

REVIEW

Dehydroepiandrosterone, obesity and cardiovascular disease risk: a review of human studies

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Abstract

The age-related decline in serum dehydroepiandrosterone (DHEA) and its sulfated ester (DHEA-S) has suggested that a relative deficiency of these steroids may be causally related to the development of chronic diseases generally associated with aging, including insulin resistance, obesity, cardiovascular disease, cancer, reductions of the immune defense, depression and a general deterioration in the sensation of well-being. The numerous studies which have focused on the link between DHEA and cardiovascular disease have generally been inconsistent, generating much debate and controversy on this issue. The present article is an analysis of studies on the relationship between endogenous DHEA or DHEA-S, obesity and cardiovascular disease risk, as well as DHEA treatment studies. Elevated plasma levels of free DHEA are associated with reduced obesity in both men and women, and with smaller abdominal body fat accumulations in men. However, contradictory results have been reported regarding the relationships between the sulfate ester DHEA-S and adiposity. Age differences in the populations studied may have been a confounding factor in these associations. On the other hand, DHEA-S level is not a predictor of cardiovascular disease endpoints in women, and appears to be a relatively weak one in men. DHEA intervention studies suggest that the effects of DHEA on serum lipids are, at best, modest or non-significant. The uncertainty as to whether endogenous and exogenous DHEA should be considered cardioprotective is related to discrepancies in the literature on this topic. Several studies may have been plagued by methodological problems such as low power, unreliable analytical methods, confounding factors or other differences in the populations studied. As a consequence, the original reports demonstrating dramatic effects of either endogenous or exogenous DHEA on cardiovascular disease risk have never been replicated. We propose that the effects of DHEA on cardiovascular disease risk (either favorable or unfavorable) should be considered to be much more modest than previously believed.

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Introduction

Humans and other primates are unique in having elevated circulating levels of dehydroepiandrosterone (DHEA) and its sulfated ester (DHEA-S). In fact, in humans, DHEA-S concentration is 100- to 500-fold higher than that of testosterone and 1000 to 10 000 times greater than that of estradiol. DHEA and DHEA-S, however, do not possess intrinsic estrogenic or androgenic activity. These inactive precursor steroids are converted into active androgens and estrogens in peripheral target tissues (1), a process that depends on the specific expression of the steroidogenic enzymes in each of these tissues, thus allowing humans and other primates to regulate locally the amounts of active steroids on a cellular basis. This newly identified mode of hormonal synthesis and action, called intracrinology, is complementary to the well-known endocrine and paracrine/autocrine modes of hormone action (1, 2).

The marked age-related decline in serum DHEA and DHEA-S (3, 4) has suggested that a relative deficiency of these steroids may be causally related to the development of a series of diseases generally associated with aging. Postulated consequences of low DHEA include insulin resistance (5), obesity (6, 7), cardiovascular disease (8), cancer (9), reduction of the immune defense (10), and psychosocial problems such as depression and a general deterioration in the sensation of well-being (11). The numerous studies which have focused on the link between DHEA and cardiovascular disease have generally been inconsistent, generating much debate and controversy on this issue (12–14). The present article is complementary to recent reviews focusing more generally on androgens and cardiovascular disease (15–17), and summarizes the information available in the literature on the relationship between endogenous DHEA or DHEA-S levels, obesity, body fat distribution and cardiovascular disease risk. The observations

made from DHEA treatment on these variables are also summarized.

Endogenous DHEA and DHEA-S

Obesity and body fat distribution

Obesity is well recognized to be associated with higher morbidity and mortality (18) through its association with hypertension and an increased risk of type 2 diabetes and cardiovascular disease (19–22). Although the association between obesity and cardiovascular morbidity and mortality is of low magnitude compared with the impact of other well-known risk factors for cardiovascular events such as smoking, dyslipidemia and hypertension (22–25), the continuing increase in this condition's prevalence and its epidemic proportions in North America have reinforced the need for research in this field (26, 27). This notion has been further emphasized by recent data from the Framingham heart study (28), which showed a graded increase in the risk of heart failure across categories of body mass index (BMI) values. A growing body of evidence suggests that metabolic complications associated with obesity may be mediated to a large extent by differences in body fat distribution (29, 30). In this regard, the accumulation of fat in the abdominal region has been associated with an increased risk of developing cardiovascular disease and related mortality (31–38). Most studies have relied on the waist-to-hip ratio (WHR) to estimate the accumulation of adipose tissue in the abdominal region (39), while other investigators have used computed tomography to measure adipose tissue located in the abdominal cavity separately from the subcutaneous adipose tissue depot (or visceral adipose tissue) (40–42). Using imaging methods, studies have shown that abdominal, and especially visceral or intra-abdominal obesity, in both men and women, is closely associated with a dyslipidemic state which includes hypertriglyceridemia, hypo- α lipoproteinemia, elevated apolipoprotein B, a greater proportion of small, dense low-density lipoprotein (LDL) particles and an increased LDL-cholesterol to high-density lipoprotein (HDL)-cholesterol ratio (43–48). This condition is also associated with hyperinsulinemia, insulin resistance (46, 49–51) and, most importantly, an increased 5-year risk of death (38).

As summarized in Table 1, several cross-sectional studies have examined the relationship between overweight, obesity and plasma levels of DHEA and DHEA-S. In both men and women, the majority of studies found a statistically significant negative correlation between plasma free DHEA levels and measures of total adiposity (52–57). Such data suggest that higher circulating DHEA is associated with lower body fat accumulation. Two studies out of six used more precise measures, such as body fat mass and percent body fat measured by hydrostatic weighing and

confirmed these findings (56, 57). These correlations were found in both pre- and postmenopausal women (52–54), as well as Caucasian men of various ages (55–57). The relationship between plasma levels of the sulfate ester DHEA-S and measures of obesity is less consistent. Indeed, in eight studies performed in pre- or postmenopausal women, with samples including from 28 to 659 subjects, plasma DHEA-S levels were not significantly related to BMI or percent body fat, with the exception of one study (58) reporting a positive correlation between DHEA-S and BMI. The other studies only reported statistically non-significant trends (Table 1). In men, the magnitude and direction of the association between DHEA-S and obesity is also equivocal. Seven studies found a significant association between plasma DHEA-S and measures of obesity (55–61), two studies found that DHEA-S was negatively associated with measures of obesity (57, 59), whereas five studies found the opposite (55, 56, 58, 60). A number of studies also found no significant association (62–67).

Studies examining the associations between measures of body fat distribution and plasma DHEA or DHEA-S levels are summarized in Table 2. In women, none of the studies found a statistically significant association between plasma DHEA and the WHR. In men, all three studies where DHEA was measured found a significant negative association between DHEA levels and measures of abdominal fat distribution (55–57), thus suggesting that low circulating DHEA is associated with a more central distribution of adipose tissue. Two studies (56, 57) have examined the correlation between computed tomography measures of visceral adipose tissue area and plasma DHEA. These studies also reported a negative correlation, suggesting that low DHEA levels are associated with greater accumulation of fat within the abdominal cavity (Table 2). Again, the association between plasma DHEA-S and body fat distribution measures is less consistent. In women, two studies reported a negative association (68, 69), whereas two studies reported a positive association between the WHR and plasma DHEA-S (52, 70). Similar results were found in men, where three studies reported a negative association between plasma DHEA-S and a central accumulation of body fat (55, 56) and two other studies reported the opposite (57, 59). The association between computed tomography-measured visceral adipose tissue areas and DHEA-S was negative in one study (56) and positive in the other (57).

The reasons for these discrepancies are unclear at the present time. However, differences do not seem to be explained by sample size, ethnicity or the methodology used in the measurement of either body fatness or DHEA-S. Some of the studies were performed in non-smokers, thus suggesting that smoking status, which has been associated with alterations in DHEA and DHEA-S dynamics (71, 72), is not involved. It

Table 1 Correlation coefficients between circulating DHEA or DHEA-S levels and measures of total adiposity.

Studies	Measurement	DHEA	DHEA-S	Population
Women				
Vettor <i>et al.</i> (62)	BMI	ns	ns	65 premenopausal
Ravaglia <i>et al.</i> (59)	BMI	nd	ns	39 older
Maccario <i>et al.</i> (151)	BMI	nd	ns	217 obese pre/postmenopausal
Evans <i>et al.</i> (73)	%IBW	nd	-0.22	80 premenopausal
de Pergola <i>et al.</i> (68)	BMI	nd	-0.31	40 premenopausal
Ivancic <i>et al.</i> (74)	BMI	nd	-0.45	70 premenopausal
Haffner <i>et al.</i> (93)	BMI	nd	+0.10	253 postmenopausal
Williams <i>et al.</i> (70)	BMI	nd	+0.15	96 premenopausal
	% fat	nd	+0.14	
Abbassi <i>et al.</i> (58)	BMI	nd	+0.24*	118 postmenopausal
	Body fat mass	nd	+0.11	
	% fat	nd	+0.09	
de Pergola <i>et al.</i> (53)	BMI	-0.57*	+0.17	28 premenopausal
Barrett-Connor & Ferrara (52)	BMI	-0.09*	-0.06	659 postmenopausal
de Pergola <i>et al.</i> (54)	BMI	-0.90*	nd	13 premenopausal
Men				
Vettor <i>et al.</i> (62)	BMI	ns	ns	46
Herranz <i>et al.</i> (63)	BMI	nd	-0.24	34
Haffner <i>et al.</i> (64-66)	BMI	nd	-0.13	178 Mexican-American/non-Hispanic whites
Haffner <i>et al.</i> (67)	BMI	nd	+0.03	87 Finnish
Ravaglia <i>et al.</i> (59)	BMI	nd	+0.41*	36 older
Vermeulen <i>et al.</i> (60)	BMI	+0.09	-0.28*	250
Field <i>et al.</i> (55)	BMI	-0.13*	-0.09*	1241
Abbassi <i>et al.</i> (58)	BMI	nd	-0.15	144 older
	Body fat mass	nd	-0.27*	
	% fat	nd	-0.30*	
Couillard <i>et al.</i> (56)	BMI	-0.17*	-0.17*	217
	Body fat mass	-0.25*	-0.28*	
	% fat	-0.20*	-0.23*	
Pritchard <i>et al.</i> (61)	Body fat mass	nd	-0.46*	12 pairs of male twins
Tchernof <i>et al.</i> (57)	BMI	-0.42*	+0.52*†	80
	Body fat mass	-0.38*	+0.48*†	
	% fat	-0.35*	+0.44*†	

* Statistically significant association; nd, not determined; ns, non-significant correlation coefficient not provided in the paper. †not provided in the original paper; %IBW, percent ideal body weight determined from the midpoint for medium frame using tables from the Metropolitan Life Insurance Co.

can be hypothesized that the age-related decline in DHEA-S concentrations (3, 4) may have been a significant confounding factor in these associations, given that adiposity increases with age, while DHEA-S decreases. It is important to indicate that most of the associations presented in Tables 1 and 2 were not statistically adjusted for age (54-59, 62, 67-69, 73, 74). In the study by Abbassi *et al.* (58), the association between DHEA-S and age was non-significant in women, which suggests that the positive association between BMI and DHEA-S was presumably independent of age in that study. Moreover, statistical adjustment for age did not abolish the negative association found in males between DHEA-S and body fat mass or percent body fat (58). Adjustment for age led to a non-significant correlation between DHEA-S and BMI in the women studied by Barrett-Connor & Ferrara (52). On the other hand, statistical adjustment for age eliminated the negative association between total body fatness and DHEA-S in the study by Couillard *et al.* (56, C. Couillard, personal communication), whereas the positive association was not affected by such adjustment in our study (57). Non-significant

associations between DHEA-S and measures of abdominal fat were reported in two studies after adjustment for age, or age and BMI (53, 63) and a significant, positive, age-independent association was found in women in two studies (52, 70). Thus, differences in the age of subjects may have represented an important confounding factor in the study of the relationships between obesity, body fat distribution and endogenous DHEA-S.

The mechanisms linking obesity, body fat distribution and serum DHEA or DHEA-S have not been fully elucidated, although several possibilities have been raised. Gordon *et al.* (75) observed that cell conversion to mature adipocytes is impeded in the presence of DHEA, whereas DHEA-S exhibited a minor inhibitory effect on glucose-6-phosphate dehydrogenase activity (75). The role of DHEA as precursor for active androgens and estrogens may also play a role in the relationship between obesity, body fat distribution and circulating DHEA. Steroids are lipophilic compounds which are highly soluble in adipose tissue (76, 77). Moreover, adipose tissue expresses the several steroid-converting enzymes necessary for local synthesis of active androgens/estrogens from inactive precursors such as DHEA

Table 2 Correlation coefficients between circulating DHEA or DHEA-S levels and measures of body fat distribution.

Studies	Measurement	DHEA	DHEA-S	Population
Women				
Maccario <i>et al.</i> (151)	WHR	nd	ns	217 obese pre/postmenopausal
Evans <i>et al.</i> (73)	WHR	nd	- 0.06	80 premenopausal
Williams <i>et al.</i> (70)	WHR	nd	- 0.02	96 premenopausal
	% trunk fat	nd	+ 0.28*	
de Pergola <i>et al.</i> (68)	WHR	nd	- 0.38*	40 premenopausal
De Simone <i>et al.</i> (69)	WHR	nd	- 0.69*	29 massively obese adolescents
	Visceral AT	nd	- 0.94*	
Abbassi <i>et al.</i> (58)	WHR	nd	- 0.18	118 postmenopausal
Ivandic <i>et al.</i> (74)	WHR	nd	- 0.44	70 premenopausal
Ravaglia <i>et al.</i> (59)	WHR	nd	ns	39 older
Barrett-Connor & Ferrara (52)	WHR	+ 0.06	+ 0.08*	659 postmenopausal
de Pergola <i>et al.</i> (53)	WHR	- 0.09	+ 0.28	28 premenopausal
de Pergola <i>et al.</i> (54)	WHR	+ 0.03	nd	13 premenopausal
Men				
Pritchard <i>et al.</i> (61)	Visceral AT	nd	ns	12 pairs of male twins
Herranz <i>et al.</i> (63)	WHR	nd	- 0.17	34
Haffner <i>et al.</i> (67)	WHR	nd	- 0.07	87 Finnish
Haffner <i>et al.</i> (64–66)	WHR	nd	- 0.29*	178 Mexican-American non-Hispanic whites
Ravaglia <i>et al.</i> (59)	WHR	nd	+ 0.47*	36 older
Abbassi <i>et al.</i> (58)	WHR	nd	- 0.16	144 older
Field <i>et al.</i> (55)	WHR	- 0.11*	- 0.10*	1241
Couillard <i>et al.</i> (56)	WHR	- 0.37*	- 0.32*	217
	Visceral AT	- 0.32*	- 0.36*	
Tchernof <i>et al.</i> (57)	WHR	- 0.38*	+ 0.64*†	80
	Visceral AT	- 0.33*	+ 0.48*†	

* Statistically significant association; nd, not determined; ns, non-significant correlation coefficient not provided in the paper; †not provided in the original paper; WHR, waist-to-hip ratio; visceral AT, visceral adipose tissue area measured by computed tomography.

(76, 78–82). The enzymes responsible for the inactivation of androgens/estrogens are also present in adipose tissue (83), thereby modulating the intracellular levels of active steroids. The intracrine conversion of DHEA to either androgens or estrogens in a site-specific fashion could affect adipocyte physiology and modulate adipose tissue accumulation and mobilization.

Insulin resistance and hyperinsulinemia

A series of studies have shown that insulin may act as a down-regulator of DHEA biosynthesis in the adrenal gland by inhibiting the activity of the enzyme 17,20-lyase (84–87). This effect of insulin on DHEA secretion has been observed in studies where experimental hyperinsulinemia was induced (85–87). In this regard, it has been proposed that reduced DHEA may mediate the relationship with an increased risk of cardiovascular disease through a diminished inhibition of fibroblast growth and differentiation, alterations in the plasma lipid profile and through a diminished inhibition of platelet aggregation (88). It has also been shown that insulin may increase the metabolic clearance of DHEA (89), and studies by our group have demonstrated that hyperinsulinemia induced during DHEA infusion stimulated DHEA fatty acid esterification through the action of plasma lecithin: cholesterol acyltransferase (90). On the other hand, DHEA-S may have direct effects on insulin sensitivity by increasing insulin binding to its own receptor (91).

The above-mentioned data suggest the possibility that reduced DHEA may directly contribute to insulin resistance. DHEA may also be related to insulin resistance and hyperinsulinemia through its association with obesity. In agreement with this possibility, we have observed that statistical control for differences in adiposity and abdominal fat accumulation eliminated the association between DHEA and glucose tolerance in men (92). These results suggest that adiposity may mediate a significant portion of the association between DHEA and hyperinsulinemia/insulin resistance. Further studies are needed, however, to help identify the primary factor(s) responsible for these complex inter-relationships.

Plasma lipids and lipoproteins

A number of cross-sectional studies have examined the relationships between endogenous DHEA or DHEA-S and plasma levels of lipids and lipoproteins (58, 64, 93–97). Results from these studies have been somewhat inconsistent. The most consistent association has been found between plasma DHEA-S and triglyceride levels. Indeed, three studies (59, 64, 94) have reported a significant negative relationship between these two variables. Some studies have also found that elevated plasma DHEA or DHEA-S levels may be related to a favorable plasma lipid-lipoprotein profile through positive associations with the HDL-cholesterol concentration (58, 64), and negative associations with

total cholesterol (95). A number of studies, however, reported no significant relationships (64, 93, 94). Again, several variables such as differences in age as well as the degree of obesity and abdominal fat accumulation may have represented important confounding factors in the evaluation of these associations. Accordingly, we have found that the associations between plasma DHEA and variables of the lipid-lipoprotein profile could be explained to a large extent by concomitant variations in adiposity and abdominal body fat accumulation (95). Interestingly, at least in men, the associations of DHEA with variables of the lipid profile are similar to those of testosterone with these variables (95); namely, elevated plasma androgens appear to be related to a favorable plasma lipid-lipoprotein profile in men (98), which supports the notion that DHEA may be related to the lipid profile through its conversion to androgenic steroids.

Cardiovascular disease

A number of prospective studies comparing serum DHEA or DHEA-S levels in cardiovascular disease cases versus controls have been published (summarized in Table 3). Most of these studies were nested case-control designs, which provide useful information on risk factors for various cardiovascular disease endpoints, but generally have the caveat of overestimating the relative risk associated with a given factor. Results have been inconclusive in both men and women (Table 3). In women, one study found lower DHEA-S levels in ischemic heart disease cases compared with controls (99), whereas this association was not found in the other study (100). In men, results are even more contradictory, as one study found lower DHEA-S levels in myocardial infarction cases compared with

controls (101), while another smaller size study actually found increased DHEA-S in myocardial infarction cases (102). Two other studies did not find a significant association (103, 104).

Epidemiological prospective population studies have examined the relationship of endogenous serum DHEA-S levels with cardiovascular disease mortality rates. These studies are summarized in Tables 4 and 5. The studies performed in women (Table 4) are very consistent in demonstrating that there is no relationship between plasma DHEA-S levels and mortality from cardiovascular disease or other causes. Indeed, no significant association was found in all seven population studies performed to date (105–112). A trend for higher mortality rates in women with elevated DHEA-S was found in the study by Barrett-Connor & Khaw Gruen (110). However, no *P* value was provided in this short communication, and a later examination of the same cohort, when more women were included (111, 112), generated a non-significant relationship.

Prospective population studies on DHEA-S and mortality rates in men are summarized in Table 5. As opposed to the statistically non-significant studies in women, most studies in men (five out of seven) found that elevated levels of DHEA-S were associated with lower mortality rates, either from cardiovascular disease or any other cause (8, 106, 108, 109, 112), while the two others generated non-significant results. Odds ratios calculated for the risk increase associated with low DHEA-S values ranged from 1.17 to 3.3. The highest value was obtained by Barrett-Connor *et al.* (8) in the first analysis of the Rancho Bernardo population. A later analysis of the same population demonstrating a much lower odds ratio (1.17) revealed that the risk associated with low DHEA-S may have

Table 3 Prospective nested case-control studies on DHEA, DHEA-S and cardiovascular disease endpoints.

Studies	Follow-up duration (years)	CVD endpoint	Population	Hormone measured	Result
Women					
Hill Golden <i>et al.</i> (100)	3	Carotid IMT	182 cases 182 controls	DHEA-S	ns
Haffner <i>et al.</i> (99)*	5	IHD mortality	40 cases 80 controls	DHEA-S	DHEA-S lower in cases
Men					
Hautanen <i>et al.</i> (102)	4	Non-fatal MI, death	62 cases 97 controls	DHEA DHEA-S	DHEA-S higher in cases
Newcomer <i>et al.</i> (103)	5	Fatal, non-fatal MI	196 cases 196 controls	DHEA-S	ns
Haffner <i>et al.</i> (99)*	5	IHD mortality	41 cases 82 controls	DHEA-S	ns
Contoreggi <i>et al.</i> (104)	9.5	MI, angina ECG**	46 cases 124 controls	DHEA-S	ns
LaCroix <i>et al.</i> (101)	18	Fatal, non-fatal MI	238 cases 476 controls	DHEA-S	DHEA-S lower in fatal MI cases

CVD, cardiovascular disease; IHD, ischemic heart disease; IMT, intimal media thickness measured by B-mode ultrasound; MI, myocardial infarction; ECG, electrocardiography; *this study was performed in diabetic patients; **in this study, cases included men with acute events (MI or death), angina pectoris or combinations of resting and/or exercise ECG alterations; ns, not significantly different among cases and controls.

Table 4 Prospective population studies on DHEA-S and mortality in women.

Studies	Follow-up duration (years)	Outcome	Population	Hormone measured	Result (elevated DHEA-S =)
Legrain <i>et al.</i> (105)	3	All-cause mortality	81 (82.9 years) in long-term hospital care	DHEA-S	ns
Berr <i>et al.</i> (106)	4	All-cause mortality	356 (> 65 years) PAQUID study	DHEA-S	ns
Tilvis <i>et al.</i> (107)	5	All-cause and CVD mortality	421 (75–85 years) Helsinki aging study	DHEA-S	ns
Trivedi & Khaw (108)	7.4	All-cause and CVD mortality	1171 (65–76 years) CGPH study	DHEA-S	ns
Mazat <i>et al.</i> (109)	8	All-cause mortality	171 (> 65 years) PAQUID study	DHEA-S	ns
Barrett-Connor & Khaw (110)	12	All-cause and CVD mortality	289 (60–79 years) Rancho Bernardo	DHEA-S	Trend for higher all-cause or CVD mortality rates*
Barrett-Connor & Goodman-Gruen (111, 112)	19	All-cause, CVD and IHD mortality	942 (65.2 years) Rancho Bernardo	DHEA-S	ns

CVD, cardiovascular disease; IHD, ischemic heart disease; ns, not significantly related to outcome; CGPH, Cambridge General Practice Health Study; PAQUID, Personnes Agées Quid Study; *P values or confidence intervals not provided in this study.

Table 5 Prospective population studies on DHEA-S and mortality in men.

Studies	Follow-up duration (years)	Outcome	Population	Hormone measured	Result (elevated DHEA-S =)
Legrain <i>et al.</i> (105)	3	All-cause mortality	13 (82.9 years) in long-term hospital care	DHEA-S	ns
Berr <i>et al.</i> (106)	4	All-cause mortality	266 men (> 65 years) PAQUID study	DHEA-S	Lower mortality rates
Tilvis <i>et al.</i> (107)	5	All-cause and CVD mortality	150 men (75–85 years) Helsinki aging study	DHEA-S	ns
Trivedi & Khaw (108)	7.4	All-cause and CVD mortality	963 men (65–76 years) CGPH study	DHEA-S	Lower all-cause or CVD mortality rates
Mazat <i>et al.</i> (109)	8	All-cause mortality	119 men (> 65 years) PAQUID study	DHEA-S	Lower mortality rates
Barrett-Connor <i>et al.</i> (8)	12	All-cause and CVD mortality	242 men (50–79 years) Rancho Bernardo	DHEA-S	Lower all-cause or CVD mortality rates
Barrett-Connor & Goodman-Gruen (112)	19	All-cause, CVD and IHD mortality	1029 men (60.4 years) Rancho Bernardo	DHEA-S	Lower CHD or IHD rates*

CVD, cardiovascular disease; IHD, ischemic heart disease; ns, not significantly related to outcome; CGPH, Cambridge General Practice Health Study; PAQUID, Personnes Agées Quid Study; *Association significant only when excluding deaths from other causes.

been overestimated in the first study (112). Thus, the available studies on mortality rates and serum DHEA-S in men suggest that low DHEA-S values are associated with a moderate, though significant, increase in the relative risk of mortality (approximately 1.5-fold) (108, 109, 112).

Several other longitudinal, cross-sectional and retrospective analyses have examined the relationship between DHEA-S levels and the presence or the extent of various aspects of cardiovascular disease. Several studies have identified plasma DHEA or DHEA-S as being cardioprotective (113–118). In both men and women, elevated DHEA-S levels were associated with retarded progression of atherosclerosis measured by coronary artery angiography (113), ultrasound carotid wall thickness (117) and pulse wave velocity aorta calcification (114). On the other hand, other groups did

not confirm these findings using coronary angiography in two male samples (119, 120). Retrospective studies have examined whether myocardial infarction survivors were characterized by reduced DHEA-S levels compared with healthy controls (115, 116, 118). Two of these studies demonstrated that DHEA-S levels were lower in myocardial infarction survivors compared with healthy controls (115, 116), while the third one found the opposite (116). A study by Jansson *et al.* (121) examined male and female myocardial infarction survivors over a 10-year follow-up period and found that although a low DHEA-S level was a predictor of cardiovascular mortality, the association was not independent of age (121). A recent large-scale, community based prospective study by Kiechl *et al.* (Bruneck study) (122) found no association between plasma DHEA-S and high resolution duplex ultrasound-measured

carotid atherosclerosis progression after a 5-year follow-up. No correlation was found between atherosclerosis or intimal media thickness. Finally, a 6.5-year prospective study on radiography-detected atherosclerosis progression (aortic calcification) in non-smoking men and women from the Rotterdam study found that although low DHEA-S levels tended to be associated with increased atherosclerosis progression, this relationship did not reach statistical significance (123).

The reasons for the numerous discrepancies among studies are unclear at the present time. It has been suggested that they may be due to the possible confounding effect of smoking on both DHEA-S and cardiovascular disease, or to differences in the analytical methods used or to the cardiovascular endpoint selected (115, 124), although some studies cited above have already avoided these caveats. It has also been hypothesized that differences may be attributable to population variability. For example, the prospective study by Mazat *et al.* (109), demonstrated that the relative risk of 8-year mortality associated with low DHEA-S was 3.4 times higher in males under 70 years compared with older men (odds ratios of 6.5 versus 1.9 respectively), suggesting substantial heterogeneity in this population according to age (109). Adjustment for BMI in most studies may have attenuated the relationship of DHEA-S to cardiovascular disease endpoints. Finally, most studies have relied on a single measure of plasma DHEA-S performed several years before the disease events. Diurnal variations in the levels of this hormone and possible alterations in frozen samples over time may have had an impact on the associations observed (15).

In summary, data available on the potential role of DHEA as a predictor of cardiovascular disease indicate that plasma DHEA-S is not a predictor of cardiovascular disease outcome in women, and is a relatively weak one in men. Endogenous DHEA appears to be more closely associated with other cardiovascular disease risk factors such as insulin resistance or abdominal fat distribution. Accordingly, low DHEA has recently been suggested to represent a non-specific marker of poor health and lack of adaptive capacity to the diseases of aging (15).

Exogenous DHEA

Whether pharmacological DHEA treatment should be used to replace declining DHEA and DHEA-S levels in aging individuals has attracted much attention and debate (12–14). Claims have been made that such treatment could have beneficial effects on a series of aging-related conditions or diseases. Intervention trials have the advantage of avoiding several caveats of epidemiological studies. However, possibly due to the small size of many of the studies performed, discrepancies in the effects of DHEA have been reported. Reviewing all of the potential effects of DHEA treatment

is beyond the scope of the present article. The following section will focus on DHEA treatment versus cardiovascular disease risk factors and body fatness.

As summarized in Table 6, more than a dozen studies have examined the effects of DHEA treatment on the plasma lipid-lipoprotein profile (6, 11, 125–137). These studies were performed in both men and women of various ages and health conditions, using various doses of oral or transdermal DHEA. Treatments lasted from 4 to 52 weeks and the number of patients in each study was relatively small (from 6 to 60 subjects), although most studies used randomized, double-blind designs. One study was performed in a large sample of men and women ($n = 280$) (138). A total of eight studies indicated no effect of DHEA replacement on plasma lipids. These studies were performed with dosage ranging from 25 to 1600 mg/day oral DHEA and durations from 4 to 36 weeks (127, 129–131, 134–137). Examining the effects of DHEA replacement in subjects with previously documented hypercholesterolemia did not lead to the finding of significant effects of the treatment in a 12-week randomized placebo-controlled study using 25 mg/day oral DHEA (127). On the other hand, some studies reported significant effects of DHEA on blood lipids (6, 11, 125, 126, 128, 132, 133). All the studies reporting significant effects of DHEA on lipid-lipoprotein levels found a slight but significant decrease in HDL-cholesterol levels, which appeared to occur mostly in women (11, 125, 126, 128, 132, 133). In most instances, this effect was paralleled by a reduction in total cholesterol (125, 126, 133). One study reported a decrease in HDL-cholesterol and total cholesterol in healthy older men (132). The studies reporting significant effects of DHEA on blood lipids employed sample sizes that varied from 6 to 39 subjects, with oral doses varying from 25 to 1600 mg/day, or 300–500 mg/day transdermal doses in one instance (125). The only study to find a significant favorable effect of DHEA on the lipid profile was the one published by Nestler *et al.* (6), in which total and LDL-cholesterol were decreased in men after 4 weeks of a 1600 mg/day dose of DHEA (6).

With respect to changes in body composition and body fat distribution following DHEA treatment, ten studies reported no significant effect of oral DHEA treatment on anthropometric measures such as BMI or WHR or other measures of adiposity such as underwater weighing, dual energy X-ray absorptiometry and bioimpedance, with oral doses varying from 25 to 1600 mg/day, and treatments lasting from 4 to 52 weeks (11, 126, 128, 130, 134, 136–140). On the other hand, four studies found a significant effect of DHEA on body composition or body fat distribution (6, 125, 129, 132). The study by Nestler *et al.* (6) reported a 31% decrease in underwater weighing-measured percent body fat after only 4 weeks of DHEA treatment at 1600 mg/day (6). However, these results were not repeated in obese or normal men

Table 6 Studies on DHEA replacement, adiposity and plasma lipid levels.

Studies	Design	Duration (weeks)	Dose (mg/day)	Population	Effects on adiposity	Effects on blood lipids
Nestler <i>et al.</i> (6)	dbRPC	4	1600 oral	10 men healthy	↓ FM	↓ CHOL ↓ LDL-C
Mortola & Yen (126)	dbRPC*	4	1600 oral	6 women postmenopausal	ns	↓ CHOL ↓ HDL-C
Welle <i>et al.</i> (140)	dbRPC*	4	1600 oral	8 men healthy	ns	nr
Usiskin <i>et al.</i> (136)	Seq.Pla-DHEA	4	1600 oral	6 men obese	ns	ns
Vogiatzi <i>et al.</i> (134)	dbRPC	8	80 oral	3 men/10 women morbid obese	ns	ns
Kawano <i>et al.</i> (127)	dbRPC	12	25 oral	24 men with hypercholesterol	nr	ns
Flynn <i>et al.</i> (132)	dbRPC*	12	100 oral	39 men healthy	↓ Body wt (trend)	↓ CHOL ↓ HDL-C
Barnhart <i>et al.</i> (135)	dbRPC	12	50 oral	60 women perimenopausal	nr	ns
Jedrzejuk <i>et al.</i> (137)	dbRPC*	12	50 oral	12 men healthy	ns	ns
Callies <i>et al.</i> (139)	dbRPC*	16	50 oral	24 women adrenal insufficiency	ns	nr
Arlt <i>et al.</i> (130)	dbRPC*	16	50 oral	22 men healthy	ns	ns
Arlt <i>et al.</i> (133)	dbRPC*	16	50 oral	24 women adrenal insufficiency	nr	↓ CHOL ↓ HDL-C
Casson <i>et al.</i> (128)	dbRPC	24	25 oral	13 women postmenopausal	ns	↓ HDL-C ↓ Apo-A1
Villareal <i>et al.</i> (129)	CT	24	50 oral	10 women/8 men 10 matched cont.	↓ FM ↓ Trunk fat	ns
Morales <i>et al.</i> (11)	dbRPC*	24	50 oral	13 men 17 women	ns	↓ HDL-C (women)
Lovas <i>et al.</i> (131)	dbRPC	36	25 oral	39 women adrenal failure	nr	ns
Percheron <i>et al.</i> (138)	dbRPC	52	50 oral	140 men 140 women	ns	nr
Diamond <i>et al.</i> (125)	DHEA only	52	300-500 transderm	15 women postmenopausal	↓ Skinfold thickness	↓ CHOL ↓ HDL-C

dbRPC, double-blind randomized placebo-controlled; *cross-over design; Seq.Pla-DHEA, placebo and DHEA taken in sequence in that study (no washout); CT, controlled-trial; matched cont., age- and sex-matched control subjects; FM, body fat mass; Body wt, body weight; CHOL, total cholesterol; HDL-C, HDL cholesterol; ns, no significant effect; nr, not reported.

following similar protocols (136, 140). The study by Flynn *et al.* (132) reported a trend for a decrease in body weight, with no changes in body composition after 12 weeks of 100 mg/day oral DHEA in 39 healthy older men (132). The study by Diamond *et al.* (125) found a 9% reduction in fat mass as estimated by skinfold thickness, in a sample of postmenopausal women receiving 300–500 mg/day transdermal DHEA for 1 year. More recently, the study of Villareal and colleagues (129) examined the effects of a 24-week oral DHEA (50 mg/day) treatment in men and women with low DHEA-S levels. This study demonstrated a clear and significant reduction in dual energy X-ray absorptiometry-measured total body fatness and trunk fat, as well as an increase in fat-free mass. The selection of patients with low values of DHEA may have been an important factor for the finding of significant effects on body composition and fat distribution in that study, although other studies performed in men with low DHEA-S or women with adrenal insufficiency found no effects of DHEA on body composition (130, 139). Finally, in the study by Kawano *et al.* (127), although no effect on the lipid profile or body fatness were observed, other cardiovascular disease-related outcomes such as endothelial function and insulin sensitivity were significantly improved in response to DHEA supplementation in this sample of 24

hypercholesterolemic men, which may be considered as a cardioprotective effect of DHEA (127).

Ebeling & Koivisto (141) made the suggestion that the outcome of DHEA treatment may depend on the initial hormonal milieu. For example, in premenopausal women, potential androgenic actions of DHEA may be counterbalanced by high estrogen concentrations in these subjects. This most interesting hypothesis is consistent with the above-mentioned findings from Villareal *et al.* (129) in subjects with low DHEA-S and, in our opinion, deserves further investigation. On the other hand, the same authors have suggested that, in men, estrogen-like effects of DHEA may explain the results of DHEA treatment studies (141). However, this last statement is not supported by current literature on sex hormones and cardiovascular disease risk factors. In fact, in men, elevated endogenous testosterone, rather than estradiol, has generally been associated with a favorable risk profile for cardiovascular disease including reduced obesity, lower abdominal and visceral fat accumulation, increased HDL-cholesterol, lower triglyceride levels and apolipoprotein B, as well as reduced insulin resistance (57, 92, 95, 98). High-dose androgen treatment in men (i.e. anabolic steroid treatment) has been reported to drastically alter the plasma lipoprotein profile in several studies (reviewed in 142). However, data on physiological

testosterone replacement suggests that low-dose testosterone treatment may be favorable by reducing adiposity (especially visceral adiposity) and improving insulin sensitivity (143–146). Thus, the protective effects of DHEA observed in the studies of Villareal *et al.* (129) and Nestler *et al.* (6) may be related to androgenic rather than estrogenic effects of DHEA.

In agreement with this suggestion, the reductions in HDL-cholesterol observed with DHEA treatment in some studies is believed to be the result of DHEA conversion to androgens (128, 129, 133). These effects are possibly mediated through androgen-induced increases in the activity of hepatic lipase, a critical enzyme of HDL metabolism that appears to be regulated by both androgens and estrogens, or by an increased scavenger receptor B1-mediated uptake of HDL lipids (15). Interestingly, the moderate inhibitory effect on HDL-cholesterol levels reported in some DHEA studies (11, 125, 126, 128, 132, 132, 133) is also consistent with the effects of low-dose testosterone replacement on blood lipids. As reviewed by Barrett-Connor (147) and Gruenewald & Matsumoto (148), the effects of physiological testosterone treatment on HDL-cholesterol and other variables of the lipid profile in men appear to be neutral or non-significant.

A detailed study of the hormonal response to DHEA treatment (149) provides further support for the notion of an androgenic conversion of DHEA, at least in men. In that study (149), we showed that the plasma levels of glucuronide androgen metabolites mirror those of plasma DHEA following treatment and are, therefore, more sensitive and valid indicators of the androgenic milieu. On the other hand, plasma testosterone or estradiol concentrations were unaffected by this treatment in men. It was thus observed that DHEA was preferentially converted to androgens, most likely peripherally, providing each tissues with locally produced active androgens (149). Supporting the hypothesis of a predominantly peripheral conversion of DHEA to androgens is the highly variable response of plasma testosterone to DHEA treatment among studies. Some but not all demonstrated significant increases in plasma testosterone, suggesting variability in the capacity and availability of peripheral tissues, such as adipose tissue for example, for peripheral conversion.

Taken together, the available data demonstrate that the effects of DHEA on the plasma lipid-lipoprotein profile are at best modest, or usually non-significant. The fact that HDL-cholesterol levels decrease slightly following DHEA treatment in women (11, 125, 126, 133) may be of some concern, although these changes were not unanimous and were balanced by a concomitant decrease in total cholesterol in some studies (125, 126, 133). In addition, the recent finding that the anti-atherogenicity of HDLs may be explained by their kinetics and functionality rather than by plasma HDL-cholesterol levels *per se* raises questions on the

negative impact of DHEA-induced or androgen-induced decreases in HDL-cholesterol levels (15, 150). Most studies on body composition and fat distribution failed to demonstrate significant effects of DHEA replacement, although one recent study in older subjects with low baseline DHEA-S values reported significant reductions after 6 months. Similar to any hormonal replacement, the results of DHEA intervention studies emphasize the need to evaluate the ratio of risk versus benefit of DHEA treatment, by considering both cardiovascular disease- and non-cardiovascular disease-related outcomes. Given the high variability in the hormonal responses to DHEA treatment and the potentially important influence of the initial hormonal milieu (141), it is possible that specific patient populations will display different quantitative responses to DHEA.

Conclusion

In summary, elevated plasma levels of free DHEA are associated with reduced obesity and a smaller accumulation of abdominal body fat. The relationships between the sulfate ester DHEA-S and adiposity is less consistent, as contradictory results have been reported. Age differences in the populations studied may have confounded these associations. The mechanisms linking obesity and abdominal fat accumulation are unclear at the present time, but we suggest that the intracrine adipose tissue conversion of DHEA to active androgens, which are known to be involved in the direct regulation of adipocyte physiology, body fat accretion and regional fat distribution, may be a significant factor in these associations. Cross-sectional studies on the associations between DHEA, DHEA-S and plasma lipoproteins have demonstrated that elevated levels of these hormones may be beneficial, especially regarding triglyceride levels. On the other hand, serum DHEA-S is not a predictor of cardiovascular disease endpoints in women, and appears as a relatively weak one in men. It is suggested that adiposity and body fat distribution, which are associated both with plasma DHEA and cardiovascular disease risk, may play a predominant role in this relationship. DHEA intervention studies suggest that the effects of DHEA on serum lipids are, at best, modest or non-significant, and most studies reported no significant effects on body composition and body fat distribution.

Much debate has been generated about whether endogenous and exogenous DHEA should be considered as cardioprotective. The uncertainty on this important issue is most definitely related to striking discrepancies noted in the literature on this topic. Several studies may have been plagued by various methodological problems, such as low statistical power, unreliable analytical methods, confounding factors or other differences in the clinical endpoints or populations studied. As a consequence, the original reports

demonstrating dramatic effects of either endogenous or exogenous DHEA on cardiovascular disease endpoints have never been replicated. We propose that the effects of DHEA on cardiovascular disease risk (either favorable or unfavorable) should be considered as much more modest than previously believed. More studies may help identify the factors that have contributed to the study variability in this field. On the other hand, the impact of DHEA on cardiovascular disease risk may vary in populations with different hormonal characteristics and different capacities to convert DHEA to active estrogens/androgens peripherally. Sub-populations of DHEA responders and non-responders may be identified in future experiments.

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