve well-being and sexual function in women? Most hormones interact with hormone-specific receptors, but with the exception of bone, no DHEA-specific receptors have been identified anywhere in the body. Androgen receptors, capable of interacting with testosterone and other endogenous anabolic steroids, however, are present in abundance.

Thus, transdermal testosterone patch therapy increases serum testosterone levels, activates androgen receptors, and restores sexual function in menopausal oophorectomized women, but only when testosterone doses are high enough to catapult serum testosterone and dihydrotestosterone levels into the supra physiologic female range (21).

In contrast, DHEA, the adrenal androgen hormone precursor, provides the hormonal substrate that a woman's body

can use to convert (to normal young adult female levels) the more potent androgenic sexual steroids — testosterone, androstenediol glucuronide, and dihydrotestosterone — which then interact with androgen receptors.

Dehydroepiandrosterone supplements have not had a significant impact on male sexuality, possibly because, in the presence of adequate testicular testosterone secretion, the addition of adrenal androgens does not materially augment a man's total testosterone pool. It should be noted that not all studies show beneficial effect of DHEA on female sexual function. Some have reported an improved sense of well-being but no improvement in libido or sexual function when high DHEA doses (100 mg per day) are administered for 3 months to older men and women (22). Others have found neither an improvement in well-being nor sexual function after 6 months treatment with DHEA, 50 mg per day (23).

To date, DHEA has proven to be most effective in improving female sexual function when either a lack of adrenal DHEAS synthesis (adrenal insufficiency) or a loss of ovarian

testosterone secretion (menopause) is responsible for the androgen deficit.

It remains to be determined whether those premenopausal women with diminished libido and lower than expected age-matched serum DHEAS levels represent another category of women for whom DHEA supplements would be appropriate. We now know that, in many instances, the DHEAS deficient woman can use DHEA as an androgen precursor building block to gently allow her serum testosterone levels to waft up into, but not above, the normal female range.

Female androgen deficiency is characterized by low libido and low dehydroepiandrosterone sulfate (DHEAS) levels. Dehydroepiandrosterone 50 mg/d restores young adult female DHEAS and androgen levels and may improve sexual function.

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