

DHEA Replacement for Postmenopausal Women

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Context: It has been proposed that because dehydroepiandrosterone (DHEA) and its sulfate, DHEAS, are important precursors for estrogen and androgen production, treatment with DHEA is a physiologically based strategy for the alleviation of hormone deficiency symptoms in postmenopausal women. We have summarized the physiology of DHEA in women and reviewed the findings from randomized controlled trials (RCT) of the effects of DHEA therapy in postmenopausal women with normal adrenal function.

Evidence Acquisition: We reviewed the medical literature for key papers investigating DHEA physiology and RCT of the use of DHEA in postmenopausal women through November 2010. The focus was on sexual function, well-being, metabolic parameters, and cognition as study endpoints.

Evidence Synthesis: Although cross-sectional studies have indicated a link between low DHEA levels and impaired sexual function, well-being, and cognitive performance in postmenopausal women, placebo-controlled RCT do not show benefits of oral DHEA for any of these outcomes or favorable effects on lipids and carbohydrate metabolism.

Conclusions: Taken together, findings from this review of the published literature of studies do not support the use of DHEA in postmenopausal women at this time. (*J Clin Endocrinol Metab* 96: 1642–1653, 2011)

The role of dehydroepiandrosterone (DHEA) in women and its potential as a therapeutic agent continues to attract controversy. First isolated as the 3-chloro derivative of DHEA from 143,000 liters of urine in 1934 by Butenandt and Dannenbaum (1), its more abundant 3 β sulfate, DHEAS, was isolated by Munson in 1944 (2). DHEA was isolated from human plasma in 1954 (3). Symington *et al.* (4) first identified the adrenal cortex as a key site of DHEA production. DHEA is also produced by the testes (5) and ovaries (6) and can be synthesized within the brain (7), whereas DHEAS is a unique secretory product of the adrenal zona reticularis. With the loss of ovarian follicular activity at menopause, adrenal DHEA, DHEAS, and androstenedione become major precursors for the extragonadal production of estrogens and androgens in

postmenopausal women (8). Various studies have raised the possibility that DHEA may improve lipid metabolism and insulin sensitivity (9–12), enhance the immune response (13–15), and boost physical and psychological well-being in older men and women (16). Much of the evidence supporting these potential benefits is from studies in rodents, whose adrenals do not produce DHEA. The initial human studies that provoked substantial interest in DHEA mostly involved small subject numbers and were conducted over short time frames (17). More recently it has been proposed that because DHEA and DHEAS are important precursors for estrogen and androgen production, treatment with DHEA is a physiologically based strategy for the alleviation of hormone deficiency symptoms in postmenopausal women (18). To explore this hy-

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Abbreviations: ADT, Androsterone; AR, androgen receptor; BMD, bone mineral density; CI, confidence interval; CVD, cardiovascular disease; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; 3 α -diol, 3G, 3 α -diol-3-glucuronide; 5-diol, 5-androstene-3 β ,17 β -diol; ER, estrogen receptor; G, glucuronide; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; OR, odds ratio; RCT, randomized controlled trial; T, testosterone.

pothesis, we have briefly summarized the known physiology of DHEA and DHEAS in women and reviewed the more recent evidence provided by randomized controlled trials (RCT) that have evaluated the effects of DHEA therapy in postmenopausal women with normal adrenal function.

Physiology

In adult women, DHEAS is the most abundant steroid hormone, with daily production rates being approximately 8 to 16 mg/d, which are almost exclusively adrenal (19). DHEAS is formed from DHEA in the highly specialized zona reticularis of the adrenals, which has high sulfuryl transferase activity. The hydrophilic DHEAS is the major circulating form of DHEA and is interconverted in various tissues with DHEA by DHEA sulfotransferases and hydroxysteroid sulfatases (19). In premenopausal women, the production rate of DHEA is approximately 6–8 mg/d. Approximately 50% of DHEA is secreted by the adrenals, with the ovaries producing approximately 1 to 2 mg of DHEA per day; the remaining DHEA production occurs in peripheral tissues (19). In contrast, the production of testosterone (T) in premenopausal women is approximately 0.2 to 0.25 mg/d, which is about 25–40 times less than that of DHEA and even much lower than that of DHEAS (20). The ovaries of some postmenopausal women continue to produce some T (20, 21), but not DHEA (20). In the circulation, DHEAS and DHEA are found in low micromolar and low nanomolar concentrations, respectively. Rosenfeld *et al.* (22) reported a circulating half-life of 1 to 3 h for DHEA and 10 to 20 h for DHEAS. SHBG weakly binds DHEA but not DHEAS (23).

The production of DHEA(S) increases at the age of 6 to 8 yr as a consequence of the maturation of the zona reticularis of the adrenal cortex, with the resultant initiation of adrenarche (24). Maximal levels of circulating DHEA and DHEAS are achieved between the ages of 20 and 30 yr, after which the levels decline with age during adult life (25–27). However, the interindividual variability across adulthood is substantial, and the normal range of serum DHEA(S) is therefore very wide at each decade of life (27). DHEAS levels in women in their mid 70s are about 77% lower than women in their third decade of life, with age alone explaining about 30% of the variation in DHEAS levels (27). Despite the overall decline in DHEAS with age, levels across the menopausal transition vary according to the transitional phase (28). Between the early and late perimenopause, DHEAS appears to increase on average by 3.95% in most women and then decline to levels seen in the early perimenopause by the late postmenopause. Women

who do not exhibit this rise in DHEAS across the menopause have lower levels as they enter menopause (28). Overall Chinese women tend to have higher levels and African-American women have lower DHEAS levels than Caucasian women (28).

Peripherally, DHEA appears to exert its primary effects through its estrogenic and androgenic metabolites because a unique DHEA receptor has not been characterized. However, DHEA has been shown to exhibit weak agonist effects on the estrogen receptors (ER) α and β and be a weak antagonist of the androgen receptor (AR) (29). There is evidence that DHEA is synthesized within the brain and may act locally as an excitatory neurosteroid by antagonizing the actions of the γ -aminobutyric acid type A receptor and stimulating the N-methyl-D-aspartate receptor and the σ -subtype 1 receptor (7, 30). A putative plasma membrane-bound G coupled receptor activated by DHEA has been identified on bovine aortic endothelial cells (31, 32). Liu *et al.* (33) subsequently have shown that physiological concentrations of DHEA activate this plasma membrane receptor on vascular endothelial cells and stimulate endothelial proliferation and angiogenesis through extracellular signal-regulated kinase 1/2-mediated mechanisms.

DHEA and DHEAS are metabolized in extragonadal target tissues such as the brain, bone, and adipose either by aromatization to estrone or by 5α -reduction to T, with the latter being converted to either estradiol or dihydrotestosterone (DHT) in the same cells (34). The transformation of DHEA into active androgens and estrogens depends upon the level of expression of the various steroidogenic and metabolizing enzymes in each cell type. With the increase in aromatase gene expression in adipose with age (35, 36), older women potentially have greater capacity to synthesize estrone from DHEA and DHEAS. Furthermore, the ultimate effects of the complex metabolism of DHEA and DHEAS will involve the absolute levels of each metabolite, their receptor content within the target cell, the presence and levels of specific coactivator and corepressor proteins that modify the transcriptional response, and the up- or down-regulation of receptor levels by other hormones. DHEA and DHEAS can be converted to many different metabolites; Fig. 1 depicts some of the more important ones.

DHEA can be metabolized to androstenedione and then converted to 5α - or 5β -androstane-3,17-dione, which in turn are converted to androsterone or etiocholanone, respectively, and finally to androsterone glucuronide (ADT-G) and etiocholanone glucuronide for urinary excretion. ADT-G provides a good indication of adrenal androgen secretion because DHEAS is its major precursor, accounting for 70–80% of ADT-G levels (37,

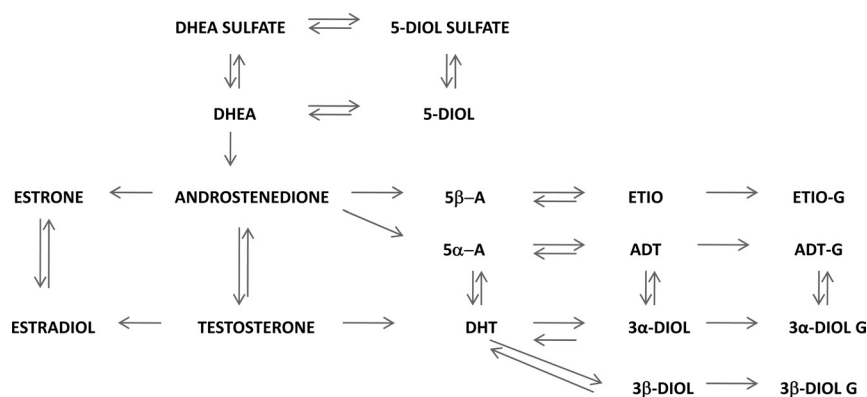


FIG. 1. Metabolism of DHEA in women. DHT, Dihydrotestosterone; 5 α -A, 5 α -androstenedione; 5 β -A, 5 β -androstenedione; 3 α -diol, 5 α -androstane-3 α ,17 β -diol; 3 β -diol, 5 β -androstane 3 α ,17 β -diol; ETIO, etiocholanone; ETIO-G etiocholanone glucuronide.

38). Alternatively, DHEA can be converted to T, after first being transformed to androstenedione; T can undergo 5 α -reduction to form DHT. DHT can then be converted to androstane-3 α ,17 β -diol (3 α -diol), which in turn can be glucuronidated at carbons 3 or 17 to form 3 α -diol-3-glucuronide (3 α -diol,3G) or 3 α -diol-17-glucuronide 3 α -diol,17G, of which 3 α -diol,17G is the predominant form. Plasma 3 α -diol,17G is a marker of peripheral androgen action and is significantly elevated in idiopathic hirsutism (39). In contrast, 3 β -diol is considered to have weak androgenic activity, binds to the ER, and shows estrogenic activity. In addition, DHEA may also be converted to estrone and estradiol after initial conversion to androstenedione and T, respectively.

An important overlooked metabolite of DHEA is 5-androstene-3 β ,17 β -diol (5-diol). This metabolite is structurally an androgen but binds not only to the AR but also to the ER and appears to be a weak estrogen. For this reason, 5-diol has been referred to as hermaphrodiol (40). Analogous to DHEA, 5-diol is readily converted to 5-diol sulfate, which is present in relatively high concentrations in the circulation. 5-Diol sulfate can also be formed from DHEAS, and it is speculated that the unconjugated forms of DHEA and 5-diol, which are interconvertible with their sulfated forms, may play a physiological role that has not yet been elucidated.

Two studies supporting the view that 5-diol is estrogenic include one in which breast cancer patients who progressed during treatment with an aromatase inhibitor showed improvement when treated with a sulfatase inhibitor (41). The sulfatase inhibitor prevents the formation of DHEA from DHEAS and consequently results in insignificant serum levels of 5-diol. In the other study, it was shown that the conversion of DHEA into 5-diol is increased in endometria from women with polycystic ovarian syndrome compared with normal cycling women (42). This finding, coupled with the high estrogen sensi-

tivity found in endometria from women with polycystic ovarian syndrome, suggests that 5-diol may account for the increase in endometrial cell proliferation observed in these women.

Splanchnic tissues are responsible for a large proportion of androgen metabolism, with the extraction of androgens by the liver approaching 100% for androgens not bound to SHBG (20). Thus, for T and DHT, which are highly bound to SHBG, only about 40 to 60% and 30 to 40%, respectively, are extracted by the liver (43, 44).

DHEA secretion is acutely stimulated by ACTH (45, 46); however, DHEAS, which has a long plasma half-life, may not acutely increase after ACTH administration (47). Adrenal DHEA, DHEAS, and cortisol production are not always linked. Circulating DHEA and DHEAS levels have been observed to be normal or suppressed in acute stress (48), severe systemic illness (49), anorexia nervosa (50), and Cushing's syndrome (51), which are otherwise characterized by elevated cortisol levels. Increased DHEA(S) production may also be seen in association with hyperprolactinemia (51), although the majority of patients with this disorder have normal levels.

Clinical Associations with Endogenous DHEA and DHEAS Levels

Taking into consideration that endogenous hormone levels may be poor indicators of their effects in target tissues, various studies have explored the relationships between androgens and clinical characteristics including sexual function, well-being, cardiovascular disease (CVD) risk, insulin resistance, and cognition. We investigated the relationships between androgens and sexual function in a cross-sectional study of 1423 non-health care-seeking women, aged 18 to 75 yr, randomly recruited from the community via the electoral roll, of whom 1021 completed a validated sexual function questionnaire (52). Androstenedione and total and free T were not related to sexual function scores. However, women aged 45 yr or more with low sexual responsiveness had a greater likelihood of having a serum DHEAS value below the 10th centile for their age [odds ratio (OR), 3.9; 95% confidence interval (CI), 1.54–9.81; $P = 0.004$]. For women aged 18 to 44 yr, having low sexual desire, sexual arousal, or sexual responsiveness was also associated with having a DHEAS value below the 10th centile for their age (OR,

3.86; 95% CI, 1.27–11.67; $P = 0.02$; OR, 6.39; 95% CI, 2.3–17.73; $P < 0.001$; and OR, 6.59; 95% CI, 2.37–18.34; $P < 0.001$, respectively) (52). Because the normal range for serum DHEAS among young women is relatively large and a significant proportion of women with low DHEAS do not have low sexual function, a cutoff level below which women can be said to be more likely to have low sexual function cannot be identified. A smaller study of women attending a sexual medical center diagnosed with hypoactive sexual desire disorder, compared with controls, also reported an association between low DHEA and DHEAS and impaired sexual function (53). The interpretation of data from this more recent study is limited by the statistics used because the data were not normally distributed and logarithmic transformations do not appear to have been applied.

In a study in which 1224 women completed a validated psychological general well-being questionnaire, no relationship between the overall well-being score of the Psychological General Well-Being Index (PGWBI) and DHEAS was identified (54). For premenopausal women, there was a significant relationship between having a low DHEAS level and low vitality, although the total variation in the domain of vitality explained by the model was less than 5%. DHEAS levels were found to be inversely correlated with depressed mood in a study of 699 women aged 50 to 90 yr, with a subset of women diagnosed with depression having lower levels than nondepressed women (55).

We have also observed that for postmenopausal women, taking into account age, smoking, alcohol, body mass index, and exercise, serum DHEAS has an inverse relationship with, and contributes approximately 2% to, the variation in circulating triglyceride levels (56). No relationship was found between DHEAS and high sensitivity C-reactive protein or other lipids, or with triglyceride levels in premenopausal women. An inverse relationship between DHEAS and CVD mortality has been observed in a prospective study of women undergoing coronary angiography for suspected ischemia, although when the severity of coronary artery disease was taken into account, the relationship was no longer statistically significant (57). No significant associations between DHEAS levels and body mass index, waist to hip ratio, diabetes, insulin levels, insulin resistance or other CVD risk factors were identified. DHEAS has been positively associated with both fasting glucose and insulin resistance, determined by the homeostasis model, but not with diabetes, in one large cross-sectional study of postmenopausal women (58), and positively associated with impaired glucose tolerance and diabetes in the Rancho Bernardo Study (59).

DHEA appears to have skeletal effects, being a precursor for both estrogen and androgen production in bone. DHEA levels have been positively correlated with bone mineral density (BMD) in postmenopausal women, and DHEA can be converted to estrone in osteoblasts (60). AR have been demonstrated in human osteoblast-like cell lines, and androgens have been shown to directly stimulate bone cell proliferation and differentiation (61).

Because it has been proposed that DHEA and DHEAS may exert neuroprotective effects, associations between endogenous DHEAS levels and cognitive performance in women aged 21 to 77 yr have been investigated (62). Women with higher levels of DHEAS exhibited better performance on testing of executive function, with circulating DHEAS levels being significantly positively associated with higher scores for tests of simple concentration and working memory in women with at least 12 yr of education (62). Circulating DHEAS levels were not associated with performance on tests of verbal and nonverbal learning and retention or focused attention. Valenti *et al.* (63) found a positive relationship between the Mini Mental State Examination and DHEAS in older women, whereas no relationship was observed in another similar-sized study (64).

Exogenous DHEA Treatment

It has been proposed that treatment of postmenopausal women with DHEA will result in androgenic effects and hence improve libido and well-being via its conversion to T and estrogenic effects resulting in improvements in menopausal vasomotor symptoms (18). DHEA has been administered orally and parenterally, either by the transdermal or vaginal route. When administered to postmenopausal women, DHEA is mainly transformed to androgens rather than estrogens (65). Using liquid chromatography combined with tandem mass spectrometry, an oral dose of DHEA 50 mg daily for 12 months (66) results in significant increases in estrone and estradiol, in the order of 34 and 57%, respectively, and a 200% increase in 5-diol (40). With this oral dose, total T levels increase by about 100%, serum DHT is relatively unchanged, and serum 3α -diol,3G, 3α -diol,17G, and ADT-G each increase 4- to 5-fold (66). These changes contrast with those reported in a 12-month study of transdermal DHEA using the same methodology for steroid measurements by the same laboratory (67). Irrespective of dose, with transdermal DHEA similar proportional increases in estrone, estradiol, and 5-diol were observed to those seen with oral DHEA, whereas the sum of ADT-G 3α -diol,3G and 3α -diol,17G increased by only 71% (67). Giagulli *et al.* and others have shown that hepatic 5α -reductase is a major

determinant of the conversion of precursors to plasma ADT-G. This would be consistent with the mode of administration of DHEA influencing its metabolism, such that the higher ADT-G levels seen with oral DHEA reflects first past hepatic metabolism and not peripheral androgen formation.

Studies of DHEA for Sexual Function

Although the prevalence, incidence, and antecedents of female sexual dysfunction remain underresearched, the most commonly reported sexual problems in women relate to sexual desire and interest, pleasure, and global satisfaction (68, 69). To date, there are eight published randomized trials of oral DHEA treatment for low sexual function in healthy, postmenopausal women (9, 16, 66, 70–74). These are summarized in Table 1. Some of the studies demonstrated a positive effect of DHEA treatment on sexual function (71–73), whereas others did not show any benefit (9, 16, 66, 70, 74). Of the three trials where a benefit was shown, two administered supraphysiological DHEA doses and were of short duration (72, 73). The third study was of older aged women and employed a

nonvalidated measure of sexual function that was understood by only 25% of the participants (71). The early studies in which DHEA was ineffective were also limited by small sample size (9, 16), short treatment duration (9, 70), use of nonvalidated instruments (9, 70), or supra-physiological doses (9).

More recent studies have employed validated measures of sexual function, have larger sample sizes, and are of longer duration. Two different studies with a 52-wk treatment phase have shown no improvement in sexual function with DHEA 50 mg daily. One was in 115 older, postmenopausal women, and sexual function was assessed by the Female Sexual Function Index (74). In the other, which excluded women with dyspareunia, sexual function was assessed by two methods: a validated questionnaire and a 28-d diary of satisfactory sexual events (66). In contrast, the use of vaginal DHEA has been evaluated over 12 wk in women primarily presenting with dyspareunia and subjective vaginal dryness and irritation. Vaginal atrophy was reversed with minimal changes in serum steroid hormone levels, which remained within the normal postmenopausal range (75). Beneficial effects on four aspects of sexual dys-

TABLE 1. RCT reporting the effects of DHEA on sexual function and well-being in postmenopausal women

First author, year (Ref.)	Study design	Duration (wk)	Dose (mg/d)	No. of PM women (age in yr)	Sexual function	Instrument to measure sexual function	Well-being	Instrument to measure well-being
Mortola, 1990 (9)	Placebo open label crossover	4	1600	6 (46–61)	No change	Self-reported	Not assessed	
Morales, 1994 (16)	DB placebo crossover	24	50	15 (8 on HT) (40–70)	No change	Visual Analog Scale	Not assessed	
Wolf, 1997 (70)	DB placebo crossover	2	50	15 (69 ± 1.7)	No change	Self-reported	Nonsignificant improvement in mood and wakefulness	QOL Mood questionnaire CESDS
Bloch, 1999 (77)	DB placebo crossover	6	90 oral (3 wk), 450 oral (3 wk)	3 (45–63)	Not assessed		Significant improvement in mood	BDI, HDRS, CDS
Baulieu, 2000 (71)	DB placebo parallel	52	50	140 (>60)	Improvement	Visual Analog Scale	Not assessed	
Hackbert, 2002 (72)	DB placebo crossover	1	300	16 (51–68)	Improvement	FES, DSFI, OFQ, self-report, vaginal photoplethysmograph	Not assessed	
Schmidt, 2005 (73)	DB placebo crossover	6	90–450	6	Improvement	DSFI	Significant improvement in mood	HDRS, BDI, CDS
Nair, 2006 (78)	DB placebo parallel	104		57 (>60)	Not assessed		No change	HSQ, SF-36
Kritz-Silverstein, 2008 (74)	DB placebo parallel	52	50	115 (55–85)	No change	Female Sexual Function Index	No change	BDI, SF-36, LSI-Z, SWLS
Labrie, 2009 (76)	DB placebo parallel	12	0.25, 0.5, 1.0% vaginal cream	218 (42–74)	Improvement	Abbreviated Sexual Function, MENQOL	No change	Psychological General Well-being Index
Panjari, 2009 (66)	DB placebo parallel	52	50	93 (40–65)	No change	Sabbatsberg Sexual Self-Rating Scale, sexual event diary, MENQOL	No change	Psychological General Well-being Index

DB, Double-blind; PM, postmenopausal; HT, hormone therapy; FES, Film Evaluation Scale; DSFI, Derogatis Sexual Functioning Inventory; OFQ, Orgasmic Functioning Questionnaire; MENQOL, Menopause-specific Quality of Life; BDI, Beck Depression Inventory; HDRS, Hamilton Depression Scale; CDS, Cornell Dysthymia Scale; SF-36, The Medical Outcomes Study 36-item Short Form Survey; LSI-Z, Life Satisfaction Index-Z; SWLS, Satisfaction with Life Scale; HSQ, Health Status Questionnaire; CESDS, Center for Epidemiologic Studies Depression Scale.

function, desire/interest, arousal, orgasm, and pain at sexual activity were reported for this study (76). These data suggest that local combined androgenic/estrogenic stimulation in the vagina may exert favorable effects on sexual function in women suffering from vaginal atrophy. Unfortunately, the number of women allocated to each treatment group in this study was small, and the study reports do not provide information regarding the number of women in each arm that completed the study. Hence, the findings need to be reproduced in a larger study of longer duration before DHEA can be considered a therapeutic option for the management of vaginal atrophy. Whether these effects hold for women without vaginal atrophy remains to be investigated. Overall, the evidence from published RCT does not support efficacy of systemic DHEA therapy for the treatment of female sexual dysfunction. However, vaginal application of DHEA may benefit postmenopausal women with vaginal atrophy experiencing dyspareunia.

DHEA Treatment and Well-Being and Menopausal Symptoms

Most RCT have not demonstrated a beneficial effect of DHEA on well-being in postmenopausal women (Table

1). The only trials that have reported an improvement in mood used supraphysiological doses of DHEA (73, 77). A randomized trial of 57 elderly women (age >60 yr) given 50 mg daily DHEA for 24 months showed no improvements in quality of life (78). In a recently published randomized trial, there were no beneficial effects of 50 mg DHEA on mood, quality of life, perceptions of physical and emotional health, and life satisfaction (74); likewise, another trial of 50 mg DHEA failed to demonstrate improved well-being measured by the PGWBI (66). Despite showing beneficial effects on sexual function in women with dyspareunia, intravaginally administered DHEA showed no improvement in well-being determined by PGWBI scores (76).

It has been suggested that as ovarian function declines at menopause, the only physiologically based strategy to treat symptomatic postmenopausal women is DHEA (18). No improvement was seen in the total score or subdomain scores for the Menopause-Specific Quality of Life Questionnaire (MENQOL) in a RCT of DHEA 50 mg/d orally *vs.* placebo (66). Similarly, no effect was seen on the physical (including vasomotor) and psychological domains of the MENQOL with intravaginal DHEA, whereas the sexual domain score, which includes vaginal atrophy symp-

TABLE 2. RCT reporting the effects of DHEA on blood lipids and insulin sensitivity in postmenopausal women

First author, year (Ref.)	Study design	Duration	Dose (mg/d)	No. of postmenopausal participants (age in yr)	Significant effects on blood lipids	Significant effects on insulin sensitivity
Mortola, 1990 (9)	Placebo open label crossover	4 wk	1600 oral	6 (46–61)	↓ HDL-C 20%, ↓ total cholesterol 11.3%	75 g OGTT 20%, ↑ insulin resistance
Casson, 1995 (10)	DB placebo crossover	6 wk	50 oral	11 (45–65, mean 56.1)	↓ TG -38.12 ± 14.6 , $P = 0.02$	No Δ OGTT
Morales, 1998 (88)	DB placebo crossover	24 wk	100 oral	8, 7 using HT (50–65)	No significant changes	No Δ fasting glucose and insulin
Casson, 1998 (87)	DB	24 wk	25 oral	13	↓ HDL-C $12.9 \pm 4.6\%$	Intravenous GTT with tolbutamide augmentation, minimal model program; no Δ insulin sensitivity
Barnhart, 1999 (84)	Parallel group DB placebo	12 wk	50 oral	66 Symptomatic perimenopausal (45–55)	↓ HDL 10.1% (95% CI, -15.0 , -5.1), ↓ serum Lp(a) 18.1% (95% CI, -32.2 , -3.9)	Not reported
Lasco, 2001 (92)	Parallel group DB	52 wk	25 oral	20 (57 ± 4.5)	↑ HDL-C, 11.61%, ↓ LDL-C, 11.07%, ↓ TG, 19.60%	75 g OGTT ↑ insulin sensitivity (M index $+29.55\%$, $P = 0.01$)
Villareal, 2004 (93)	Parallel group DB	24 wk	50 oral	28 (65–78)	Not reported	75 g OGTT ↑ insulin sensitivity, mean Δ (so) insulin sensitivity index 1.4 (2.6), $P = 0.005$
Dayal, 2005 (85)	Parallel group DB	12 wk	50 oral	32 (44–70)	↓ 4% HDL-C, ↓ 8% total cholesterol, ↓ 6% LDL-C, ↓ 12% TG	Not reported
Nair, 2006 (78)	Parallel group DB	104 wk	50 oral	57 (>60)	↓ HDL-C median difference 95% CI, -5 (-10 , 0)	Oral glucose minimal model, no Δ insulin sensitivity
Basu, 2007 (91)	Parallel group DB	2 yr	50 oral	60 (>60)	See Nair 2006	Labeled mixed meal and iv GTT no sig Δ in insulin secretion, action or glucose metabolism
Igwebuike, 2008 (89)	Parallel group DB	12 wk	50 oral	31 (54–72)	No significant changes	No Δ in fasting glucose and insulin
Panjari, 2009 (90)	DB placebo parallel	52 wk	50 oral	93 (40–65)	No significant changes	HOMA, no Δ insulin sensitivity
Srinivasan, 2010 (86)	DB placebo parallel	2 yr	50 oral	57 (≥ 60)	↓ HDL-C [median difference (95% CI), -5.0 (-8.0 , -2.0) mg/dl; $P = 0.002$], ↓ no. of large HDL particles [-1.0 (-1.8 , -0.2); $P = 0.003$]	Not done

DB, Double blind; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglyceride; HT, hormone therapy; ns, nonsignificant; sig, significant; Δ , change; HOMA, homeostasis model for insulin resistance; GTT, glucose tolerance test; Lp(a), lipoprotein (a); M index, glucose infusion rate required to maintain euglycemia.

toms, improved in this study of women with vaginal atrophy (76). Taken together, DHEA does not offer therapeutic benefit for women experiencing menopause-associated vasomotor or psychological symptoms.

DHEA and Metabolic Effects

In women, the lipid effects of oral androgens and estrogens differ, with oral methyltestosterone lowering high-density lipoprotein (HDL)-cholesterol (79) and oral estrogen increasing HDL-cholesterol and triglycerides and lowering low-density lipoprotein (LDL)-cholesterol and total cholesterol (80). Combined oral estrogen and methyltestosterone is associated with a lowering of HDL-cholesterol (81, 82). In contrast, transdermal estradiol and transdermal T have little or no effect on lipids (79, 83). Because DHEA can be converted to estrogens and androgens, the effect on the lipid profile could be mixed and may vary between individuals.

Table 2 summarizes the RCT that have reported effects of DHEA treatment on the plasma lipid profile in postmenopausal women. These studies were performed using doses of oral or transdermal DHEA ranging from 25 to 1600 mg daily. Treatment periods lasted from 4 to 52 wk. Most studies had a small number of participants; however, the majority of studies used a randomized, double-blind design. A number of studies reported an effect of DHEA on plasma lipids, such that there was a decrease in HDL-

cholesterol ranging from 4–20% (9, 78, 84–87), and studies reporting a concomitant decrease in total cholesterol (9, 85) and a decrease in total and large HDL-cholesterol particles (86). However, not all the studies reported significant changes in the lipid profile (88–90). The overall impression is that the effects of DHEA on the plasma lipid-lipoprotein profile are modest or nonsignificant, with oral DHEA tending to have a HDL-cholesterol-lowering effect similar to that seen with oral methyltestosterone therapy (82).

The effects of oral DHEA therapy on insulin sensitivity reported in several RCT are also shown in Table 2. The majority of studies have reported no effect of DHEA on insulin sensitivity (10, 78, 87–91). Mortola and Yen (9) reported increased insulin resistance after an oral glucose tolerance test (OGTT) in six women with a dose of 1600 mg/d, whereas two studies using doses of 25 and 50 mg/d that were both of longer duration reported increased insulin sensitivity in relation to an OGTT (92, 93). The weight of the published data, however, indicates no significant influence of oral DHEA on insulin sensitivity at doses most commonly used in the community.

DHEA Effects on Bone

Several RCT have evaluated the effects of DHEA therapy on BMD in postmenopausal women (Table 3). Most of these studies have involved women over the age of 60 yr

TABLE 3. Placebo-controlled trials reporting the effects of DHEA on bone in postmenopausal women

First author, year (Ref.)	Study design	Duration (wk)	Dose (mg/d)	Total no.	Age of postmenopausal participants (yr)	Significant effects on BMD measured by dual photon x-ray absorptiometry
Kenny, 2010 (99)	Randomized placebo-controlled double blind	26	50	99 Frail women	≥65	No significant effects on BMD or bone turnover markers
Weiss, 2009 (94)	Randomized placebo-controlled double blind in first year, open label second year	104	50	58 Women (55 men)	65–75	In women, increase lumbar spine BMD, mean $3.6 \pm 0.7\%$. No change in men
von Mühlen, 2008 (95)	Randomized placebo-controlled double blind	52	50	115 Women (110 men)	55–85	In women, increased lumbar spine BMD. No change in men C-terminal telopeptide of type-1 collagen, significant decrease in women
Jankowski, 2008 (96)	Randomized placebo-controlled double blind	52	50	58 Women (61 men)	≥60	BMD increase lumbar spine in women BMD, increase hip (total, trochanter, and shaft regions) in women and men
Nair, 2006 (78)	Randomized placebo-controlled double blind	104	50	57 Women (87 men)	62–75	Significant increase in BMD ultradistal radius in women, significant increase in BMD femoral neck
Jankowski, 2006 (97)	Randomized placebo-controlled double blind	52	50	70 Women (70 men)	60–88	Significant increase in lumbar spine BMD in women, hip BMD both women and men
Villareal, 2000 (98)	Randomized placebo-controlled double blind	26	50	20 Women (16 men)	64–82	Significant increases in total body and lumbar spine BMD in women and men
Morales, 1998 (88)	Randomized placebo-controlled double blind, crossover	26	100	10 Women (9 men)	50–65	No significant effects on BMD
Baulieu, 2000 (71)	Randomized placebo-controlled double blind	52	50	140 Women (140 men)	60–79	Increased BMD in women femoral neck and Ward's triangle in 60–69 yr group, upper and total radius in 70–79 yr group, no effect in men
Casson, 1998 (87)	Randomized placebo-controlled double blind	26	25	13 Women		No significant effects on BMD

using a daily dose of 50 mg orally. Five studies have shown improvements in BMD at the lumbar spine (94–98), four have shown improvements in hip BMD (71, 78, 96, 97), and three have reported no improvement in BMD (87, 88, 99). Of the latter, all were conducted over 26 wk, compared with most studies showing improvement that were conducted over 52 wk or more, and one selected only women who were clinically assessed as being frail, with a mean age of 76 yr (99). Overall, the effect of DHEA supplementation on BMD is small in relation to other treatments for bone loss, and no fracture data are available. The mechanism by which DHEA enhances BMD is most likely mediated by increases in serum T and androgenic effects or by aromatization to estrogens (96).

DHEA and Cognitive Performance

Few studies have evaluated the effects of DHEA on cognitive performance. A Cochrane Review concluded that there was no evidence for benefit of DHEA therapy for cognitive performance in people over 50 yr of age without dementia (100). Table 4 lists the published placebo-controlled trials that have evaluated cognitive performance in postmenopausal women. All except one have involved a treatment phase of 4 wk or less (70, 101–104). The most rigorous study was that of Kritz-Silverstein *et al.* (74) who reported no benefit of DHEA 50 mg daily for 1 yr using a comprehensive battery of tests of cognitive performance.

Other Potential Effects of DHEA Therapy

Women with hirsutism commonly have higher levels of DHEAS (105). Side effects of acne and hirsutism have been

reported being seen relatively frequently in studies employing high doses of DHEA (106). However, few studies have used objective measures of acne and hirsutism. In one RCT, hirsutism and acne were limited to women assigned to DHEA therapy (66). Increasing doses of DHEA are likely to be associated with increased T and DHT production within the pilosebaceous unit, resulting in acne and hirsutism, without any significant associated increases in circulating T or DHT. Hence, there is a concern about potential hyperandrogenic effects of the highly androgenic metabolites of DHEA, specifically T and DHT, in women ingesting large oral doses of DHEA, *e.g.* more than 100 mg/d, for prolonged periods (107). Data pertaining to the endometrial effects of DHEA are scant. One study of 14 women aged 60 to 70 yr reported that atrophic endometrial tissue in all subjects at randomization was unchanged after 12 months of DHEA therapy (108). Panjari *et al.* (90) found no differences in bleeding patterns or findings on transvaginal ultrasound in an RCT of 73 postmenopausal women randomized to placebo or DHEA 50 mg daily. However, there is a concern about potential effects of estrogenic metabolites of DHEA in women ingesting high DHEA doses (42).

Labrie *et al.* (34) have investigated the effects of DHEA on mammary tissue extensively in *in vitro* and rodent models. They have consistently reported an inhibitory effect of DHEA on mammary carcinoma development. However, this warrants further investigation in women. No RCT of DHEA in women have been of sufficient size to provide data pertaining to safety in terms of breast cancer, endometrial cancer, or cardiovascular events.

Conclusions

DHEA continues to be promoted as having antiaging properties that have not been substantiated in a number of

TABLE 4. Placebo-controlled trials reporting the effects of DHEA on cognitive performance in postmenopausal women

First author, year (Ref.)	Study design	Treatment duration (wk)	n	Dose (mg)	Participants (age)	Cognition
Kudielka, 1998 (101)	Placebo-controlled DB	2	36	50	Postmenopausal	No change in perceived stress on Trier Social Stress test
Wolf, 1997 (70)	DB crossover placebo controlled	2	15	50	Postmenopausal (69.1 ± 1.7 yr)	No effects on tests of concentration, visual short- and long-term memory, Stroop Test, digit span, psychometric speed, or auditory verbal learning.
Wolf, 1998 (102)	DB placebo controlled	2	37	50	Postmenopausal (60–77 yr)	Visual-verbal recall reduced, attention increased after stress with DHEA
Hirshman, 2003 (103)	RCT placebo DB crossover	4	30	50	Postmenopausal (39–70 yr) (21 HT)	DHEA enhanced memory discrimination
Hirshman, 2004 (104)	RCT placebo DB crossover	4	6	50	Postmenopausal	Overall effects only presented as correlates to estrogen and androgen levels
Kritz-Silverstein, 2008 (74)	RCT DB placebo parallel	52	115	50	Postmenopausal (55–85 yr)	No effects on modified Mini-Mental State Exam; Trail Making Test B; Category Fluency; Word List Memory/Recall; modified Boston Naming Test

DB, Double blind; HT, hormone therapy.

RCT. It is sold over the counter and via the internet under the U.S. Dietary Supplement Health and Education Act of 1994 as a nutritional supplement, despite not being found in any food, and appears to be in widespread use.

Whereas early studies of DHEA supplementation were not large or of long duration, the efficacy of DHEA for the treatment of menopausal symptoms and female sexual dysfunction has now been studied in larger RCT of sufficient duration to demonstrate whether there are any benefits for these endpoints. Because no benefit has been demonstrated, one must conclude that oral DHEA therapy is not effective for the management of sexual dysfunction or menopausal symptoms in postmenopausal women with intact adrenal function. Although one study has suggested potential benefit of transvaginal DHEA for postmenopausal women with dyspareunia secondary to vaginal atrophy, this needs to be confirmed in independent studies. The weight of data does not support favorable effects of DHEA therapy in terms of lipid profiles or insulin sensitivity and, despite extensive claims in the lay literature, DHEA has not been shown in well-designed studies to enhance cognitive performance or prevent cognitive decline. DHEA supplementation has been shown to have modest effects on bone density, but studies evaluating the effects of DHEA on fracture prevention have not been conducted. This is one potential benefit of DHEA that warrants further investigation because DHEA may indeed provide a safe therapeutic option for fracture prevention in postmenopausal women.

Although DHEA levels decline with age, DHEA and DHEAS circulate in sufficient concentrations in older individuals to provide an adequate concentration of precursor hormone for the production of its estrogenic and androgenic metabolites throughout life. This may in part explain the failure of studies to demonstrate clinical benefits of DHEA therapy, other than bone density effects, in postmenopausal women with normal adrenal function. Our review was restricted to the use of DHEA in postmenopausal women with intact adrenals. The use of DHEA therapy in women with adrenal insufficiency has been reviewed in detail elsewhere (17, 109). These reviews suggest that women with adrenal insufficiency are the group most likely to derive health benefits, albeit modest, from DHEA supplementation. In particular, impaired mood and reduced libido may respond to DHEA replacement.

Taken together, findings from this review of the published literature of studies do not support the use of DHEA in postmenopausal women with intact adrenal function at this time.

Acknowledgments

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References

1. Butenandt A, Dannenbaum H 1934 Über Androsteron III. Isolierung eines neuen physiologisch unwirksamen Sterinderivates aus Mannerharn, seine Verknüpfung mit Dehydro-androsteron und Androsteron: ein Beitrag zur Konsitution des Androsterones. *Z Physiol Chem* 229:192–195
2. Munson PL, Gallagher TF, Koch FC 1944 Isolation of dehydroisandrosterone sulfate from normal male urine. *J Biol Chem* 152: 67–77
3. Migeon CJ, Plager JE 1954 Identification and isolation of dehydroepiandrosterone from peripheral human plasma. *J Biol Chem* 209:767–772
4. Symington T, Duguid WP, Davidson JN 1956 Effect of exogenous corticotropin on the histochemical pattern of the human adrenal cortex and a comparison with the changes during stress. *J Clin Endocrinol Metab* 16:580–598
5. Hall PF, Sozer CC, Eik-Nes KB 1964 Formation of dehydroepiandrosterone during in vivo and in vitro biosynthesis of testosterone by testicular tissue. *Endocrinology* 74:35–43
6. Aakvaag A, Hagen AA, Eik-Nes KB 1964 Biosynthesis in vivo of testosterone and Δ -4-androstenedione from dehydroepiandrosterone-sodium sulfate by the canine testis and ovary. *Biochim Biophys Acta* 86:622–627
7. Baulieu EE 1998 Neurosteroids: a novel function of the brain. *Psychoneuroendocrinology* 23:963–987
8. Simpson ER, Davis SR 2001 Minireview: aromatase and the regulation of estrogen biosynthesis—some new perspectives. *Endocrinology* 142:4589–4594
9. Mortola JF, Yen SS 1990 The effects of oral dehydroepiandrosterone on endocrine-metabolic parameters in postmenopausal women. *J Clin Endocrinol Metab* 71:696–704
10. Casson PR, Faquin LC, Stentz FB, Straughn AB, Andersen RN, Abraham GE, Buster JE 1995 Replacement of dehydroepiandrosterone enhances T-lymphocyte insulin binding in postmenopausal women. *Fertil Steril* 63:1027–1031
11. de Heredia FP, Larqué E, Zamora S, Garaulet M 2009 Dehydroepiandrosterone modifies rat fatty acid composition of serum and different adipose tissue depots and lowers serum insulin levels. *J Endocrinol* 201:67–74
12. Pérez-de-Heredia F, Sánchez J, Priego T, Nicolás F, Portillo Mdel P, Palou A, Zamora S, Garaulet M 2008 Adiponectin is involved in the protective effect of DHEA against metabolic risk in aged rats. *Steroids* 73:1128–1136
13. Meikle AW, Dorchuck RW, Araneo BA, Stringham JD, Evans TG, Spruance SL, Daynes RA 1992 The presence of a dehydroepiandrosterone-specific receptor binding complex in murine T cells. *J Steroid Biochem Mol Biol* 42:293–304
14. Loria RM, Inge TH, Cook SS, Szakal AK, Regelson W 1988 Protection against acute lethal viral infections with the native steroid dehydroepiandrosterone (DHEA). *J Med Virol* 26:301–314

15. Rasmussen KR, Martin EG, Healey MC 1993 Effects of dehydroepiandrosterone in immunosuppressed rats infected with *Cryptosporidium parvum*. J Parasitol 79:364–370
16. Morales AJ, Nolan JJ, Nelson JC, Yen SS 1994 Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. J Clin Endocrinol Metab [Erratum (1995) 80:2799] 78:1360–1367
17. Panjari M, Davis SR 2007 DHEA therapy for women: effect on sexual function and wellbeing. Hum Reprod Update 13:239–248
18. Labrie F, Martel C, Balser J 2011 Wide distribution of the serum dehydroepiandrosterone and sex steroid levels in postmenopausal women: role of the ovary? Menopause 18:30–43
19. Kalimi M, Regelson M 1990 The biological role of dehydroepiandrosterone (DHEA). New York: Walter de Gruyter
20. Longcope C 1986 Adrenal and gonadal androgen secretion in normal females. Clin Endocrinol Metab 15:213–228
21. Fogle RH, Stanczyk FZ, Zhang X, Paulson RJ 2007 Ovarian androgen production in postmenopausal women. J Clin Endocrinol Metab 92:3040–3043
22. Rosenfeld RS, Rosenberg BJ, Hellman L 1975 Direct analysis of dehydroisoandrosterone in plasma. Steroids 25:799–805
23. Dunn JF, Nisula BC, Rodbard D 1981 Transport of steroid hormones. Binding of 21 endogenous steroids to both testosterone-binding globulin and cortico-steroid-binding globulin in human plasma. J Clin Endocrinol Metab 53:58–68
24. Havelock JC, Auchus RJ, Rainey WE 2004 The rise in adrenal androgen biosynthesis: adrenarche. Semin Reprod Med 22:337–347
25. Orentreich N, Brind JL, Rizer RL, Vogelmann JH 1984 Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. J Clin Endocrinol Metab 59:551–555
26. Labrie F, Bélanger A, Cusan L, Gomez JL, Candas B 1997 Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. J Clin Endocrinol Metab 82:2396–2402
27. Davison SL, Bell R, Donath S, Montalto JG, Davis SR 2005 Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab 90:3847–3853
28. Crawford S, Santoro N, Laughlin GA, Sowers MF, McConnell D, Sutton-Tyrrell K, Weiss G, Vuga M, Randolph J, Lasley B 2009 Circulating dehydroepiandrosterone sulfate concentrations during the menopausal transition. J Clin Endocrinol Metab 94:2945–2951
29. Chen F, Knecht K, Birzin E, Fisher J, Wilkinson H, Mojena M, Moreno CT, Schmidt A, Harada S, Freedman LP, Reszka AA 2005 Direct agonist/antagonist functions of dehydroepiandrosterone (DHEA). Endocrinology 146:4568–4576
30. Maninger N, Wolkowitz OM, Reus VI, Epel ES, Mellon SH 2009 Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). Front Neuroendocrinol 30:65–91
31. Liu D, Dillon JS 2002 Dehydroepiandrosterone activates endothelial cell nitric-oxide synthase by a specific plasma membrane receptor coupled to $G\alpha(i2,3)$. J Biol Chem 277:21379–21388
32. Liu D, Dillon JS 2004 Dehydroepiandrosterone stimulates nitric oxide release in vascular endothelial cells: evidence for a cell surface receptor. Steroids 69:279–289
33. Liu D, Iruthayanathan M, Homan LL, Wang Y, Yang L, Wang Y, Dillon JS 2008 Dehydroepiandrosterone stimulates endothelial proliferation and angiogenesis through extracellular signal-regulated kinase 1/2-mediated mechanisms. Endocrinology 149:889–898
34. Labrie F, Luu-The V, Labrie C, Bélanger A, Simard J, Lin SX, Pelletier G 2003 Endocrine and intracrine sources of androgens in women: inhibition of breast cancer and other roles of androgens and their precursor dehydroepiandrosterone. Endocr Rev 24:152–182
35. Bulun SE, Simpson ER 1994 Competitive RT-PCR analysis indicates levels of aromatase cytochrome P450 transcripts in adipose tissue of buttock, thighs, and abdomen of women increase with advancing age. J Clin Endocrinol Metab 78:428–432
36. Misso ML, Jang C, Adams J, Tran J, Murata Y, Bell R, Boon WC, Simpson ER, Davis SR 2005 Adipose aromatase gene expression is greater in older women and is unaffected by postmenopausal estrogen therapy. Menopause 12:210–215
37. Giagulli VA, Giorgino R, Vermeulen A 1993 Origin and significance of plasma androsterone glucuronide levels: a parameter of adrenal androgen secretion and hepatic 5 α -reductase activity. J Clin Endocrinol Metab 76:918–923
38. Young J, Couzinet B, Nahoul K, Brailly S, Chanson P, Baulieu EE, Schaison G 1997 Panhypopituitarism as a model to study the metabolism of dehydroepiandrosterone (DHEA) in humans. J Clin Endocrinol Metab 82:2578–2585
39. Horton R, Hawks D, Lobo R 1982 3 α , 17 β -androstenediol glucuronide in plasma. A marker of androgen action in idiopathic hirsutism. J Clin Invest 69:1203–1206
40. Adams JB, Martyn P, Lee FT, Phillips NS, Smith DL 1990 Metabolism of 17 β -estradiol and the adrenal-derived estrogen 5-androstene-3 β ,17 β -diol (hermaphrodiol) in human mammary cell lines. Ann NY Acad Sci 595:93–105
41. Stanway SJ, Purohit A, Woo LW, Sufi S, Vigushin D, Ward R, Wilson RH, Stanczyk FZ, Dobbs N, Kulinskaya E, Elliott M, Potter BV, Reed MJ, Coombes RC 2006 Phase I study of STX 64 (667 Coumate) in breast cancer patients: the first study of a steroid sulfatase inhibitor. Clin Cancer Res 12:1585–1592
42. Plaza F, Gabler F, Romero C, Vantman D, Valladares L, Vega M 2010 The conversion of dehydroepiandrosterone into androst-5-ene-3 β ,17 β -diol (androstenediol) is increased in endometria from untreated women with polycystic ovarian syndrome. Steroids 75:810–817
43. Longcope C, Sato K, McKay C, Horton R 1984 Aromatization by splanchnic tissue in men. J Clin Endocrinol Metab 58:1089–1093
44. Ishimaru T, Edmiston WA, Pages L, Horton R 1978 Splanchnic extraction and conversion of testosterone and dihydrotestosterone in man. J Clin Endocrinol Metab 46:528–533
45. Vaitukaitis JL, Dale SL, Melby JC 1969 Role of ACTH in the secretion of free dehydroepiandrosterone and its sulfate ester in man. J Clin Endocrinol Metab 29:1443–1447
46. Vermeulen A, Ando S 1978 Prolactin and adrenal androgen secretion. Clin Endocrinol (Oxf) 8:295–303
47. Haning Jr RV, Chabot M, Flood CA, Hackett R, Longcope C 1989 Metabolic clearance rate (MCR) of dehydroepiandrosterone sulfate (DS), its metabolism to dehydroepiandrosterone, androstenedione, testosterone, and dihydrotestosterone, and the effect of increased plasma DS concentration on DS MCR in normal women. J Clin Endocrinol Metab 69:1047–1052
48. Parker L, Eugene J, Farber D, Lifrak E, Lai M, Juler G 1985 Dissociation of adrenal androgen and cortisol levels in acute stress. Horm Metab Res 17:209–212
49. Parker LN, Levin ER, Lifrak ET 1985 Evidence for adrenocortical adaptation to severe illness. J Clin Endocrinol Metab 60:947–952
50. Zumoff B, Walsh BT, Katz JL, Levin J, Rosenfeld RS, Kream J, Weiner H 1983 Subnormal plasma dehydroepiandrosterone to cortisol ratio in anorexia nervosa: a second hormone parameter of ontogenic regression. J Clin Endocrinol Metab 56:668–672
51. Cunningham SK, McKenna TJ 1994 Dissociation of adrenal androgens and cortisol secretion in Cushing's syndrome. Clin Endocrinol (Oxf) 41:795–800
52. Davis SR, Davison SL, Donath S, Bell RJ 2005 Circulating androgen levels and self-reported sexual function in women. JAMA 294:91–96
53. Basson R, Brotto LA, Petkau AJ, Labrie F 2010 Role of androgens in women's sexual dysfunction. Menopause 17:962–971
54. Bell RJ, Donath S, Davison SL, Davis SR 2006 Endogenous an-

- drogen levels and wellbeing: differences between pre- and postmenopausal women. *Menopause* 13:65–71
55. Barrett-Connor E, von Mühlen D, Laughlin GA, Kripke A 1999 Endogenous levels of dehydroepiandrosterone sulfate, but not other sex hormones, are associated with depressed mood in older women: the Rancho Bernardo Study. *J Am Geriatr Soc* 47:685–691
 56. Bell RJ, Davison SL, Papalia MA, McKenzie DP, Davis SR 2007 Endogenous androgen levels and cardiovascular risk profile in women across the adult life span. *Menopause* 14:630–638
 57. Shufelt C, Bretsky P, Almeida CM, Johnson BD, Shaw LJ, Azziz R, Braunstein GD, Pepine CJ, Bittner V, Vido DA, Stanczyk FZ, Bairey Merz CN. DHEA-S 2010 Levels and cardiovascular disease mortality in postmenopausal women: results from the National Institutes of Health–National Heart, Lung, and Blood Institute (NHLBI)-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Clin Endocrinol Metab* 95:4985–4992
 58. Golden SH, Dobs AS, Vaidya D, Szklo M, Gapstur S, Kopp P, Liu K, Ouyang P 2007 Endogenous sex hormones and glucose tolerance status in postmenopausal women. *J Clin Endocrinol Metab* 92:1289–1295
 59. Barrett-Connor E, Ferrara A 1996 Dehydroepiandrosterone, dehydroepiandrosterone sulfate, obesity, waist-hip ratio, and noninsulin-dependent diabetes in postmenopausal women: the Rancho Bernardo Study. *J Clin Endocrinol Metab* 81:59–64
 60. Nawata H, Tanaka S, Tanaka S, Takayanagi R, Sakai Y, Yanase T, Ikuyama S, Haji M 1995 Aromatase in bone cell: association with osteoporosis in postmenopausal women. *J Steroid Biochem Molec Biol* 53:165–174
 61. Kasperk CH, Wergedal JE, Farley JR, Linkhart TA, Turner RT, Baylink DJ 1989 Androgens directly stimulate proliferation of bone cells *in vitro*. *Endocrinology* 124:1576–1578
 62. Davis SR, Shah SM, McKenzie DP, Kulkarni J, Davison SL, Bell RJ 2008 Dehydroepiandrosterone sulfate levels are associated with more favorable cognitive function in women. *J Clin Endocrinol Metab* 93:801–808
 63. Valenti G, Ferrucci L, Lauretani F, Ceresini G, Bandinelli S, Luci M, Ceda G, Maggio M, Schwartz RS 2009 Dehydroepiandrosterone sulfate and cognitive function in the elderly: the InCHIANTI Study. *J Endocrinol Invest* 32:766–772
 64. Barrett-Connor E, Edelstein SL 1994 A prospective study of dehydroepiandrosterone sulfate and cognitive function in an older population: the Rancho Bernardo Study. *J Am Geriatr Soc* 42:420–423
 65. Labrie F, Bélanger A, Bélanger P, Bérubé R, Martel C, Cusan L, Gomez J, Candas B, Chaussade V, Castiel I, Deloche C, Leclaire J 2007 Metabolism of DHEA in postmenopausal women following percutaneous administration. *J Steroid Biochem Mol Biol* 103:178–188
 66. Panjari M, Bell RJ, Jane F, Wolfe R, Adams J, Morrow C, Davis SR 2009 A randomized trial of oral DHEA treatment for sexual function, well-being, and menopausal symptoms in postmenopausal women with low libido. *J Sex Med* 6:2579–2590
 67. Labrie F, Cusan L, Gomez JL, Martel C, Bérubé R, Bélanger P, Chaussade V, Deloche C, Leclaire J 2008 Changes in serum DHEA and eleven of its metabolites during 12-month percutaneous administration of DHEA. *J Steroid Biochem Mol Biol* 110:1–9
 68. Laumann EO, Paik A, Rosen RC 1999 Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 281:537–544
 69. Hayes RD, Dennerstein L, Bennett CM, Fairley CK 2008 What is the “true” prevalence of female sexual dysfunctions and does the way we assess these conditions have an impact? *J Sex Med* 5:777–787
 70. Wolf OT, Neumann O, Hellhammer DH, Geiben AC, Strasburger CJ, Dressendorfer RA, Pirke KM, Kirschbaum C 1997 Effects of a two-week physiological dehydroepiandrosterone substitution on cognitive performance and well-being in healthy elderly women and men. *J Clin Endocrinol Metab* 82:2363–2367
 71. Baulieu EE, Thomas G, Legrain S, Lahlou N, Roger M, Debuire B, Faucounau V, Girard L, Hervy MP, Latour F, Leaud MC, Mokrane A, Pitti-Ferrandi H, Trivalle C, de Lacharrière O, Nouveau S, Rakoto-Arison B, Souberbielle JC, Raison J, Le Bouc Y, Raynaud A, Girerd X, Forette F 2000 Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge Study to a sociobiomedical issue. *Proc Natl Acad Sci USA* 97:4279–4284
 72. Hackbert L, Heiman JR 2002 Acute dehydroepiandrosterone (DHEA) effects on sexual arousal in postmenopausal women. *J Womens Health Gend Based Med* 11:155–162
 73. Schmidt PJ, Daly RC, Bloch M, Smith MJ, Danaceau MA, St Clair LS, Murphy JH, Haq N, Rubinow DR 2005 Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. *Arch Gen Psychiatry* 62:154–162
 74. Kritz-Silverstein D, von Mühlen D, Laughlin GA, Bettencourt R 2008 Effects of dehydroepiandrosterone supplementation on cognitive function and quality of life: the DHEA and Well-Ness (DAWN) Trial. *J Am Geriatr Soc* 56:1292–1298
 75. Labrie F, Archer D, Bouchard C, Fortier M, Cusan L, Gomez JL, Girard G, Baron M, Ayotte N, Moreau M, Dubé R, Côté I, Labrie C, Lavoie L, Berger L, Gilbert L, Martel C, Balser J 2009 Intravaginal dehydroepiandrosterone (Prasterone), a physiological and highly efficient treatment of vaginal atrophy. *Menopause* 16:907–922
 76. Labrie F, Archer D, Bouchard C, Fortier M, Cusan L, Gomez JL, Girard G, Baron M, Ayotte N, Moreau M, Dubé R, Côté I, Labrie C, Lavoie L, Berger L, Gilbert L, Martel C, Balser J 2009 Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. *Menopause* 16:923–931
 77. Bloch M, Schmidt PJ, Danaceau MA, Adams LF, Rubinow DR 1999 Dehydroepiandrosterone treatment of midlife dysthymia. *Biol Psychiatry* 45:1533–1541
 78. Nair KS, Rizza RA, O'Brien P, Dhatriya K, Short KR, Nehra A, Vittone JL, Klee GG, Basu A, Basu R, Cobelli C, Toffolo G, Dalla Man C, Tindall DJ, Melton 3rd LJ, Smith GE, Khosla S, Jensen MD 2006 DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med* 355:1647–1659
 79. Somboonporn W, Davis S, Seif M, Bell R 2005 Testosterone for peri- and postmenopausal women. *Cochrane Database Syst Rev*: CD004509
 80. Darling GM, Johns JA, McCloud PI, Davis SR 1997 Estrogen and progestin compared with simvastatin for hypercholesterolemia postmenopausal women. *N Engl J Med* 337:595–601
 81. Flöter A, Nathorst-Böös J, Carlström K, von Schoultz B 2004 Serum lipids in oophorectomized women during estrogen and testosterone replacement therapy. *Maturitas* 47:123–129
 82. Leão LM, Duarte MP, Silva DM, Bahia PR, Coeli CM, de Farias ML 2006 Influence of methyltestosterone postmenopausal therapy on plasma lipids, inflammatory factors, glucose metabolism and visceral fat: a randomized study. *Eur J Endocrinol* 154:131–139
 83. Davis SR, Goldstat R, Newman A, Berry K, Burger HG, Meredith I, Koch K 2002 Differing effects of low dose estrogen and progestin replacement therapy and pravastatin in hypercholesterolemic postmenopausal women. *Climacteric* 5:341–350
 84. Barnhart KT, Freeman E, Grisso JA, Rader DJ, Sammel M, Kapoor S, Nestler JE 1999 The effect of dehydroepiandrosterone supplementation to symptomatic perimenopausal women on serum endocrine profiles, lipid parameters, and health-related quality of life. *J Clin Endocrinol Metab* 84:3896–3902
 85. Dayal M, Sammel MD, Zhao J, Hummel AC, Vandenbourn K, Barnhart KT 2005 Supplementation with DHEA: effect on muscle size, strength, quality of life, and lipids. *J Womens Health (Larchmt)* 14:391–400
 86. Srinivasan M, Irving BA, Frye RL, O'Brien P, Hartman SJ, McConnell JP, Nair KS 2010 Effects on lipoprotein particles of long-term dehydroepiandrosterone in elderly men and women and testosterone in elderly men. *J Clin Endocrinol Metab* 95:1617–1625
 87. Casson PR, Santoro N, Elkind-Hirsch K, Carson SA, Hornsby PJ,

- Abraham G, Buster JE 1998 Postmenopausal dehydroepiandrosterone administration increases free insulin-like growth factor-I and decreases high-density lipoprotein: a six-month trial. *Fertil Steril* 70:107–110
88. Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SS 1998 The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. *Clin Endocrinol (Oxf)* 49:421–432
 89. Igwebuike A, Irving BA, Bigelow ML, Short KR, McConnell JP, Nair KS 2008 Lack of dehydroepiandrosterone effect on a combined endurance and resistance exercise program in postmenopausal women. *J Clin Endocrinol Metab* 93:534–538
 90. Panjari M, Bell RJ, Jane F, Adams J, Morrow C, Davis SR 2009 The safety of 52 weeks of oral DHEA therapy for postmenopausal women. *Maturitas* 63:240–245
 91. Basu R, Dalla Man C, Campioni M, Basu A, Nair KS, Jensen MD, Khosla S, Klee G, Toffolo G, Cobelli C, Rizza RA 2007 Two years of treatment with dehydroepiandrosterone does not improve insulin secretion, insulin action, or postprandial glucose turnover in elderly men or women. *Diabetes* 56:753–766
 92. Lasco A, Frisina N, Morabito N, Gaudio A, Morini E, Trifiletti A, Basile G, Nicita-Mauro V, Cucinotta D 2001 Metabolic effects of dehydroepiandrosterone replacement therapy in postmenopausal women. *Eur J Endocrinol* 145:457–461
 93. Villareal DT, Holloszy JO 2004 Effect of DHEA on abdominal fat and insulin action in elderly women and men: a randomized controlled trial. *JAMA* 292:2243–2248
 94. Weiss EP, Shah K, Fontana L, Lambert CP, Holloszy JO, Villareal DT 2009 Dehydroepiandrosterone replacement therapy in older adults: 1- and 2-y effects on bone. *Am J Clin Nutr* 89:1459–1467
 95. von Mühlen D, Laughlin GA, Kritz-Silverstein D, Bergstrom J, Bettencourt R 2008 Effect of dehydroepiandrosterone supplementation on bone mineral density, bone markers, and body composition in older adults: the DAWN trial. *Osteoporos Int* 19:699–707
 96. Jankowski CM, Gozansky WS, Kittelson JM, Van Pelt RE, Schwartz RS, Kohrt WM 2008 Increases in bone mineral density in response to oral dehydroepiandrosterone replacement in older adults appear to be mediated by serum estrogens. *J Clin Endocrinol Metab* 93:4767–4773
 97. Jankowski CM, Gozansky WS, Schwartz RS, Dahl DJ, Kittelson JM, Scott SM, Van Pelt RE, Kohrt WM 2006 Effects of dehydroepiandrosterone replacement therapy on bone mineral density in older adults: a randomized, controlled trial. *J Clin Endocrinol Metab* 91:2986–2993
 98. Villareal DT, Holloszy JO, Kohrt WM 2000 Effects of DHEA replacement on bone mineral density and body composition in elderly women and men. *Clin Endocrinol (Oxf)* 53:561–568
 99. Kenny AM, Boxer RS, Kleppinger A, Brindisi J, Feinn R, Burleson JA 2010 Dehydroepiandrosterone combined with exercise improves muscle strength and physical function in frail older women. *J Am Geriatr Soc* 58:1707–1714
 100. Grimley Evans J, Malouf R, Huppert F, van Niekerk JK 2006 Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. *Cochrane Database Syst Rev*: CD006221
 101. Kudielka BM, Hellhammer J, Hellhammer DH, Wolf OT, Pirke KM, Varadi E, Pilz J, Kirschbaum C 1998 Sex differences in endocrine and psychological responses to psychosocial stress in healthy elderly subjects and the impact of a 2-week dehydroepiandrosterone treatment. *J Clin Endocrinol Metab* 83:1756–1761
 102. Wolf OT, Kudielka BM, Hellhammer DH, Hellhammer J, Kirschbaum C 1998 Opposing effects of DHEA replacement in elderly subjects on declarative memory and attention after exposure to a laboratory stressor. *Psychoneuroendocrinology* 23:617–629
 103. Hirshman E, Wells E, Wierman ME, Anderson B, Butler A, Senholzi M, Fisher J 2003 The effect of dehydroepiandrosterone (DHEA) on recognition memory decision processes and discrimination in postmenopausal women. *Psychon Bull Rev* 10:125–134
 104. Hirshman E, Merritt P, Wang CC, Wierman M, Budescu DV, Kohrt W, Templin JL, Bhasin S 2004 Evidence that androgenic and estrogenic metabolites contribute to the effects of dehydroepiandrosterone on cognition in postmenopausal women. *Horm Behav* 45:144–155
 105. Karrer-Voegeli S, Rey F, Reymond MJ, Meuwly JY, Gaillard RC, Gomez F 2009 Androgen dependence of hirsutism, acne, and alopecia in women: retrospective analysis of 228 patients investigated for hyperandrogenism. *Medicine (Baltimore)* 88:32–45
 106. van Vollenhoven RF 2002 Dehydroepiandrosterone for the treatment of systemic lupus erythematosus. *Expert Opin Pharmacother* 3:23–31
 107. Stanczyk FZ, Slater CC, Ramos DE, Azen C, Cherala G, Hakala C, Abraham G, Roy S 2009 Pharmacokinetics of dehydroepiandrosterone and its metabolites after long-term oral dehydroepiandrosterone treatment in postmenopausal women. *Menopause* 16:272–278
 108. Labrie F, Diamond P, Cusan L, Gomez JL, Bélanger A, Candas B 1997 Effect of 12-month dehydroepiandrosterone replacement therapy on bone, vagina and endometrium in postmenopausal women. *J Clin Endocrinol Metab* 82:3498–3505
 109. Arlt W 2009 The approach to the adult with newly diagnosed adrenal insufficiency. *J Clin Endocrinol Metab* 94:1059–1067