Effect of Dehydroepiandrosterone Replacement on Lipoprotein Profile in Hypoadrenal Women

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Context: Levels of dehydroepiandrosterone (DHEA) and its sulfate form (DHEAS) are inversely associated with cardiovascular mortality in men but not women. Very little evidence is available on the impact of DHEA administration on lipoprotein profile in women. DHEAS levels are very low/undetectable in hypoadrenal women.

Objective: The objective of the study was to determine the impact of DHEA replacement on lipoprotein profile in hypoadrenal women.

Design and Setting: A double-blind, randomized, placebo-controlled, cross-over design study was conducted at the Mayo Clinic.

Participants: Thirty-three hypoadrenal Caucasian women (mean $\pm$ SD; age 50.3 $\pm$ 15.2 yr, body mass index 26.6 $\pm$ 4.4 kg/m^2) took part in the study.

Intervention: Study participants were assigned to receive either a placebo or 50 mg/d of DHEA for 3 months each. Lipid levels and lipoprotein profile were analyzed using the Lipo Science Lipoprotein nuclear magnetic resonance system.

Main Outcome Measures: Changes in various lipoprotein sizes and levels were measured.

Results: The DHEA period had higher plasma DHEAS levels than during placebo ($<$0.3 $\pm$ 0.0 *vs.* 3.5 $\pm$ 1.3 nmol/liter, $P < 0.001$). DHEA replacement significantly reduced total cholesterol (20.0 *vs.* $-$22, $P = 0.02$) and high-density lipoprotein (HDL) levels (2.0 *vs.* $-$6.0, $P = 0.006$) and tends to reduce triglyceride and total low-density lipoprotein levels. Although, DHEA replacement had no effect on low-density lipoprotein particle size, it significantly reduced larger HDL particles and to modest extent small HDL particles.

Conclusions: Our study findings showed that oral DHEA administration in hypoadrenal women results in an unfavorable lipoprotein profile. The results warrant long-term studies to determine the impact of DHEA replacement on cardiovascular risk. **(*J Clin Endocrinol Metab* 94: 761–764, 2009)**

Dehydroepiandrosterone (DHEA) is widely available as a health food supplement in the United States. It has been promoted as an antiaging agent and also claimed to protect against chronic conditions such as Coronary Artery Disease (CAD) and diabetes. There is conflicting evidence in the literature regarding DHEA and cardiovascular events in the epidemiological studies (1). Levels of DHEA and its sulfate form (DHEAS) are inversely associated with cardiovascular mortality in men but not women (2). DHEA is thought to influence various cardiovascular risk factors, especially hyperlipidemia. Because DHEAS levels are very low/undetectable in hypoadrenal women, we sought to determine the effect of DHEA replacement on lipoprotein profile in hypoadrenal women.

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Abbreviations: CAD, Coronary Artery Disease; DHEA, dehydroepiandrosterone; DHEAS, sulfated form of DHEA; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; NMR, nuclear magnetic resonance; VLDL, very low density lipoprotein.

TABLE 1. Summary of baseline differences in lipoproteins between groups

Lipoproteins	Placebo median (interquartile range)	DHEA median (interquartile range)	*P* value
NMR triglycerides (mg/dl)	114 (102, 154)	115 (87, 139)	0.662
NMR total cholesterol (mg/dl)	192 (171, 197)	186 (177, 199)	0.730
VLDL mean particle size (nm)	50 (47, 53)	52 (47, 57)	0.333
LDL mean particle size (nm)	21.3 (21.2, 21.6)	21.4 (20.8, 22.0)	> 0.999
HDL mean particle size (nm)	8.9 (8.7, 9.2)	9.0 (8.7, 9.6)	0.532
NMR VLDL triglycerides (mg/dl)	78 (68, 102)	80 (43, 91)	0.629
NMR LDL cholesterol (mg/dl)	129 (95, 133)	119 (107, 131)	0.872
Total HDL cholesterol (mg/dl)	45 (42, 56)	49 (43, 58)	0.764
Total VLDL and chylomicron particles (nmol/liter)	78 (55, 95)	65 (42, 78)	0.316
Large VLDL and chylomicron particles (nmol/liter)	3.7 (1.9, 4.6)	2.5 (0.9, 4.8)	0.564
Medium VLDL particles (nmol/liter)	22.6 (15.1, 23.7)	18.5 (11.9, 25.5)	0.596
Small VLDL particles (nmol/liter)	51.2 (39.3, 59.0)	41.4 (19.6, 56.5)	0.235
Total LDL particles (nmol/liter)	1287 (1030, 1382)	1342 (918, 1547)	0.928
IDL particles (nmol/liter)	47 (23, 84)	61 (30, 86)	0.596
Large LDL particles (nmol/liter)	479 (408, 660)	492 (390, 592)	0.683
Total small LDL particles (nmol/liter)	584 (536, 762)	581 (362, 1091)	0.964
Medium small LDL particles (nmol/liter)	144 (109, 160)	107 (70, 238)	0.764
Very small LDL particles (nmol/liter)	468 (414, 617)	474 (286, 860)	0.890
Total HDL particles (μmol/liter)	33.1 (27.4, 38.6)	32.3 (30.0, 36.7)	0.765
Large HDL particles (μmol/liter)	6.2 (3.7, 7.2)	7.7 (3.8, 11.0)	0.387
Medium HDL particles (μmol/liter)	3.3 (1.3, 7.3)	1.2 (0.8, 6.3)	0.394
Small HDL particles (μmol/liter)	23.3 (20.0, 29.6)	23.3 (23.2, 26.6)	0.433

Subjects and Methods

The study was approved by the Mayo Clinic Institutional Review Board, Rochester, MN. A detailed description of the study design and methodology has already been described in a publication that described DHEA effect on insulin sensitivity (3). Briefly, this was a single-center, randomized, placebo-controlled, double-blind study. After initial screening, 33 hypoadrenal Caucasian women were enrolled in the present study. The women had been hypoadrenal for more than 24 months. Five of the 33 subjects did not complete the study due to various reasons. One participant experienced diarrhea, which stopped after discontinuation of DHEA; two declined to come for the second part of the study and dropped out of the study; one withdrew from the study in the middle, citing work pressure (on DHEA); and one unblinded herself by having blood levels taken (on DHEA). The causes of hypoadrenalism in the 28 women who completed the study include Addison's disease (n = 20) and bilateral adrenalectomy for Cushing's disease (n = 8). To minimize any confounding effects due to the use of varying glucocorticoids, standardization onto 10 mg hydrocortisone on rising, 10 mg at 1600 h, and 5 mg at bedtime was attempted for all subjects from 3 wk before entry into the study. If subjects were on either a lower equivalent dose of prednisone or a lower overall hydrocortisone dose before entry into the study, then they

TABLE 2. The impact of DHEA treatment on lipoprotein profiles

Lipoproteins	Placebo median change (interquartile range)	DHEA median change (interquartile range)	*P* value
NMR triglycerides (mg/dl)	2.0 (−4, 35)	−5 (−26, 06)	0.076
NMR total cholesterol (mg/dl)	20.0 (−3, 36)	−22 (−34, 6)	**0.021**
VLDL mean particle size (nm)	−0.3 (−2.0, 2.3)	−2.3 (−3.7, −0.2)	0.101
LDL mean particle size (nm)	−0.1 (−0.2, 0.0)	−0.1 (−0.2, 0.1)	0.889
HDL mean particle size (nm)	0.0 (−0.1, 0.1)	−0.1 (−0.2, 0.0)	0.129
NMR VLDL triglycerides (mg/dl)	2 (−13, 24)	−3 (−21, 6)	0.160
NMR LDL cholesterol (mg/dl)	6.0 (−2, 22)	−4.0 (−25.5, 7)	0.084
Total HDL cholesterol (mg/dl)	2.0 (−1, 16)	−6.0 (−10, −2)	**0.006**
Total VLDL and chylomicron particles (nmol/liter)	0.2 (−0.6, 1.1)	−2.1 (−14.5, 8.4)	0.345
Large VLDL and chylomicron particles (nmol/liter)	0.2 (−0.6, 1.1)	−0.3 (−1.0, 0.5)	0.279
Medium VLDL particles (nmol/liter)	0.7 (−2.0, 6.3)	−3.8 (−9.2, 5.7)	0.369
Small VLDL particles (nmol/liter)	0.1 (−6.6, 9.2)	0.8 (−10.6, 7.2)	0.549
Total LDL particles (nmol/liter)	90 (−14, 317)	−42 (−272, 75)	0.058
IDL particles (nmol/liter)	23 (−14, 73)	−8 (−43, 3)	**0.040**
Large LDL particles (nmol/liter)	−39 (−76, 129)	3 (−81, 11)	0.890
Total small LDL particles (nmol/liter)	73 (−24, 179)	−14 (−208, 105)	0.147
Medium small LDL particles (nmol/liter)	10 (−11, 18)	−6 (−37, 1)	0.123
Very small LDL particles (nmol/liter)	63 (−15, 151)	−11 (−183, 89)	0.170
Total HDL particles (μmol/liter)	1.7 (−1.3, 4.0)	−3.2 (−5.7, 0.3)	**0.022**
Large HDL particles (μmol/liter)	0.5 (0.2, 2.6)	−1.0 (−2.7, −0.4)	**0.006**
Medium HDL particles (μmol/liter)	−0.6 (−1.4, 0.8)	−0.7 (−1.9, 1.2)	0.782
Small HDL particles (μmol/liter)	1.2 (−0.8, 3.7)	−1.8 (−3.5, −0.1)	0.062

P values in *bold* denote statistically significant results.

were asked to stay on their current dose. For those on hydrocortisone, subjects were asked to go to a regimen of at least a twice or three times a day. All of these changes were made with full approval of the volunteer's primary physician and/or endocrinologist. Average total daily dose at entry into the study was 24.4 ± 7.0 mg, divided between one and three times per day. Eight subjects had been on prednisone (average dose 4.5 ± 1.4 mg) and been changed to hydrocortisone several weeks before randomization.

The lipoprotein size and concentrations were assessed in plasma samples collected in the fasted state at the baseline states and after 12 wk each of DHEA and placebo administration by nuclear magnetic resonance (NMR) spectroscopy (lipoprotein NMR system; LipoScience, Raleigh, NC). DHEAS and total and bioavailable testosterone levels were also measured by RIA as previously reported (3).

DHEA therapy

In a randomized fashion, each participant self-administered either a 50-mg DHEA pill of micronized pharmaceutical grade (Spectrum Chemicals and Laboratory Products, Gardena, CA) or an identically encapsulated placebo pill (Clinical Encapsulation Services, Schenectady, NY) daily for 12 wk. There was a 2-wk washout period between treatments.

Statistical analysis

Baseline data are presented as median (interquartile range). Wilcoxon two-sample rank sum tests were used to examine baseline differences between treatment groups. Difference scores (after, before treatment) are presented as the median (interquartile range). Wilcoxon two-sample rank sum tests of differences were used to assess the impact of the treatments (placebo *vs.* DHEA) on the lipoprotein profile.

Results

The mean age and body mass index (±SE) were 50.25 ± 5.93 yr and 26.6 ± 4.4 kg/m^2, respectively. The DHEA period had higher plasma DHEAS levels (3.5 ± 1.3 nmol/liter) than during placebo (<0.3 ± 0.0 nmol/liter) ($P < 0.001$). Changes from baseline were also significantly higher for total (0.42 ± 0.21 *vs.* 1.2 ± 0.23 nmol/liter, $P < 0.00001$) and bioavailable testosterone (10.9 ± 0.87 *vs.* 12.6 ± 0.96 nmol/liter, $P < 0.032$). There was no significant effect on body weight (72.5 ± 2.31 *vs.* 72.3 ± 2.5 kg, $P = 0.72$), fat-free mass (39.67 ± 4.69 *vs.* 39.81 ± 4.56 kg, $P = 0.75$), fasting glucose levels (4.8 ± 0.11 *vs.* 4.7 ± 0.10 mmol/liter, $P = 0.22$), and IGF-I levels (32.2 ± 2.85 *vs.* 36.5 ± 2.50 mmol/liter, $P = 0.058$). DHEA significantly reduced fasting plasma insulin levels (53 ± 6.58 *vs.* 42 ± 4.94 pmol/liter, $P = 0.005$).

Table 1 summarizes the baseline values for both groups. There were no significant differences seen between the groups with regard to various lipids and lipoprotein fractions.

The effect of DHEA on various lipoprotein concentrations and particle sizes are summarized in Table 2. The significant change occurred in total cholesterol (20.0 *vs.* −22.0, $P = 0.02$), and statistically nonsignificant reduction occurred in triglyceride (2.0 *vs.* −5.0, $P = 0.08$) and low-density lipoprotein (LDL) cholesterol ($P = 0.08$). No significant impact was seen on mean LDL particle size, and although the total LDL particles were reduced with DHEA treatment ($P = 0.05$), there was no change in the concentration of small dense atherogenic LDL particles (73 *vs.* −14, $P = 0.2$). With regard to very low-density lipoproteins (VLDL), no significant changes were seen in terms of total VLDL and chylomicrons, large VLDL and chylomicrons, VLDL mean particle size, or small and medium VLDL particles between groups. DHEA supplementation modestly reduced intermediate-density lipoproteins (IDL) particles number ($P = 0.04$). In relation to high-density lipoprotein (HDL), the total level was significantly lower in the DHEA group ($P = 0.006$). Larger HDL particles concentration was markedly lower ($P = 0.006$), and smaller HDL particles were modestly lower ($P = 0.06$) in the DHEA group.

Discussion

The main findings of our study are that in hypoadrenal women, 12 wk of DHEA therapy were: 1) significantly reduced total and HDL cholesterol, 2) significantly reduced large HDL particles and to some extent small HDL particles, and 3) no significant effect on mean LDL size or particle concentration.

DHEA is secreted primarily by the adrenal glands and is the most abundant steroid in the circulation. However, to date, it remains an enigmatic hormone, and its biological significance is unknown. Despite the lack of evidence from randomized, controlled trials, its popularity still continues to grow (4). The role of DHEA in the pathogenesis of atherosclerosis and coronary artery disease has always been a controversial issue (5–8). Previous epidemiological data suggest that DHEA may play a protective role in men but not women, suggesting that DHEA actions are possibly through sex hormone metabolic pathways. Potential mechanisms by which DHEA could influence atherogenic processes include modifying lipid spectrum, inhibiting platelet aggregation, enhancing fibrinolysis, *etc.*

Lipoproteins and CAD risk

Over the last few decades, it was generally thought that total cholesterol and LDL had a relatively clear link to CAD. However, this is disputed by the fact that many patients still continue to experience cardiac events despite good control of LDL and total cholesterol. Recently more evidence is emerging about the role of different lipoprotein subclasses, particle sizes, numbers, and their role in the pathogenesis of atherosclerosis and CAD (9). Small LDL particles have been included as an emerging risk factor for cardiovascular events and progression of coronary artery disease by the National Cholesterol Education Program Adult Treatment Panel III (10). Although elevated levels of HDL are considered to be protective against development of atherosclerosis, controversy exists regarding particle size and CAD risk. Low levels of larger and less dense HDL particles (HDL2b) have been shown to be associated with severity and progression of CAD (11). However, a recently reported trial suggests that small dense HDL may be atheroma protective and larger HDL particle size in fact may be associated with increased risk of CAD (12). With regard to triglyceride rich lipoproteins, smaller IDL and VLDL are shown to be independently associated with risk of development of atherosclerosis (13, 14).

DHEA effect on lipoproteins

Previous studies regarding the impact of exogenous DHEA administration on lipid profile in women measured only lipid concentrations and showed reductions in total cholesterol and

HDL levels (15–17). The current study additionally reports the effect of DHEA supplementation on various lipoprotein sizes and concentrations in women. Because the hypoadrenal women have negligible or no endogenous DHEA in the circulation, it is presumed that the changes in lipoproteins observed were primarily due to the exogenously administered DHEA. As compared with previous studies, our study also demonstrated reductions in total cholesterol with DHEA. This is mainly due to the marked reduction in HDL. Although there was a tendency to reduce LDL and triglyceride levels, no obvious impact was seen with regard to atherogenic small dense LDL particles. The most notable effect is seen with regard to HDL particles. There was a significant reduction in larger HDL particles and to a moderate extent small HDL particles. Although the significance of this observed change is unclear, it may represent a detrimental effect and needs to be confirmed in a larger trial. It also is possible that orally administered DHEA that directly increases hepatic levels may have a different effect on lipids than endogenous DHEA that has similar DHEA levels in the systemic and hepatic circulation.

In summary the current study suggests that oral DHEA administration alters lipoprotein profiles in predominantly unfavorable fashion in hypoadrenal women and warrants long-term outcome measures to determine the impact on cardiovascular risk.

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