The association of apolipoprotein E with sex hormones in a population-based sample of postmenopausal Caucasian women

Elizabeth Barrett-Connor and Denise von Mühlen
Division of Epidemiology, Department of Family and Preventive Medicine, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093-0607, USA

Zofkova et al. (1) reported a cross-sectional study of 113 postmenopausal women, in whom those with the apolipoprotein E (ApoE) 4 allele had significantly higher levels of serum testosterone and dehydroepiandrosterone (DHEA). Since these hormones are thought to be associated with increased risk factors for coronary heart disease in women (2), this observation suggests a novel mechanism whereby ApoE 4 increases cardiovascular risk. It is well known, however, that many reports of genotype–phenotype associations cannot be replicated. Such associations require confirmation.

We report here the association of ApoE 4 with sex hormones in a population-based sample of 391 Caucasian women, aged 51–89 years, who were postmenopausal and not taking hormone therapy when blood (fasting morning samples) for hormone assays was obtained. Hormones were measured by radioimmunoassay after solvent extraction and Celite column chromatography, in an endocrinology research laboratory. The sensitivity and the intra- and interassay coefficients of variation for the androgens were 0.07 nmol/l, 4.0% and 4.9% for testosterone; 0.02 nmol/l, 6.5% and 10.7% for bioavailable testosterone; 0.14 nmol/l, 6.1% and 7.1% for DHEA, and 0.22 μmol/l, 3.1% and 7.3% for DHEA sulfate (DHEAS). Genotyping was done by Sequana Therapeutics (La Jolla, CA, USA). Cholesterol was measured in a lipid research clinic laboratory using an ABA-200 biocromatic analyzer (Abbott Laboratories, Irving, TX, USA). Body mass index (BMI; kg/m²) was used as an estimate of obesity.

Among these women, there were 299 women with no ApoE 4 and 92 with an ApoE 4 allele, compatible with the Hardy–Weinberg equilibrium. These groups did not differ significantly by mean age (73 years) or BMI (24 kg/m²). As expected, plasma cholesterol levels were higher among women with ApoE 4 compared with those without (6.17 vs 5.90 mmol/l; P = 0.03). As shown in Table 1, DHEA and total and bioavailable testosterone levels did not differ by ApoE 4 status, but DHEAS levels were significantly lower in women with an ApoE 4 allele.

Thus, we were unable to replicate the testosterone or DHEA differences by ApoE 4 status reported by Zofkova et al. (1). Both studies were restricted to Caucasian non-hormone-using women. Participants in our cohort were older and probably had lower levels of DHEA, but mean levels are not shown in the European study. Distribution of ApoE 4 allele frequency in both studies is compatible with reported frequencies in other Caucasian cohorts (3, 4), but the expected association of ApoE 4 genotype with higher cholesterol levels was seen only in our cohort.

Because hysterectomy is much more common in the US than in Europe (5), and because women in our cohort who had had a hysterectomy had lower testosterone levels than women without a hysterectomy (6), we repeated the analysis excluding women who reported a hysterectomy. In this analysis (167 women in the no ApoE 4 group and 51 women in the ApoE 4 group), there was no significant difference for DHEA or DHEAS or total or bioavailable testosterone levels by ApoE 4 status.

Postmenopausal estrogen use is also more common in the US than in Europe; in our cohort, 65% of the women had used hormones several years prior to the time at which blood was obtained for hormone assays; adjusting for prior use did not change our results.

Thus, it is premature to conclude that ApoE 4 genotype is associated with higher levels of testosterone or DHEA in postmenopausal women.

Table 1 DHEA, DHEAS, testosterone and bioavailable testosterone levels by ApoE 4 status.

<table>
<thead>
<tr>
<th></th>
<th>No ApoE 4 (n = 299)</th>
<th>ApoE 4 (n = 92)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA (nmol/l)</td>
<td>3.74</td>
<td>3.46</td>
<td>0.26</td>
</tr>
<tr>
<td>DHEAS (μmol/l)</td>
<td>1.53</td>
<td>1.29</td>
<td>0.02</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>0.56</td>
<td>0.50</td>
<td>0.16</td>
</tr>
<tr>
<td>Bioavailable testosterone (nmol/l)</td>
<td>0.16</td>
<td>0.15</td>
<td>0.58</td>
</tr>
</tbody>
</table>

* Age and BMI adjusted; measured by Ancova.
References


Received 10 January 2003
Accepted 15 January 2003