Dehydroepiandrosterone: Is There a Role for Replacement?

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Dehydroepiandrosterone (DHEA) and its sulfated ester are found in high concentrations in the plasma; however, their role in normal human physiology, other than as precursors for sex hormones, remains incompletely defined. Studies of rodent models have shown that these hormones have beneficial effects on a wide variety of conditions, such as diabetes, obesity, immune function, atherosclerosis, and many of the disorders associated with normal aging. However, rodents are not the best models to study the actions of these hormones because they have very little endogenous DHEA; thus, the doses given to these animals are usually suprapharmacological. Human studies have been performed to determine the potential beneficial effects of

DHEA replacement in persons with low DHEA levels. Results have been conflicting. Human studies suggest a potential role for DHEA replacement in persons who have undergone adrenalectomy and possibly in the aging population. However, long-term studies assessing the benefits vs adverse effects must be done before DHEA replacement can be recommended.

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AD = Alzheimer disease; BMD = bone mineral density; DHEA = dehydroepiandrosterone; DHEAS = DHEA sulfate; IL = interleukin; MID = multi-infarct dementia; NMDA = *N*-methyl-D-aspartate; REM = rapid eye movement

D ehydroepiandrosterone (DHEA) and its sulfated ester (DHEAS) have been studied increasingly during the past few years, with substantial evidence emerging about their possible roles in normal human physiology. Recent data have shown that DHEA levels are highly correlated with longevity in healthy nonhuman primates,[1] and headline phrases such as "mother of all hormones," "superhormone," and "fountain of youth" have brought these hormones to the attention of the lay public. Use of the Internet search engine Google (www.google.com) in the last week of August 2003 revealed more than 400,000 Web sites mentioning DHEA. This review includes a MEDLINE search of English language articles thought to be relevant with the terms *DHEA* or *Prasterone*. Any related articles were also examined for potential inclusion in this review.

Low or absent levels of DHEA are found in healthy elderly individuals and those with adrenal insufficiency (hypoadrenal subjects). Long-term trials of DHEA replacement in these groups are currently in progress in the United Kingdom and in the United States. With the availability of DHEA as an over-the-counter product in the United States and on the Internet worldwide, this review provides generalists and specialists with information about these hormones and will aid them in determining whether DHEA replacement has a role in individuals in whom levels are low.

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BIOCHEMISTRY AND PHYSIOLOGY OF DHEA

DHEA and DHEAS are 2 of the major C_{19} steroids secreted by the zona reticularis region of the adrenal glands. As with all C_{19} steroids, these hormones are products of cholesterol metabolism and are derived from the action of CYP11A (cytochrome P-450scc) on the inner membrane of the highly active mitochondria found in the adrenal cortex.[2] In humans, DHEA and DHEAS are the most abundant circulating steroid hormones. Their role remains to be fully elucidated. DHEAS can be readily converted to unconjugated DHEA by ubiquitous tissue steroid sulfatases and thus probably serves as a reservoir for DHEA. A simplified illustration of the steroid synthesis pathway is shown in Figure 1. Note that DHEA, testosterone, and estrogens are derived from the precursor 17-hydroxypregnenolone by the action of 17α-hydroxyprogesterone aldolase, a reaction catalyzed by cytochrome P-450$_{c17}$. Investigators have proposed that the decline in DHEA levels (Figure 2) with senescence is associated with a decline in activity of this enzyme, resulting in low levels of DHEA and testosterone.[4-6] This theory has yet to be confirmed.

Often, DHEA and DHEAS are referred to as weak androgens; however, there is no evidence that they bind to the androgen receptor. Thus, DHEA and DHEAS have little or no intrinsic androgenic activity. However, they are converted into androstenedione and then further into potent androgens and estrogens in the liver and other target organs.[7] These transformations depend on the tissue activity of steroidogenic and metabolizing enzymes such as 3β-hydroxysteroid dehydrogenase/Δ^5-Δ^4-isomerase, 17β-hydroxysteroid dehydrogenase, 5α-reductase, and aromatase.[8]
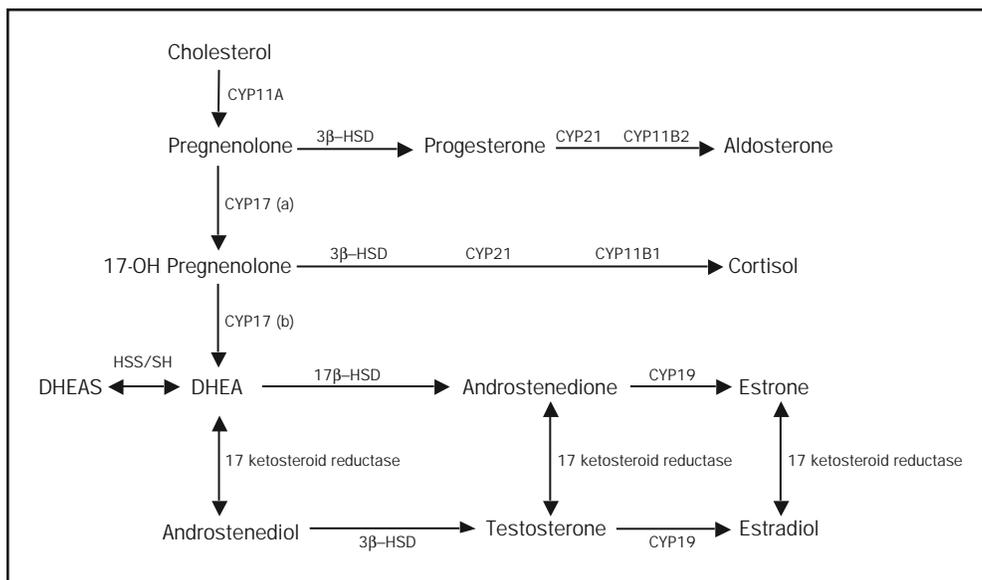
Figure 1. Simplified steroid synthesis pathway. CYP11A = 20,22 hydroxylase, 20,22-desmolase; CYP11B1 = 11β hydroxylase; CYP11B2 = 11β hydroxylase, 18-hydroxylase and 18-oxidase; CYP17 (a) = 17α hydroxylase (catalyzed by P-450$_{c17}$); CYP17 (b) = 17α-hydroxyprogesterone aldolase (catalyzed by P-450$_{c17}$); CYP19 = aromatase; CYP21 = 21 hydroxylase; DHEA = dehydroepiandrosterone; DHEAS = DHEA sulfate; 3β-HSD = 3β-hydroxysteroid dehydrogenase; 17β-HSD = 17β-hydroxysteroid dehydrogenase; HSS = 3β-hydroxysteroid sulfotransferase; SH = sulfohydrolase.

DHEA and DHEAS are adrenal precursor sex steroids produced in vast quantities. The active form is DHEA, and DHEAS is enzymatically converted into DHEA in peripheral tissues in an intracrine fashion.[9] Although both DHEA and DHEAS are bound to albumin in the plasma, DHEAS is bound more firmly, and, unlike DHEA, DHEAS is not bound to sex hormone–binding globulin but is free in the circulation. In addition, because DHEA is rapidly cleared from the circulation and has a half-life of 1 to 3 hours, it has a circadian rhythm related to that of the secretion of corticotropin.[10,11] However, DHEAS is cleared at a much slower rate and has a half-life of 10 to 20 hours; thus, levels do not vary substantially in the plasma.[12]

The direct mechanism of action of DHEA, if any, is unknown. The effects of DHEA are due to the actions of the sex hormones into which it is converted. Although recent studies found specific receptors to help explain some of the actions of DHEA, the mechanisms of other actions of this hormone remain elusive. An example of these receptors includes skeletal muscle binding sites.[13] These receptors may have therapeutic value in the treatment of disorders associated with low DHEA levels, such as myotonic dystrophy.[13] Other receptors include those thought to be responsible for some of the protective cardiovascular effects of DHEA. These effects are mediated through a specific G protein–coupled plasma membrane receptor leading to an increase in endothelial nitric oxide synthase.[14] A DHEA-specific receptor-binding complex has also been found in murine and human T cells. In this model, DHEA binding to this receptor complex led to an increase in interleukin (IL) 2 production.[15,16]

In both sexes, DHEA levels vary profoundly throughout life (Figure 2). Levels are high at birth but quickly decline within a few months. Levels start to increase in children 8 to 10 years of age, peaking by the middle or end of the second decade of life. Levels then decline by 10% per decade, plateauing after a person is older than 80 years.[3,12,17,18] As mentioned previously, a recent theory is that high circulating plasma DHEA levels are a marker for longevity in primates.[1] Evidence for this in humans is based on analyzing ethnic differences in DHEA levels, which suggests that life expectancy may be greatest in populations in whom DHEA levels are highest.[19] An alternative explanation for this finding is that people who are healthier have higher DHEA levels.

The decline in circulating DHEA levels parallels many age-related changes, such as sarcopenia and osteopenia. In studies of men who have undergone castration, approximately 30% to 50% of circulating androgens are derived from DHEA. The remaining androgens come from the testes as testosterone. Both DHEA and testosterone are then converted into the active androgen dihydrotestos-

terone in the peripheral tissues.[20] In postmenopausal women, the origin of most circulating androgens is controversial. Some authors state that androgens are derived from DHEA and that production from the ovaries is minimal,[21,22] whereas others state that the ovaries remain an important source of testosterone.[23,24] Subjects (especially female) with adrenal insufficiency have chronic DHEA deficiency because routine replacement therapy with glucocorticoids and mineralocorticoids fails to restore DHEA-derived androgens.[25] Therefore, replacement of these androgens in subjects with adrenal insufficiency should aim to restore concentrations to levels equivalent to those before the onset of the condition. A substantial amount of work has been done in both elderly subjects[26,27] and hypoadrenal subjects[28] to determine the optimal dose to restore DHEA levels to those seen in young adults; 50 mg/d is sufficient to increase DHEA levels into the reference range of age-matched young adults.[29,30]

Clearly, differences are to be expected between the normal physiological process of aging and the pathological state of adrenal insufficiency. Hypoadrenal individuals have little or no circulating DHEA; however, elderly persons, although having substantially lower levels than healthy individuals in their second or third decade, have levels that may be several-fold greater than in those with adrenal insufficiency. These differences mean that relating and inferring results from one group to another is difficult; however, the premise of much of the current clinical research in both aging and hypoadrenal subjects is that the 2 groups are interchangeable. This link between elderly and hypoadrenal subjects is compounded by the findings of studies that have analyzed different measures of general well-being, libido, and mood and have found similar results in both groups.[29,31-33] Despite this, there are clearly differences in the clinical presentation of a hyporenal subject vs an elderly subject.[34]

Many disorders of aging, such as reduced immunocompetence, obesity, diabetes, and cancers, have been attributed to changes in DHEA based on animal studies[9,35] and human epidemiological data.[36-39]

EXPERIMENTAL EVIDENCE OF BIOLOGIC AND CLINICAL EFFECTS
Mood and Well-being

Sex hormones are known to play an important role in mood and well-being in both sexes (Table 1). Because levels of these hormones decline with aging, there is a parallel deterioration of mental function, and DHEA replacement is thought to be of potential benefit.

As a neuroactive neurosteroid, DHEA has become more important with the discovery that both DHEA and DHEAS are produced in the brain independently and are not influ-
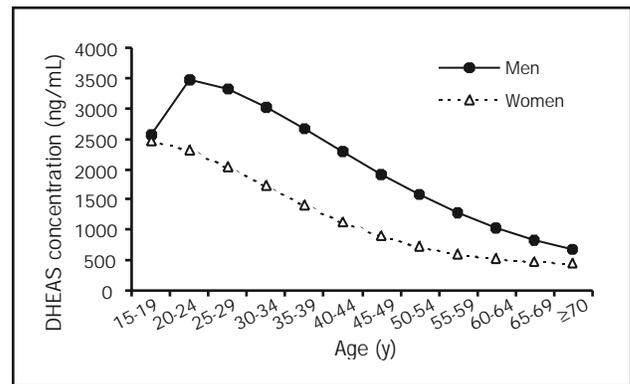

Figure 2. Changes in levels of circulating dehydroepiandrosterone sulfate (DHEAS) with aging. Reproduced from Orentreich et al[3] with permission from the Endocrine Society.

enced by factors that control adrenal DHEA secretion.[54] Some reports have shown high concentrations in the brain, with the brain-plasma ratio being 4:6.5.[55,56] It is known that pregnenolone and its sulfated ester are the precursors for DHEA, but how pregnenolone is produced in neural tissue remains unclear.[11] The role of DHEA in the brain also remains unclear, but recent work in mice suggests that the hormone is important in guiding thalamic fibers to their cortical targets in the embryonic brain by the regulation of motility and growth of corticothalamic projections.[57]

Some in vitro and animal data provide biologic plausibility for the psychotropic effects of DHEA; DHEA acts as an antagonist on the receptor of the major inhibitory neurotransmitter γ-aminobutyric acid,[58] perhaps by acting close to or at the sites where barbiturates act. Administration of DHEA in rats has been shown to increase hypothalamic serotonin levels.[59] Further work in rats has shown that DHEA binds to the excitatory N-methyl-D-aspartate (NMDA) receptor.[60] γ-Aminobutyric acid and serotonin are known to be mood-related receptors, and both have targeted, prescribable pharmacological agents (benzodiazepines and selective serotonin reuptake inhibitors, respectively) used as antidepressants, whereas NMDA ("ecstasy') is a psychotropic drug of abuse.

There are several reasons why estrogens may play a role in ameliorating the cognitive and emotional disturbances associated with menopause. Estrogens have been shown to produce an increase in attention span, concentration, libido, and memory in postmenopausal women.[61] However, in aging men, despite DHEA administration increasing circulating estrogens and androgen metabolites, this beneficial effect on mood has been an inconsistent finding,[29,44] possibly because endogenous production of androgens from the testes compensates for the effects of the declining levels of DHEA in such men.[44]

Table 1. **Summary of Human Studies Analyzing Effect of DHEA on Mood, Well-being, Cognition, and Memory***

Type of subject and age (y)	Sex (No.)	Type of study	DHEA Dose (mg/d)	Duration	Results	Reference
Healthy elderly						
>65	M and F (622)	O	NA	NA	Low DHEA levels associated with depression (significant in women, trend in men)	Berr et al[40]
40-60	F (141)	O	NA	NA	DHEA levels positively correlated to well-being	Cawood & Bancroft[41]
50-90	F (699)	O	NA	NA	DHEA levels positively correlated to well-being	Barrett-Connor et al[42]
69 (mean)	M (25); F (15)	P, R	50	2 wk	Nonsignificant trend toward improvement in mood	Wolf et al[43]
40-70	M (13); F (17)	P, R, C	50	3 mo	Improvement in mood	Morales et al[29]
50-69	M (22)	P, R, C	50	4 mo	No change in mood	Arlt et al[44]
>50, M; >55, F	M (270); F (167)	O	NA	NA	DHEA levels not correlated with cognitive decline	Barrett-Connor & Edelstein[45]
Healthy institution-alized elderly						
55-104	M (111)	O	NA	NA	DHEA levels lowest in those with AD or MID	Rudman et al[46]
Elderly with dementia						
80	M (35); F (51)	O	NA	NA	DHEA levels lower in those with AD or MID vs controls	Näsman et al[47]
Healthy elderly and elderly with AD						
75 (healthy mean); 76 (AD mean)	M (22); F (32)	O	NA	NA	Women with AD had significantly higher DHEA levels	Rasmuson et al[48]
69	M (30); F (40)	O	NA	NA	DHEA levels not correlated with cognitive function	Schneider et al[49]
Hypoadrenal						
26-69	M (15); F (24)	P, R, C	50	3 mo	Improvement in mood	Hunt et al[33]
23-59	F (24)	P, R, C	50	4 mo	Improvement in mood	Arlt et al[32]
With depression						
51-72	M (3); F (3)	OL	90	6 wk	DHEA significantly improved all measures of mood and well-being	Wolkowitz et al[50]
33-53	M (12); F (10)	P, R	90	6 wk	DHEA significantly improved all measures of mood and well-being	Wolkowitz et al[51]
Healthy with midlife dysthymia						
45-63	M (12); F (3)	P, R, C	90, 450	3 wk†	DHEA significantly improved all measures of mood and well-being	Bloch et al[52]
With anorexia						
14-28	F (61)	R	50	12 mo	Improvement in mood	Gordon et al[53]

*AD = Alzheimer disease; C = crossover design; DHEA = dehydroepiandrosterone; MID = multi-infarct dementia; NA = not applicable; O = observational; OL = open label; P = placebo controlled; R = randomized.
†Each dose.

Evidence from small-scale open-label studies in healthy elderly human volunteers shows that DHEA supplementation increases levels of β-endorphin,[62] an endogenous opioid that causes an increase in well-being. Long-term large epidemiological studies in humans have shown that mood in elderly women correlates with DHEA, with low levels found in those with depression.[40]

Quality of life in hypoadrenal subjects has been found to be lower compared with that in healthy controls.[63-65] Studies assessing the effects of DHEA replacement on sexual and psychological well-being have been performed in hypoadrenal subjects who have undergone adrenalectomy[32,66,67] and in elderly subjects.[29,41,62] However, of the studies analyzing DHEA replacement, one used only a nonvalidated personal interview to assess general and psychological well-being,[31] whereas others showed conflicting results when evaluating sexuality.[42] The various results are summarized in Table 1. Clearly, based on the reported studies, no consensus is available. In most studies, DHEA replacement in hypoadrenal subjects seems to lead to an improvement in mood. The effect on depression and other conditions appears to be dose dependent and is probably related to duration of administration. Carefully conducted long-term studies in well-defined populations are critical to make definitive conclusions on the effects of DHEA on mood and well-being.

Cognition and Memory

Alzheimer disease (AD) and multi-infarct dementia (MID) are relatively common in the aging population.[68,69] Some evidence shows that AD is due to hippocampal damage induced by free radicals, resulting in increased lipid peroxidation and alteration in free radical defense mechanisms.[70] Animal studies using the centrally administered β_{25-35}-amyloid peptide as a model for AD have shown that administration of DHEA reduces the rate of decline of cognitive function usually associated with the introduction of this protein.[71] In addition, some in vitro work suggests that DHEA can reduce this free radical–induced damage.[72] The manner in which this protection is afforded has yet to be fully established. In addition, DHEA use in vivo seems limited because doses were suprapharmacological.

The hippocampus is thought to be the area of the brain associated with memory. A substantial portion of the biochemical work analyzing the effects of DHEA is from in vitro and animal studies. In vitro work evaluating rat embryo hippocampal cultures showed a decline in cell numbers, a change in morphology, and an increase in the production of the stress-activated protein kinase 3 in those cultures exposed to corticosterone.[73] With aging, the rate of loss of hippocampal neurons in rats increases, and this loss is substantially accelerated with the addition of glucocorticoids.[73] All these changes were attenuated when DHEA was added.[74] In other experiments that used cell cultures exposed to the excitatory amino acids NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, the expected decline in the hippocampal cell number was not seen when DHEA was added, but DHEA alone did not increase the number of cells in culture.[75]

Evidence is accumulating that high glucocorticoid levels are neurotoxic,[76] and this may be a mechanism for the psychological disturbances seen in patients with hypercortisolism.[77] In vitro work has shown that DHEA modulates this response.[74]

The mechanism of DHEA neuroprotection is unknown. However, it has been shown that in the rat hippocampus levels of the immediate precursor to DHEA production, pregnenolone sulfate, are highly correlated with spatial memory performance.[78] Confirmation that this occurs in humans has yet to be established. In the developing rat embryo, the rates of cell birth, migration, and survival are highly dependent on adrenal steroid levels. Whether this occurs in humans is unknown; however, in a postmortem study of 1 patient with Addison disease, there was evidence of dentate gyrus neuronal loss, suggesting a similar requirement for adrenal steroids.[79]

Large-scale epidemiological work specifically analyzing DHEA and cognitive function has been conflicting. One study showed that the reduction in DHEA levels with normal aging did not correlate with cognitive decline.[45] That study also evaluated mortality and showed that subjects with a DHEA level in the lowest quartile at baseline were more likely to die at follow-up 15 years later compared with those whose levels were in the upper quartile.[45] This represented an increase in mortality of 40% and 24% in men and women, respectively. However, decline in cognitive function was not greater among those who died before follow-up.

Other epidemiological studies have supported the hypothesis of the link between low DHEA levels and AD. Luchsinger et al[80] reported that reducing caloric intake might reduce the risk of AD in individuals carrying the apolipoprotein E epsilon4 (*APOE4*) allele. People with *APOE4* are more vulnerable to AD at an earlier age.[81] Roth et al[1] also found that caloric restriction delays the age-related decline in DHEAS levels in nonhuman primates and suggest this may also be true in humans. Moreover, recent work from France analyzed DHEAS levels in postmortem specimens from 11 elderly subjects with and without AD; a significant correlation was found between areas of the brain that have high levels of both β-amyloid protein and the pathological tau protein seen in patients with AD and low levels of DHEAS.[82]

Some evidence from observational studies of the relationship between DHEA levels and AD and MID is conflicting.[46,48] Early data show that low DHEA levels were associated with both AD and MID. One such study compared DHEA levels in 50 independently living community men aged 55 to 94 years with levels in 61 male nursing home residents aged 57 to 104 years.[46] There was an inverse relationship between DHEA levels and the presence of either AD or MID. In addition, there was an inverse relationship between DHEA levels and the degree of dependence in activities of daily living. Further analysis showed that the plasma DHEA level was lowest in 80% of the male nursing home residents who required total care. In another observational study of patients requiring total care who had either AD or MID, the prevalence of low DHEA levels was 68% and 100%, respectively.[46] This last-mentioned finding is consistent with that of Näsman et al[47] that elderly patients with organic brain disease have low DHEA levels. This group also found that the cortisol/DHEA ratio was high. High DHEA levels are associated with a lower cortisol/DHEA ratio, and this has been proposed as a mechanism that prevents cognitive decline in these individuals.[83]

However, these results conflict with those from an observational study of 35 subjects with AD that found no differences in DHEA levels compared with age- and sex-matched controls.[49] Moreover, it remains to be determined whether decreases in DHEA levels cause physical and

cognitive changes or whether DHEA levels represent an overall decline in physical function. However, data suggesting that DHEA levels are low in patients with organic brain disease conflict with more recent work suggesting that DHEA levels are increased in patients with AD and MID.[48]

Low levels of DHEAS rather than of DHEA may be the cause of these dementias. In a descriptive study analyzing 40 elderly subjects with either AD or vascular dementia and their age-matched controls, serum concentrations of DHEA did not significantly differ.[84] However, subjects with dementia had lower concentrations of serum DHEAS and a lower DHEAS/DHEA ratio compared with normal controls. The significance of this has yet to be determined.

Evidence for the potential benefits of DHEA is available from several sources. A randomized double-blind study of 17 individuals showed that a supraphysiological dose of 90 mg of DHEA was associated with a substantial benefit in the treatment of midlife-onset dysthymia in both men and women.[52] Smaller-scale studies have shown that DHEA is as effective as more "traditional" therapies for major depression.[50,51] However, the latter study[51] was randomized, whereas the first study[50] was open-label. Results of these studies are summarized in Table 1.

Preliminary work with 10 healthy young volunteers showed that a single pharmacological dose of 500 mg of DHEA enhanced relaxation by increasing the amount of time spent in rapid eye movement (REM) sleep,[85] the time of sleep during which memory is established and which has a key role in language and emotional learning.[86] A study with electroencephalography analyzed the effects of various glucocorticoids, their biosynthetic precursors, and their metabolites on sleep patterns.[87] This work showed that the effects could be attributed to the mode of action of these neuronally produced steroids. Specifically, steroids such as pregnenolone and DHEA were thought to be produced in glial cells and act in a paracrine fashion, thus modifying the sleep electroencephalogram in humans in a manner that suggested their potential as memory enhancers.[87]

However, a recent review article challenged this viewpoint, stating that REM sleep is not necessary for establishing memory because REM deprivation in humans is not associated with memory dysfunction.[88] Thus, the effects of glucocorticoids and DHEA on memory and sleep remain to be fully clarified.

Together, these findings suggest that reducing caloric intake extends the availability of DHEA and may be a causative factor in the delay or prevention of AD. This experimental evidence from observational studies remains to be established in interventional human studies.

Sexual Functioning

Various studies on the effect of DHEA on sexual function are summarized in Table 2.

The role of testosterone in the sexuality and sexual functioning of hypogonadal women was recently shown in a randomized crossover study involving 75 women who had undergone oophorectomy. Shifren et al[94] showed that testosterone supplementation in women taking estrogen replacement significantly improved sexual function and psychological well-being. Thus, the role of estrogens alone in sexual well-being is potentially limited.

A retrospective open-label study revealed an association between the complex relationship of sexual physiology, desire, arousal, and orgasm with DHEA levels.[93] This study also suggested that DHEA was important in genital smooth muscle relaxation and genital sensation.[93]

Free testosterone and DHEA levels are reduced in women taking estrogen.[95,96] The impact that this decrease in DHEA and testosterone has on overall sexual functioning is unknown because observational studies have shown a positive correlation between libido and testosterone levels.[89]

In hypoadrenal women who have undergone natural or surgical menopause, androgens given in addition to estrogens provided a beneficial effect on sexuality.[97,98] In a randomized study of 24 women with adrenal insufficiency, Arlt et al[32] showed that 50 mg/d of DHEA was associated with a highly significant improvement in all aspects of sexual well-being. In a randomized controlled trial, Johannsson et al[67] gave either placebo or DHEA to 38 androgen-deficient women with hypopituitarism. In the DHEA group, the subjects were further divided by age: women older than 45 years received 20 mg/d and women younger than 45 years received 30 mg/d of DHEA for 6 months. With both doses, there was an improvement in androgen-dependent effects such as in skin (oil, moisture, and elasticity) and increases in both axillary hair and pubic hair. In addition, with the dose of 30 mg/d, all subjects had an increased score in sexual interest and activity. With the dose of 20 mg/d, only 41% of subjects had these changes. Although there was a trend, this improvement was not statistically significant because a few subjects taking placebo also showed an improvement. In that same study, the women's partners were asked to grade changes in personality and mood. The partners of subjects taking DHEA replacement recorded a statistically significant overall improvement in alertness, stamina, and initiative. This difference in perception of well-being between participants and their partners remains unclear. As part of the trial, the last 6 months were an open-label treatment with DHEA. During that time, subjects who had initially been taking placebo reported changes similar to those who had been taking DHEA for the entire trial.

Table 2. **Summary of Human Studies Analyzing Effect of DHEA on Sexual Functioning***

Type of subject and age (y)	Sex (No.)	Type of study	DHEA Dose (mg/d)	Duration	Results	Reference
Healthy						
With decreased libido						
24-78	F (105)	O	NA	NA	70% of subjects had low DHEA levels	Guay & Jacobson[89]
31-48	F (8)	OL	50-100	Not given (minimum 8 wk)	6 of 8 women regained normal sexual desire	Guay[90]
Premenopausal						
24-34	F (12)	P, R, C	300	Single dose	No effect on sexual arousal	Meston & Heiman[91]
Postmenopausal						
51-68	F (16)	P, R, C	300	Single dose	Increased sexual arousal	Hackbert & Heiman[92]
With sexual dysfunction						
43.5 (mean)	F (113)	OL	50	4±2 mo	Improvement in sexual well-being	Munarriz et al[93]
Hypoadrenal						
23-59	F (24)	R, C	50	4 mo	Improvement in sexual well-being	Arlt et al[32]
25-65	F (38)	R (OL)	30 (<45 y), 20 (≥45 y)	6 mo	Nonsignificant trend toward improvement in 30-mg group only	Johansson et al[67]
26-69	M (15); F (24)	P, R, C	50	3 mo	No improvement in sexual function	Hunt et al[33]
Healthy						
40-70	M (13); F (17)	P, R, C	50	3 mo	No improvement in sexual function	Morales et al[29]

*See footnote to Table 1 for expansion of abbreviations.

Further uncertainty about DHEA effects on sexual functioning in women was revealed in 2 recent placebo-controlled randomized studies of 16 postmenopausal and 12 premenopausal healthy volunteers who received a single 300-mg dose of DHEA.[91,92] All the women were sexually active. They were shown erotic videos after a period of "neutral" visual stimulation. Physical sexual responses were assessed using measurements of vaginal pulse amplitude and vaginal blood flow. These studies showed significantly greater mental and physical sexual arousal to visual stimulation in only the DHEA-treated postmenopausal women.[92] There were no differences seen in the DHEA-treated premenopausal group compared with the placebo group.[91] The reason for these differences is unclear but may be due to the effects of endogenous ovarian steroids negating the effects of DHEA.

Other studies have shown a correlation between serum levels of DHEA and testosterone with libido in young women who have a decreased or absent sexual desire[89,99] (Figure 3). An interventional study with 12 premenopausal women with sexual dysfunction and low libido showed that low libido occurred most frequently in women with low DHEA levels and that replacement of DHEA, either 50 mg/d or 100 mg/d, restored sexual function[90] (Table 2).

Use of DHEA in men has not been researched as extensively as in women. In randomized crossover studies with healthy elderly or hypoadrenal men given 50 mg/d or 100 mg/d of DHEA for 3 months, there was no benefit in any of the indices of sexual function.[29,33,100] This outcome may have occurred because the endogenous testosterone canceled the effects of the DHEA. This result contrasts that in a small randomized trial in elderly men that showed a daily dose of 50 mg of DHEA may be useful in the treatment of erectile dysfunction.[101]

In summary, results are conflicting regarding the effects of DHEA administration in men, in premenopausal and postmenopausal women, and in normal and hypoadrenal subjects. Furthermore, large long-term randomized studies are needed to address this issue. Another issue that needs to be determined is whether replacement doses or pharmacological doses of DHEA are needed to achieve beneficial effects.

Insulin Sensitivity

Most of the work done on insulin sensitivity has been in animal models. Extrapolating these results to human studies is difficult because rodents produce very little endogenous DHEA and the demonstrated effect is pharmacological rather then physiological. However, human studies have been done and are reviewed subsequently along with relevant animal studies.

DHEA lowers serum insulin levels and increases insulin sensitivity in rodent models.[102-104] The mechanism of action is unclear because this reduction is achieved without im-
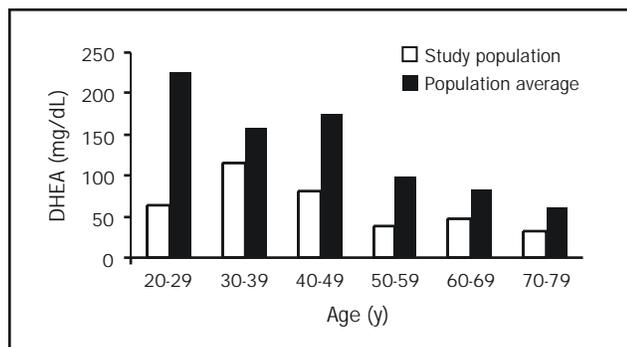
Figure 3. Dehydroepiandrosterone (DHEA) levels in women of all ages with reduced or absent libido compared with women with normal libido. *P*<.05 in all groups. Data from Guay and Jacobson.[89]

provement in insulin resistance in peripheral tissues and without lowering pancreatic insulin content. The decrease in insulin levels with DHEA supplementation may be a contributing factor in lowering body weight or altering metabolic efficiency in DHEA-treated rats. Lowered serum insulin levels may be responsible for reduced activities of lipoprotein lipase, glucose-6-phosphate dehydrogenase, and fatty acid synthetase measured in DHEA-treated obese rats.[102] Proposed mechanisms for this include improved muscle insulin signaling, as reflected in binding of phosphatidylinositol 3-kinase to the insulin receptor substrate 1. However, despite the decrease in insulin levels, there appears to be a lack of effect of DHEA on the glucose tolerance test, suggesting no effect on peripheral glucose metabolism. This is supported by other studies that showed no effect of DHEA on muscle glucose transport protein 4 content[103] or glucose metabolism either in isolated adipocytes[105] or in rat soleus muscle.[104] Thus, the antiobesity effect of DHEA in rats may be due to a combination of elevated mitochondrial respiration and lowered insulin levels. There are divergent effects on food intake in lean and obese rats given DHEA. In obese Zucker rats, DHEA reduced food intake, whereas in lean rats, food intake was increased.[106] The mechanism for this difference is unknown.

Studies analyzing the relationship between insulin sensitivity and DHEA-testosterone ratios have found it to be strongly associated, suggesting that DHEA affects insulin sensitivity.[107] However, a trial of DHEA infusion in hyperandrogenic women with polycystic ovarian syndrome failed to improve any index of insulin sensitivity.[108] Nevertheless, there was an increase in pyruvate dehydrogenase enzyme activity after DHEA administration in these women.[108] Pyruvate dehydrogenase in T lymphocytes reflects the degree of glucose intolerance of hyperandrogenic women and diabetic subjects in whom enzyme activity is impaired.[109] A theory is that the 17-hour infusion of DHEA used in that study[108] to achieve a serum level of 2.5 times greater than baseline may not have been long enough to produce a clinically significant change in insulin sensitivity in vivo.

Some results suggest that DHEA has a role in reducing age-related increases in insulin levels, insulin resistance, and blood glucose. In a few randomized studies of healthy elderly men and postmenopausal women, insulin sensitivity improved significantly.[110-112] Insulin sensitivity was measured indirectly by serum insulin or by formal testing. These results contrast those of studies in women with adrenal insufficiency that found that either 50 mg/d or 200 mg/d of DHEA supplementation had no effect on insulin sensitivity.[113,114] Again, the issue arises when the absolute DHEA deficiency in hypoadrenal subjects is compared with the relative DHEA deficiency in healthy elderly subjects. These studies are summarized in Table 3. Insulin sensitivity is currently one of the outcomes being assessed in long-term DHEA replacement studies of hypoadrenal and healthy elderly subjects.[120,121]

In summary, in contrast to animal studies, in humans, although there are intriguing measurable effects of DHEA on plasma insulin and glucose levels, these changes have not been translated into a clinically significant beneficial effect on insulin sensitivity and glucose disposal.[115]

Cardiovascular Effects

Animal studies have shown that administration of DHEA reduces the buildup of atherosclerotic plaque in animals fed a high-fat diet.[122,123] In addition, DHEA has been shown to reduce platelet adhesion in vivo.[124] Thus, an increase in plaque formation may explain the increase in cardiovascular events in persons with low DHEA levels.[36,125] Nestler et al[126] showed that hyperinsulinemia reduces serum DHEA levels. Because insulin is thought to be proatherogenic, this reduction in DHEA levels is a possible explanation for the loss of antiatherogenic actions of DHEA.[125] Although this hypothesis remains to be formally tested in human studies, some animal data and human epidemiological data suggest that this is the case.[36,118,122-124] Most of the current data are summarized in Table 4. The epidemiological evidence in humans is conflicting because some studies show an inverse relationship between DHEA levels and increased cardiovascular risk in men but not in women.[36,37,127-129] In a large ongoing observational study analyzing cardiovascular risk factors, diabetes in men older than 50 years was associated with a low DHEA level.[130] This relationship was not seen in all large epidemiological studies.[131]

DHEA may affect various other risk factors. In women, there is a positive relationship between DHEA levels and

Table 3. **Summary of Human Studies Analyzing Effect of DHEA on Insulin Sensitivity***

Type of subject and age (y)	Sex (No.)	Type of study	DHEA Dose (mg/d)	Duration	Results	Reference
Hyperandrogenic						
15	F (1)	OL	300	1 mo	Marked improvement in insulin sensitivity	Buffington et al[115]
Hyperandrogenic or obese						
18-36	F (5 with PCOS, 5 obese)	OL	1 mg/h	17-h infusion	No change in insulin sensitivity in either group	Schriock et al[108]
Healthy overweight volunteers						
21-37	M (6)	P, R	1600	28 d	No change in insulin sensitivity	Usiskin et al[116]
Healthy volunteers						
60-70	F (15)	OL	10% cream	12 mo	Significant improvement in indirect measures of insulin sensitivity but not oral glucose tolerance testing	Diamond et al[111]
64-82	M (8); F (10)	OL	50	6 mo	Nonsignificant improvement in indirect measures of insulin sensitivity	Villareal et al[117]
40-70	M (13); F (17)	P, R, C	50	3 mo	No change in insulin sensitivity	Morales et al[29]
40-70	M (130); F (17)	P, R, C	50	6 mo	No change in insulin sensitivity	Yen et al[31]
22-25	M (10)	P, R	1600	28 d	No change in insulin sensitivity	Nestler et al[118]
56 (mean)	F (20)	P, R	25	12 mo	Significant improvement in insulin sensitivity	Lasco et al[110]
57 (mean)	M (22)	P, R	1000	30 d	Significant improvement in indirect measures of insulin sensitivity	Jakubowicz et al[112]
Hypoadrenal						
26-69	M (15); F (24)	P, R, C	50	3 mo	No change in insulin sensitivity	Hunt et al[33]
23-59	F (24)	P, R, C	50	4 mo	No effect on indirect measures of carbohydrate metabolism	Callies et al[119]
22-54	F (10)	R, P, C	50	9 d	No change in insulin sensitivity	Christiansen et al[114]
27-51	F (9)	R	50 or 200	3 mo	No change in insulin sensitivity	Gebre-Medhin et al[113]

*PCOS = polycystic ovarian syndrome. See footnote to Table 1 for expansion of other abbreviations.

the development of glucose intolerance.[132,133] Further difficulties in interpreting data come from evidence that shows that DHEA administration lowers high-density lipoprotein levels.[134,135]

Muscle Strength and Body Composition

Animal studies have shown that DHEA in the diet can either prevent weight gain or even cause weight loss.[136-139]

In healthy volunteers, some observational studies attempting to correlate DHEA levels with muscle strength and body composition failed to find an association,[33,140] whereas other data in obese men and women found opposing relationships.[141,142] However, in both the observational studies, body composition was determined by anthropomorphic measure only, whereas the studies that showed no association used dual x-ray absorptiometry.

Several interventional studies in healthy subjects and hypoadrenal women failed to show any changes in body composition with DHEA administration.[29,100,113,116,119,135,143] This conflicts with other work showing that DHEA administration alters body composition.[111,117,118,144] Morales et al[144] showed that a 100-mg daily dose of DHEA for 6 months was associated with a reduction in fat mass in healthy

elderly men but not in women. Additionally, the study by Diamond et al[111] showed that topical application of a 10% cream of DHEA for 1 year was associated with a statistically significant reduction in femoral fat, an increase in femoral muscular area, and decreased skinfold thickness. These findings are consistent with those in a smaller study by Nestler et al,[118] who found a change in body composition in a small number of healthy young men given a highly suprapharmacological dose of 1600 mg/d of DHEA for 28 days. They showed that body fat decreased, with an overall increase in skeletal muscle tissue. Villareal et al[117] showed that a 50-mg daily dose of DHEA for 6 months was associated with a statistically significant reduction in body fat and an increase in lean mass in 18 healthy elderly men and women.

Muscle strength in healthy elderly volunteers has been assessed. In observational studies, quadriceps strength was positively correlated with circulating DHEA levels in men[143,145] but not in women.[143] This correlated with the findings of the interventional study by Morales et al,[144] in which an increase was noted in quadriceps and lumbar strength in men but not in women. These studies are summarized in Table 5.

Table 4. **Summary of Human Studies Analyzing Effect of DHEA on Cardiovascular Outcomes***

Type of subject and age (y)	Sex (No.)	Type of study	Results	Reference
Healthy volunteers				
50-79	M (242)	O	Low DHEA levels associated with higher death rates	Barrett-Connor et al[36]
40-70	M (1709)	O	Low DHEA levels associated with higher rates of cardiovascular disease	Feldman et al[127]
60-79	F (289)	O	High DHEA levels associated with higher death rates	Barrett-Connor & Khaw[37]
65 (mean)	F (942)	O	DHEA levels not associated with fatal cardiovascular outcomes	Barrett-Connor & Goodman-Gruen[128]
After myocardial infarction				
26-40	M (32 subjects, 76 controls)	O	Significantly lower DHEA levels found in subjects after myocardial infarction	Slowinska-Srzednicka et al[125]

*DHEA = dehydroepiandrosterone; O = observational.

In general, long-term studies tend to show changes in body composition and muscle strength. Long-term placebo-controlled double-blind studies are needed to determine the effects of DHEA on body composition and muscle strength.

Bone

Rat studies have shown that DHEA administration reduces the rate of bone loss usually seen after oophorectomy.[146] Evidence concerning the influence of DHEA on bone turnover in humans is conflicting. Gonadal androgen deficiency is associated with osteoporosis in men.[147] Studies of individuals with receptor defects or enzyme deficiencies have shown that in men estrogens are also necessary for normal bone maturation and formation.[148-150] In women, aging is associated with a decline in estrogens and adrenally derived androgens. This decline may be causally associated with the development of osteoporosis because DHEA is converted to estrone within osteoblast-like cells by aromatase cytochrome P-450 in culture.[151,152] Thus, DHEA may contribute to the maintenance of bone mineral density (BMD) in postmenopausal women. In addition, cross-sectional and longitudinal data show a correlation between DHEA levels and lumbar BMD.[153,154] However, these findings are discordant with long-term studies that have shown no such relationship in either men or women.[155] Interventional studies of healthy subjects showed that DHEA supplementation had no effect on markers of bone turnover or on BMD measured by dual x-ray absorptiometry.[44,134,156] However, open-label studies showed that DHEA administration made a significant difference in BMD in healthy elderly subjects.[117,157]

In hypoadrenal subjects, the issue of whether osteoporosis is due to a lack of adrenally derived androgens or to overtreatment with glucocorticoids is controversial. Some evidence of uncertain importance from 1 study showed that DHEA replacement is useful in hypoadrenal subjects.[119] In that study, serum osteocalcin levels were increased significantly, but there was no corresponding increase in the excretion of urinary cross-links.[119] This finding was not seen in other interventional studies of hypoadrenal subjects.[33,67] These studies are summarized in Table 6.

Thus, the role of DHEA in preventing osteoporosis in elderly or hypoadrenal subjects remains uncertain.

Immune Function

On the basis of animal and in vitro studies, DHEA has several effects on immune function. Work with rodent models has shown that DHEA protects mice from lipopolysaccharide-induced endotoxic shock.[159] These endotoxins are released from bacterial cell walls during gram-negative infections and are associated with high mortality.[160] That study reported that mortality of mice exposed to a lethal dose of endotoxin was reduced from 95% to 24% by treatment with a single dose of DHEA, given 5 minutes before the intervention.[160] The applicability of these findings to humans is unknown.

In humans, there is a strong correlation between DHEA levels and helper T-cell type 1 cytokine levels. These cytokines are IL-2 and interferon γ. However, levels of the helper T-cell type 2 cytokines, IL-4, IL-5, and IL-6, increase with age.[161,162] High IL levels are implicated as a causal factor in many conditions, such as rheumatoid arthritis, osteoporosis, B-cell cancers, atherosclerosis, and Parkinson disease.[163] Because these ILs help regulate immune activity, it is possible that the increased susceptibility to illness associated with chronic disease and aging occurs as a result of changes in the levels of these cytokines.[163,164]

In a crossover trial of 11 postmenopausal women taking 50 mg of DHEA daily, Casson et al[165] found a decrease in CD4+ cells, with an associated enhancement in natural killer cell (CD8+/CD56+) activity and cytotoxicity. Also,

Table 5. **Summary of Human Studies Analyzing Effect of DHEA Replacement on Muscle Strength and Body Composition***

Type of subject and age (y)	Sex (No.)	Type of study	DHEA Dose (mg/d)	Duration	Results	Reference
Healthy volunteers						
21-96	M (578)	O	NA	NA	Positive association between DHEAS levels and muscle strength in men >56 y	Valenti et al[145]
60-70	F (15)	OL	10% cream	12 mo	Decrease in femoral fat, increase in femoral muscle, decrease in skinfold thickness	Diamond et al[111]
64-82	M (8); F (10)	OL	50	6 mo	Significant decrease in fat mass with significant increase in fat-free mass	Villareal et al[117]
50-65	M (9); F (10)	P, R, C	100	6 mo	Decrease in fat mass in men only; increase in knee and lumbar strength in men only	Morales et al[144]
40-70	M (13); F (17)	P, R, C	50	3 mo	No change in body composition	Morales et al[29]
46-61	F (60)	P, R, C	1600	28 d	No change in body composition	Mortola & Yen[135]
60-84	M (39)	P, R, C	100	3 mo	No change in body composition	Flynn et al[100]
22-25	M (10)	P, R	1600	28 d	31% decrease in body fat in 4 of 5 subjects	Nestler et al[118]
Healthy overweight volunteers						
21-37	M (6)	P, R	1600	28 d	No change in anthropological measurements of body composition	Usiskin et al[116]
With anorexia						
14-28	F (61)	R	50	12 mo	Significant weight gain	Gordon et al[53]
Hypoadrenal						
22-54	F (10)	R, P, C	50	9 d	No change in body composition	Christiansen et al[114]
26-69	M (15); F (24)	P, R, C	50	3 mo	No change in body composition	Hunt et al[33]
27-51	F (9)	R	50 or 200	3 mo	No change in body composition	Gebre-Medhin et al[113]

*DHEAS = DHEA sulfate. See footnote to Table 1 for expansion of other abbreviations.

DHEA appeared to suppress the increase in stimulated IL production seen in the placebo group.[165]

Daynes and Araneo[166] showed that the effect of DHEA on T cells is to enhance their ability to produce other cytokines, such as IL-2, IL-3, and interferon γ. Such effects occur only if the cells are activated while under the influence of this hormone, and they appear to be most prominent in lymphoid organs that contain the greatest ability to convert DHEAS to DHEA. Investigators argue that replacement therapy with DHEA should restore the normal immunocompetence that tends to be lost with aging.[166]

In an open-label 20-week study of 9 healthy men (mean age, 63 years) taking 50 mg of DHEA daily, Khorram et al[167] found that DHEA had beneficial effects on immune function by increasing the number of B cells, monocytes, natural killer cells, T-cell receptors, and IL-2 receptors. This increase in the expression of the IL-2 receptor enabled enhancement of the T-cell responsiveness to mitogen stimulation. All these effects decline during physiological aging. The significant increase in natural killer cell cytotoxicity in DHEA-treated subjects was potentially related to the increased number of natural killer cells, both events being mediated by DHEA-induced IL-2 stimulation.[167] This potential enhancement of the immune system has led to studies using DHEA as a vaccine adjuvant. Although responses in animals have been good,[168] its use in humans is controversial.[169,170]

Randomized controlled trials with several hundred women have analyzed the effect of DHEA supplementation on autoimmune conditions such as systemic lupus erythematosus, with some success in reducing glucocorticoid dose and symptom scores without increases in disease activity.[171,172] However, in a smaller open-label trial of 6 postmenopausal women and 5 elderly men with rheumatoid arthritis, supplementation with 200 mg of DHEA daily for 16 weeks was of no benefit in either clinical or laboratory measures of disease activity.[173]

ADVERSE EFFECTS AND POTENTIAL LIMITATIONS OF DHEA USE

In most studies, adverse effects are common but minor. They usually occur in women and are due to the androgenic effects. The most common adverse effect is increased skin sebum production, leading to perceived "greasiness" and acne.[172] However, many women previously reported that this change is beneficial and that before DHEA replacement their skin was excessively dry. This effect is reversible when DHEA is withdrawn.

Of greater concern are the reports of mild elevations in serum transaminase levels. These occur within a few weeks after initiation of DHEA. However, these increases have

Table 6. **Summary of Human Studies Analyzing Effects of DHEA Replacement on Bone***

Type of subject and age (y)	Sex (No.)	Type of study	DHEA Dose (mg/d)	Duration	Results	Reference
Healthy volunteer						
50-74	M (260); F (162)	O	NA	NA	No correlation between DHEA levels and BMD at any site	Barrett-Connor et al[155]
Not given†	F (13)	P, R	25	6 mo	No effects on bone turnover markers or BMD	Casson et al[134]
60-79	M (140); F (140)	P, R, C	50	12 mo	In men, no effects on bone turnover markers or BMD; in women, positive effect in BMD at several sites	Baulieu et al[158]
50-69	M (22)	P, R, C	50	4 mo	No effects on bone turnover markers	Arlt et al[44]
56-80	M (43)	P, R	90	6 mo	No effects on bone turnover markers	Kahn & Halloran[156]
60-70	F (14)	OL	10% cream	12 mo	Significant increase in BMD and significant decrease in bone turnover markers	Labrie et al[157]
64-82	M (8); F (10)	OL	50	6 mo	Significant increases in total body and spinal BMD	Villareal et al[117]
Hypoadrenal						
23-59	F (24)	P, R, C	50	4 mo	Increase in serum osteocalcin with no change in urinary cross-link excretion	Callies et al[119]
26-69	M (15); F (24)	P, R, C	50	3 mo	No effects on bone turnover markers or BMD	Hunt et al[33]
25-65	F (38)	R (OL)	30 (<45 y), 20 (≥45 y)	6 mo	No effects on bone turnover markers or BMD	Johannsson et al[67]
With anorexia						
14-28	F (61)	R	50	12 mo	Significantly reduced levels of bone resorption markers; nonsignificant maintenance of hip and spinal BMD	Gordon et al[53]

*BMD = bone mineral density. See footnote to Table 1 for expansion of other abbreviations.
†Postmenopausal.

not caused any subjects to withdraw from a study. Additionally, effects have either been reversed when the drug was discontinued or have regressed after a few weeks of drug therapy.[32] Nonsignificant increases in hemoglobin and hematocrit have been reported in some trials, possibly due to the androgenic effects of DHEA metabolites.[67]

Other milder adverse effects include an increase in perspiration[67,113] and body hair—especially facial, axillary, and pubic hair.[32,33,67] Rarely, hair loss has been reported.[32] Other adverse effects include abdominal pain, metrorrhagia, asthenia, insomnia, rash, weight gain, and breast tenderness.[93,172] These adverse effects occurred with higher doses of DHEA (100 mg and 200 mg), were transitory, and were reversed after withdrawal of the drug.

There are serious potential risks with the use of DHEA. Although several rodent models have shown that the use of DHEA prevents tumorigenesis,[174] the use of suprapharmacological doses of DHEA has resulted in an increase in hepatocellular carcinoma.[175] Because of the conversion of DHEA into androgens and estrogens, use of supplemental DHEA in individuals with a history of sex hormone–dependent malignancy, such as prostate, breast, or endometrial cancer, remains a valid concern.

This issue needs to be fully addressed in long-term studies in humans.

AVAILABILITY OF DHEA IN THE UNITED STATES
The International Olympic Committee banned DHEA use because of its conversion to sex hormones and thus its potential to be used as a drug of abuse. The Food and Drug Administration also banned the substance until the passage of the Dietary and Supplement Health and Education Act of 1994, when this ruling was overturned. DHEA is now freely available in pharmacies and health food stores, where it is classified as a food supplement. This is despite the fact that DHEA is not a food, that DHEA does not naturally appear in the human food chain, and that no foodstuff can perform the physiological role of DHEA. It can be sold directly to the public as long as no claims are made about therapeutic efficacy. In an attempt to reduce the potential abuse of DHEA, a bill was recently introduced to the US House of Representatives that aims to restrict over-the-counter sale of DHEA and other androgenic steroid precursors.[176] The manner in which passage of this bill would affect those who may derive benefit from DHEA, such as hypoadrenal and elderly subjects, remains to be determined.

In the United States, food supplements are not required to undergo strict safety and efficacy testing, and thus there are issues of quality control.[177] One study showed that the quantity of DHEA from different manufacturers in several different doses varied from 0% to 150% of what the label claimed was in the product.

SUMMARY AND CONCLUSIONS

DHEA and DHEAS are intriguing hormones. Their metabolites have a variety of effects on several physiological systems, and yet little is known about the role of either DHEA or DHEAS in normal physiology. It is still unclear whether aging should be classified as a DHEA-deficient state. In hypoadrenal subjects, DHEA deficiency is associated with a lower quality of life. However, these hormones are not essential for life because hypoadrenal subjects and those who have undergone adrenalectomy who have little or no circulating DHEA do not have shortened life spans.[65]

Evidence supports the use of DHEA in hypoadrenal subjects (Tables 1-5). The lay press has widely promoted the use of DHEA in normal healthy individuals, and bodybuilders promote its use as a method to increase muscle mass. However, many of the claims made on Internet Web sites ("fountain of youth," "prevents diabetes," "prevents aging," "boosts the immune system," etc) fail to mention that most of these studies were performed either in vitro or in animals. These reports are further misleading because they fail to state that the results were usually a response to highly suprapharmacological doses of DHEA. The degree of quality control of the substances currently marketed is a concern. Finally, there are valid concerns about the use of DHEA in individuals with a history of sex hormone–dependent malignancies. Large-scale human studies are needed to address these intriguing issues.

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