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 ± SD; age 50.3 ± 15.2 yr, body mass index 26.6 ± 4.4 kg/m²) 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 ± 0.0 vs. 3.5 ± 1.3 nmol/liter, P < 0.001). DHEA replacement significantly reduced total cholesterol (20.0 vs. 22.0, 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)

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.
The impact of DHEA treatment on lipoprotein profiles

<table>
<thead>
<tr>
<th>Lipoproteins</th>
<th>Placebo median change (interquartile range)</th>
<th>DHEA median change (interquartile range)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMR triglycerides (mg/dl)</td>
<td>2.0 (−4, 35)</td>
<td>−5 (−26, 06)</td>
<td>0.076</td>
</tr>
<tr>
<td>NMR total cholesterol (mg/dl)</td>
<td>20.0 (−3, 36)</td>
<td>−22 (−34, 6)</td>
<td>0.021</td>
</tr>
<tr>
<td>VLDL mean particle size (nm)</td>
<td>−0.3 (−2.0, 2.3)</td>
<td>−2.3 (−3.7, −0.2)</td>
<td>0.101</td>
</tr>
<tr>
<td>LDL mean particle size (nm)</td>
<td>−0.1 (−0.2, 0.0)</td>
<td>−0.1 (−0.2, 0.1)</td>
<td>0.889</td>
</tr>
<tr>
<td>HDL mean particle size (nm)</td>
<td>0.0 (−0.1, 0.1)</td>
<td>−0.1 (−0.2, 0.0)</td>
<td>0.129</td>
</tr>
<tr>
<td>NMR VLDL triglycerides (mg/dl)</td>
<td>2 (−13, 24)</td>
<td>−3 (−21, 6)</td>
<td>0.160</td>
</tr>
<tr>
<td>NMR LDL cholesterol (mg/dl)</td>
<td>6.0 (−2, 22)</td>
<td>−4.0 (−25.5, 7)</td>
<td>0.084</td>
</tr>
<tr>
<td>Total HDL cholesterol (mg/dl)</td>
<td>2.0 (−1, 16)</td>
<td>−6.0 (−10, −2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Total VLDL and chylomicron particles (nmol/liter)</td>
<td>0.2 (−0.6, 1.1)</td>
<td>−2.1 (−14.5, 8.4)</td>
<td>0.345</td>
</tr>
<tr>
<td>Large VLDL and chylomicron particles (nmol/liter)</td>
<td>0.2 (−0.6, 1.1)</td>
<td>−0.3 (−1.0, 0.5)</td>
<td>0.279</td>
</tr>
<tr>
<td>Medium VLDL particles (nmol/liter)</td>
<td>0.7 (−2.0, 6.3)</td>
<td>−3.8 (−9.2, 5.7)</td>
<td>0.369</td>
</tr>
<tr>
<td>Small VLDL particles (nmol/liter)</td>
<td>0.1 (−6.6, 9.2)</td>
<td>0.8 (−10.6, 7.2)</td>
<td>0.549</td>
</tr>
<tr>
<td>Total LDL particles (nmol/liter)</td>
<td>90 (−14, 317)</td>
<td>−42 (−272, 75)</td>
<td>0.058</td>
</tr>
<tr>
<td>IDL particles (nmol/liter)</td>
<td>23 (−14, 73)</td>
<td>−8 (−43, 3)</td>
<td>0.040</td>
</tr>
<tr>
<td>Large LDL particles (nmol/liter)</td>
<td>−39 (−76, 129)</td>
<td>3 (−81, 11)</td>
<td>0.890</td>
</tr>
<tr>
<td>Total small LDL particles (nmol/liter)</td>
<td>73 (−24, 179)</td>
<td>−14 (−208, 105)</td>
<td>0.147</td>
</tr>
<tr>
<td>Medium small LDL particles (nmol/liter)</td>
<td>10 (−11, 18)</td>
<td>−6 (−37, 1)</td>
<td>0.123</td>
</tr>
<tr>
<td>Very small LDL particles (nmol/liter)</td>
<td>32 (−15, 151)</td>
<td>−11 (−183, 89)</td>
<td>0.170</td>
</tr>
<tr>
<td>Total HDL particles (µmol/liter)</td>
<td>1.7 (−1.3, 4.0)</td>
<td>−3.2 (−5.7, 0.3)</td>
<td>0.022</td>
</tr>
<tr>
<td>Large HDL particles (µmol/liter)</td>
<td>0.5 (0.2, 2.6)</td>
<td>−1.0 (−2.7, −0.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>Medium HDL particles (µmol/liter)</td>
<td>−0.6 (−1.4, 0.8)</td>
<td>−0.7 (−1.9, 1.2)</td>
<td>0.782</td>
</tr>
<tr>
<td>Small HDL particles (µmol/liter)</td>
<td>1.2 (−0.8, 3.7)</td>
<td>−1.8 (−3.5, −0.1)</td>
<td>0.062</td>
</tr>
</tbody>
</table>

P values in bold denote statistically significant results.
were asked to stay on their current dose. For those on hydrocortisone, sub-
jects 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 sam-
ple 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 Chem-
icals and Laboratory Products, Gardena, CA) or an identically encap-
sulated 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 be-
tween treatment groups. Difference scores (after, before treatment) are pre-
sumed 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/m², 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 testoster-
one (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-1 levels (32.2 ± 2.85
vs. 36.5 ± 2.50 mmol/liter, P = 0.058). DHEA significantly re-
duced 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) cho-
lesterol (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

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, con-
trolled 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). Pre-
vious epidemiological data suggest that DHEA may play a pro-
tective 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 pro-
cesses include modifying lipid spectrum, inhibiting platelet ag-
gregation, 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. How-
ever, 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 fac-
tor 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 atheroscle-
rosis, 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 LDL 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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References


