Apolipoprotein E polymorphism alters the association between body fatness and plasma lipoproteins in women

Marie-Christine Pouliot, Jean-Pierre Després, Sital Moorjani, Paul J. Lupien, Angelo Tremblay, and Claude Bouchard

Physical Activity Sciences Laboratory, Lipid Research Center, and Department of Medicine, Laval University, Ste-Foy, Quebec, Canada G1K 7P4

Abstract The aim of the present study was to investigate the associations between total adiposity, body fat distribution, and plasma lipoprotein levels within groups of women defined on the basis of apolipoprotein E phenotypes, in order to verify whether apolipoprotein E polymorphism could modify these associations. In women having only apolipoprotein E3 isoforms (n = 24), body fat mass, the waist: hip circumference ratio, and computed tomography-derived total and intra-abdominal fat areas were all positively correlated with very low density lipoprotein (VLDL) and low density lipoprotein (LDL) lipids and apolipoprotein B concentrations. These body fatness variables were also negatively correlated with plasma high density lipoprotein (HDL) cholesterol concentration. These associations were, however, altered in the groups of women carrying either apoE2 or apoE4 isoforms. Indeed, in women carrying the apoE2 isoform (n = 22), body fatness variables were predominantly associated with VLDL components concentration (0.05 > P < 0.01) and with LDL triglyceride content. No association was found between adiposity and LDL cholesterol or apolipoprotein B levels in these women. In contrast, no relationship was found between total adiposity, regional fat accumulation, and VLDL fraction in women carrying the apolipoprotein E4 isoform (n = 17). In this latter group, computed tomography-measured total abdominal fat accumulation was positively correlated with LDL apolipoprotein B (r = 0.58, P < 0.05) concentration, whereas intra-abdominal fat accumulation was positively correlated with both LDL cholesterol and apolipoprotein B concentrations (P < 0.05). Moreover, the significant negative correlation that is usually reported between HDL levels and obesity was evident in women with apoE3 or apoE2 isoforms but was less pronounced in the group with apoE4. These results suggest that the relationships between body fatness, fat distribution indices, and concentrations of plasma lipoproteins that are usually observed are mainly accounted for by the high frequency of allele E3 in the population. These associations are altered in the presence of rarer apoE2 and E4 isoforms. — Pouliot, M-C., J-P. Després, S. Moorjani, P. J. Lupien, A. Tremblay, and C. Bouchard. Apolipoprotein E polymorphism alters the association between body fatness and plasma lipoproteins in women. J. Lipid Res. 1990, 31: 1023–1029.

Supplementary key words adiposity • body fat distribution • lipoprotein levels

Population studies have shown that apolipoprotein (apo) E polymorphism is associated with changes in plasma total and low density lipoprotein (LDL) cholesterol concentrations (see review by Davignon et al., ref. 1). Among the three major isoforms of apoE, which are designated apoE2, apoE3, and apoE4, apoE3 is the most common in every population studied thus far (1), and is considered to be the normal form of the protein. Compared to apoE3, apoE2 is associated with lower and apoE4 with higher plasma cholesterol levels. A unifying hypothesis of the mechanisms by which apoE polymorphism is associated with changes in the metabolism of apoB-containing lipoproteins (chylomicrons, very low density lipoproteins (VLDL), and LDL), leading to variations in plasma total and LDL-cholesterol levels, has been proposed (1–3). This hypothesis is based on the differences observed in in vitro binding affinity of the three isoproteins for the cell surface receptors (remnant and LDL receptors), and also differences in the in vivo clearance rates of radiolabeled apoE isoproteins from plasma.

Obesity and abdominal fat accumulation are conditions that are associated with increased plasma VLDL concentration (4–9). Since apoE plays an important role in the metabolic fate of these apoB-containing lipoproteins (10, 11), it appeared legitimate to verify whether apoE polymorphism could alter the relationships that are usually observed between total or abdominal obesity and the plasma lipoprotein and lipid profile. In order to test this hypothesis, we have studied the associations between total ———

Abbreviations: VLDL, very low density lipoprotein; LDL, low density lipoprotein; CT, computed tomography; C, cholesterol; TG, triglyceride; HDL, high density lipoprotein; WHR, waist:hip circumference ratio.
adiposity, abdominal fat accumulation, and plasma lipoprotein levels within groups of women classified on the basis of their apoE phenotype.

MATERIALS AND METHODS

Experimental subjects

Sixty-three healthy premenopausal Caucasian women were recruited through the media and gave their written informed consent to participate in this study, which was approved by the Medical Ethics Committee of Laval University. All participants were subjected to a full physical examination by a physician, which also included medical history. Women with cardiovascular disease, diabetes or other endocrine disorders, as well as those on medication were excluded a priori. Subjects had to be sedentary in order to participate in the study. All measurements were performed while the women were in the supine position in the follicular phase of their menstrual cycle, and in an apparent weight-stable period. Because of their potential association with lipoprotein metabolism and plasma concentrations, lifestyle variables such as the daily energy intake, the percentage of intake from proteins, lipids, and carbohydrates, the cholesterol content of the diet, as well as the alcohol consumption were estimated from a 3-day dietary record, including one weekend day, as previously described (12). Eleven women in this sample were on oral contraceptives, whereas fifteen women were regular smokers.

Computed tomography

Computed tomography (CT) was performed on a Siemens Somatom DRH scanner (Erlangen, FRG) using the methodology described by Sjöström et al. (13). The scanning was performed with 125 kV and a slice thickness of 8 mm. Briefly, the subjects were examined in the supine position with their arms stretched above their head. A CT scan was performed at the abdominal level, between the fourth and the fifth lumbar vertebrae, using a radiograph of the skeleton to determine the position of the scan to the nearest millimeter. Total and intra-abdominal fat areas were calculated by delineating these areas with a graph pen and then computing the adipose tissue surface using an attenuation range of -30 to -190 Hounsfield units (13, 14). Intra-abdominal fat area was measured by drawing a line within the muscle wall surrounding the abdominal cavity.

Measurement of body fatness

Body density was measured by the hydrostatic weighing technique (15) as previously described (7). The mean of six valid measurements was used to calculate percent body fat from density using the equation of Siri (16). Fat mass was obtained by multiplying % body fat by body weight. Pulmonary residual volume was measured before immersion in the hydrostatic tank, using the helium dilution method of Meneely and Kaltreider (17). Waist and hip circumferences were measured following the recommendations of the Airlie Conference (18).

Plasma lipoprotein-lipid and apolipoprotein levels

Blood samples were collected from an antecubital vein into Vacutainer tubes containing EDTA. Samples were taken in the morning after a 12-h fast while the subjects were in the supine position. Plasma lipoprotein fractions were prepared by the combined use of ultracentrifugation (19) and heparin-manganese precipitation (20). Plasma was centrifuged at 40,000 rpm in a Beckman 50.3 rotor at a density of 1.006 g/ml for 18 h. Tubes were sliced and the VLDL fraction was removed. The infranatant (d > 1.006 g/ml) was used for LDL and HDL determinations after LDL precipitation by addition of heparin and manganese chloride (20). The cholesterol and triglyceride concentrations in plasma and lipoprotein fractions were quantified on an AutoAnalyzer AA-II (Technicon Instruments Corp., Tarrytown, NY) as previously described (21). The rocket immunoelectrophoretic method of Laurell (22) was used to measure apoB concentration in plasma and that of LDL-apoB and HDL-apoA-I in the infranatant fraction as previously described (23). The concentrations of LDL-C, LDL-TG, and VLDL-apoB were obtained by difference. The cumulative coefficients of variation for these various lipid and apolipoprotein determinations in our laboratory are: 2.1% for high cholesterol value, 2.7% for low cholesterol value, 3.3% for HDL-cholesterol, 3.0% for triglycerides, 3.5% for total apoB, 3.4% for apoA-I, and 6% for VLDL-apoB. Recovery of cholesterol in the lipoprotein fractions isolated by ultracentrifugation averaged 96% (range 92% to 102%) of the total plasma cholesterol value.

Apolipoprotein E phenotyping

ApoE phenotypes were determined according to a modification of the method of Bouthillier, Sing, and Davignon (24) as described previously (25). In brief, the isolated VLDL fraction was delipidated with acetone-ethanol 1:1 (v/v) followed by diethyl ether at -20°C. The colorless precipitated protein was dried under N2 at room temperature and stored at -20°C. ApoVLDL was solubilized in 10 mM Tris-HCl (pH 8.2), containing 8 M urea and 30 mM dithiothreitol, just before electrophoresis. The apoE isoproteins were separated by isoelectric focusing electrophoresis in 7.5% polyacrylamide gels containing 8 M urea and 2.0% ampholytes, pH 4-6 (LKB-Produkter AB, Bromma, Sweden) and 5-7 (Bio-Rad, Richmond, CA) in the proportion of 4:1. Gels were polymerized in cylindrical tubes and run in a water-cooled column disc electrophoresis apparatus (Hoefer Scientific Instruments, San Francisco, CA) at 4°C for 16 h at 150 V. Samples of known phenotypes, E4/4 and E2/2, were in-
cluded in each run. Gels were then removed from their tubes and stained with 1-2% aqueous Coomassie brilliant blue-R (Sigma Chemical Co., St. Louis, MO) using the method of Malik and Berrie (26). The various phenotypes were assigned according to the nomenclature as described by Zannis et al. (27). ApoE phenotyping was performed without prior knowledge of the plasma lipoprotein-lipid and apolipoprotein data.

The relative allele frequencies for e2, e3, and e4 in these women were 0.201, 0.638, and 0.154, respectively. Although these allele frequencies differ significantly from those reported in other Caucasian populations (1), they are similar to our previously reported results showing allele frequencies of 0.191 (e2), 0.689 (e3), and 0.120 (e4) in a random population sample of 173 French Canadian men and women (28). The higher frequency of E2 homozygotes in this sample is due to higher prevalence of the e2 allele in the Quebec French Canadian population.

Statistical analyses

The subjects were classified into three groups according to their apoE phenotype. Due to the rarity of the homozygous phenotypes E2/2 (n = 3) and E4/4 (n = 1), we defined the groups as follows: 1) the apoE2 group (n = 22), composed of individuals carrying either the E2/2 or E2/3 phenotypes; 2) the apoE3 group (n = 24), composed of individuals carrying the E3/3 phenotype; and 3) the apoE4 group (n = 17), composed of individuals carrying either the E3/4 or E4/4 phenotypes. Two subjects carrying the E2/4 phenotype were deleted from the sample. Comparisons among three groups were performed by analysis of variance. Associations between two variables were quantified in each group using Pearson’s product-moment correlation coefficients. VLDL data were log-transformed to normalize their distribution.

RESULTS

Results presented in Table 1 indicate that mean age, body mass index, percent body fat, and proportion of abdominal fat estimated by the waist:hip ratio (WHR) were comparable in the three apoE phenotype groups. Plasma lipoprotein-lipid and apolipoprotein levels, which are also presented in Table 1, were not significantly different between the three apoE groups.

The correlation coefficients between body fat mass, the WHR, the computed tomography (CT)-measured total and intra-abdominal fat areas, and plasma lipoprotein-lipid and apolipoprotein levels were calculated within each apoE group and are presented in Tables 2, 3, and 4.

The correlation coefficients between body fatness variables and VLDL components are shown in Table 2. In the apoE2 and apoE3 groups, body fat mass, the WHR, as well as the total and intra-abdominal fat areas were all positively correlated with VLDL-cholesterol and VLDL-TG concentrations. In the apoE3 group, these body fatness variables were also positively correlated with VLDL-apoB concentration. These results are in contrast with those observed in the apoE4 group, in which no significant associations were found between body fatness variables and the VLDL fraction, other than a positive correlation between total abdominal fat area and VLDL-TG level.

The associations between body fatness and LDL lipid and protein content are presented in Table 3. In the

<table>
<thead>
<tr>
<th>ApoE Group</th>
<th>Lipoprotein Components</th>
<th>Fat Mass</th>
<th>WHR</th>
<th>Total</th>
<th>Deep</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2</td>
<td>VLDL-C</td>
<td>0.57**</td>
<td>0.58**</td>
<td>0.59**</td>
<td>0.64**</td>
</tr>
<tr>
<td></td>
<td>VLDL-TG</td>
<td>0.59**</td>
<td>0.62**</td>
<td>0.65**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VLDL-apoB</td>
<td>0.42</td>
<td>0.38</td>
<td>0.38</td>
<td>0.38</td>
</tr>
<tr>
<td>E3</td>
<td>VLDL-C</td>
<td>0.46</td>
<td>0.54**</td>
<td>0.50**</td>
<td>0.56**</td>
</tr>
<tr>
<td></td>
<td>VLDL-TG</td>
<td>0.53*</td>
<td>0.44**</td>
<td>0.58**</td>
<td>0.61**</td>
</tr>
<tr>
<td></td>
<td>VLDL-apoB</td>
<td>0.74***</td>
<td>0.58**</td>
<td>0.80***</td>
<td>0.75***</td>
</tr>
<tr>
<td>E4</td>
<td>VLDL-C</td>
<td>0.10</td>
<td>0.13</td>
<td>0.32</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>VLDL-TG</td>
<td>0.43</td>
<td>0.28</td>
<td>0.53*</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>VLDL-apoB</td>
<td>0.07</td>
<td>0.17</td>
<td>0.08</td>
<td>0.05</td>
</tr>
</tbody>
</table>

WHR, waist:hip circumference ratio; for other abbreviations, refer to Table 1; * P < 0.05; ** P < 0.01; *** P < 0.001.

*All values are log 10.
TABLE 3. Associations between body fatness variables and plasma low density lipoprotein (LDL) components in apolipoprotein E phenotype groups

<table>
<thead>
<tr>
<th>ApoE Group</th>
<th>Lipoprotein Components</th>
<th>Abdominal Fat Mass</th>
<th>WHR</th>
<th>Total Deep</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2</td>
<td>LDL-C</td>
<td>0.09</td>
<td>0.27</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>LDL-TG</td>
<td>0.57**</td>
<td>0.34</td>
<td>0.54*</td>
</tr>
<tr>
<td></td>
<td>LDL-apoB</td>
<td>0.08</td>
<td>0.38</td>
<td>0.07</td>
</tr>
<tr>
<td>E3</td>
<td>LDL-C</td>
<td>0.56**</td>
<td>0.46*</td>
<td>0.57**</td>
</tr>
<tr>
<td></td>
<td>LDL-TG</td>
<td>0.66***</td>
<td>0.51*</td>
<td>0.69***</td>
</tr>
<tr>
<td></td>
<td>LDL-apoB</td>
<td>0.43*</td>
<td>0.43*</td>
<td>0.45*</td>
</tr>
<tr>
<td>E4</td>
<td>LDL-C</td>
<td>0.16</td>
<td>0.15</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>LDL-TG</td>
<td>0.16</td>
<td>0.23</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>LDL-apoB</td>
<td>0.29</td>
<td>0.34</td>
<td>0.58*</td>
</tr>
</tbody>
</table>

For abbreviations, refer to Tables 1 and 2; *, P < 0.05; **, P < 0.01; ***, P < 0.001.

apoE3 group, body fat mass, the WHR, as well as the total and intra-abdominal fat areas were positively correlated with LDL-cholesterol and LDL-apoB concentrations. In contrast, none of these adiposity indices was associated with LDL-cholesterol or LDL-apoB levels in the apoE2 group. In the apoE4 group, CT-measured total abdominal fat area was positively correlated with LDL-apoB concentration, whereas intra-abdominal fat area was positively associated with both LDL-apoB and LDL-cholesterol concentrations (P < 0.05).

Total body fat mass, as well as abdominal fat were positively associated with LDL-TG concentration in both the apoE2 and E3 groups, but not in the apoE4 group. This is further exemplified in Fig. 1, which illustrates the association of total body fat mass with the LDL-TG/LDL-apoB ratio in the three apoE phenotype groups. Although the mean values for this ratio were not significantly different among the three subgroups (3.9 × 10⁻³ in the E2 group, 3.5 × 10⁻³ in the E3 and E4 groups), a positive association was observed between body fat mass and the LDL-TG/LDL-apoB ratio in the E2 and E3 groups (Fig. 1A and 1B), whereas no association was observed between these variables in the apoE4 group (Fig. 1C). These results suggest a triglyceride enrichment of LDL particles with increasing adiposity in the apoE2 and E3 groups, but not in the apoE4 group.

The correlation coefficients between body fatness indices and the HDL fraction are shown in Table 4. In the apoE3 group, body fat mass, the WHR, and the abdominal fat areas were all negatively associated with HDL-cholesterol concentration. In the apoE2 group, the WHR and the intra-abdominal fat area were negatively associated with HDL-cholesterol and apoA-I levels. No association was observed between body fatness variables and the HDL fraction in the apoE4 group.

As smoking, oral contraceptives (OC), energy intake, diet composition, and alcohol consumption may influence

Fig. 1. Relation of total body fat mass to the LDL-TG/LDL-apoB ratio in the group of subjects homozygous or heterozygous for the apolipoprotein E2 isoform (panel A), in the group of subjects homozygous for the apolipoprotein E3 isoform (panel B), and in the group of subjects homozygous or heterozygous for the apolipoprotein E4 isoform (panel C).
lipoprotein metabolism and plasma concentrations, we performed a posteriori analyses in order to verify whether these lifestyle variables may have affected the correlation coefficients presented in this study (results not shown). Due to the rather small size of the subgroups, we could not, however, perform multivariate analyses to evaluate the effect of these concomitant variables.

The proportion of smokers was not comparable among the three groups (7/22 in the E2 group, 6/24 in the E3 group, and 2/17 in the E4 group). However, further analyses indicated that the morphological and metabolic characteristics of smokers were not different from those of nonsmokers. Furthermore, excluding the smokers from our sample did not alter the magnitude of the correlation coefficients between body fatness and lipoprotein levels within the various apoE phenotype groups. Therefore, in order to maximize sample size, we included smokers in our study.

The proportion of subjects on oral contraceptives (OC) was similar in the three groups (4/22 in the E2 group, 4/24 in the E3 group, and 3/17 in the E4 group). Excluding the OC users from our sample also did not significantly affect the magnitude of the correlation coefficients between adiposity and plasma lipoprotein levels within the various apoE phenotypes. We have therefore included OC users in our sample.

A posteriori analyses indicated that the daily caloric intake estimated from the 3-day dietary record, as well as the composition of the diet (% of intake from proteins, lipids, and carbohydrates), were similar among the three groups. As the response of serum and LDL cholesterol to dietary cholesterol has been reported to differ depending upon the apoE phenotype (29), we also estimated the cholesterol content of the diet from the 3-day dietary record and we found it to be similar among the three subgroups. Finally, the alcohol consumption was found to be moderate and, when expressed in grams per day, not different among the three groups. These results suggest that differences in the magnitude of correlation coefficients among apoE phenotype groups were probably not the consequence of between-group differences in these lifestyle variables.

DISCUSSION

Our results failed to detect significant differences in lipoprotein-lipid and apolipoprotein levels among the three apoE phenotype groups. However, a definite trend for an increasing gradient in both LDL-cholesterol and LDL-apoB concentrations was observed, ranking apoE2 group < apoE3 group < apoE4 group. This trend is consistent with population studies that have reported decreased serum cholesterol levels in individuals carrying apoE2 isoforms, whereas carriers of apoE4 isoforms had elevated serum cholesterol levels (1). The lack of significant differences in LDL-cholesterol and LDL-apoB levels among the three groups in the present study could be attributed to the rather small sample size. However, it should be noted that, even with adequate size of sampling, the magnitude of these effects varies considerably among populations (30).

Correlational analyses of our data indicated that differences in association patterns between body fatness and the lipoprotein profile existed among subgroups of women defined on the basis of apoE phenotypes.

Relationships between body fatness variables and plasma lipoprotein-profile in E3/3 phenotype

ApoE3 is considered to be the normal form of apoE. In the group of women homozygous for this apoE isoform, body fatness variables were positively associated with both VLDL and LDL fractions, as well as negatively associated with HDL fraction. As apoE3 is the most prevalent isoform in every population studied thus far (1), it is therefore not surprising that the associations found in this group are concordant with previous studies not accounting for apoE polymorphism, and demonstrating associations between obesity, trunk and abdominal fat accumulation, and plasma lipoprotein-lipid and apolipoprotein concentrations (7, 8, 9, 31, 32).

Relationships between body fatness variables and plasma lipoprotein-profile in carriers of apolipoprotein E2 and E4 isoforms

A unifying hypothesis has already been proposed to explain the alterations in lipoprotein metabolism associated with apoE polymorphism (1-3). From the proposed mechanisms, it is clear that apoE2 is associated with lower levels of plasma total and LDL cholesterol but predisposes to hypertriglyceridemia, whereas apoE4 is associated with

### TABLE 4. Associations between body fatness variables and plasma high density lipoprotein (HDL) components in apolipoprotein E phenotype groups

<table>
<thead>
<tr>
<th>ApoE Group</th>
<th>Lipoprotein Components</th>
<th>Fat Mass</th>
<th>WHR</th>
<th>Total</th>
<th>Deep</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2</td>
<td>HDL-C</td>
<td>-0.34</td>
<td>-0.42*</td>
<td>-0.37</td>
<td>-0.42*</td>
</tr>
<tr>
<td></td>
<td>HDL-TG</td>
<td>0.14</td>
<td>0.01</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>HDL-apoA-I</td>
<td>-0.28</td>
<td>-0.43*</td>
<td>-0.24</td>
<td>-0.42*</td>
</tr>
<tr>
<td>E3</td>
<td>HDL-C</td>
<td>-0.54**</td>
<td>-0.47**</td>
<td>-0.59**</td>
<td>-0.62**</td>
</tr>
<tr>
<td></td>
<td>HDL-TG</td>
<td>0.07</td>
<td>0.72***</td>
<td>0.00</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>HDL-apoA-I</td>
<td>-0.29</td>
<td>-0.26</td>
<td>-0.42*</td>
<td>0.38</td>
</tr>
<tr>
<td>E4</td>
<td>HDL-C</td>
<td>-0.37</td>
<td>-0.35</td>
<td>0.44</td>
<td>-0.33</td>
</tr>
<tr>
<td></td>
<td>HDL-TG</td>
<td>-0.32</td>
<td>-0.12</td>
<td>0.18</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>HDL-apoA-I</td>
<td>-0.05</td>
<td>-0.12</td>
<td>-0.19</td>
<td>-0.10</td>
</tr>
</tbody>
</table>

For abbreviations, refer to Tables 1 and 2; *, P < 0.05; **, P < 0.01; ***, P < 0.001.
higher levels of plasma total and LDL cholesterol but has very little effect on triglyceride concentration. There are, however, a few exceptions besides these population-based apoE allele effects. For example, a small proportion of individuals carrying the apoE2/2 phenotype develop type III hyperlipoproteinemia in the presence of another metabolic abnormality due to either genetic or environmental factors (1).

Increased body fatness and/or abdominal fat accumulation induces increased VLDL secretion that results in higher fasting levels of VLDL-cholesterol, VLDL-TG, VLDL-apoB and also increases in LDL-cholesterol and LDL-apoB (4–9). As discussed above, both VLDL and LDL components are therefore positively correlated to body fatness variables in the group of women with apoE3 isoform. In contrast, these correlations are of a specific nature in the groups of women with apoE2 or E4 isoforms.

In the group of women with apoE2 isoform, body fatness variables were predominantly associated with concentrations of VLDL components. In these women, body fatness indices were also correlated with the concentration of LDL-TG and with the LDL-TG/LDL-apoB ratio, but not with LDL-cholesterol or LDL-apoB, suggesting TG enrichment of LDL fraction with increasing adiposity. Since LDL as measured in this study is heterogeneous, containing both light (IDL) and dense (LDLd) fractions, it is reasonable to assume that the observed correlation is due to the light TG-rich LDL fraction. This situation can result from the lower affinity of apoE2-containing IDL for apoE and/or apoB,E receptors, and it can also be the result of defective interaction of lipoprotein lipase with apoE2-containing lipoproteins (1–3). Another possibility to explain this triglyceride enrichment of the LDL fraction could be that an increased VLDL-TG concentration, which was linked to the longer circulation time of VLDL particles observed in subjects with apoE2 isoform (1), would allow a greater lipid exchange between VLDL and LDL (33). The lack of correlation of body fatness with LDL-cholesterol and LDL-apoB is in agreement with the role of apoE2 in up-regulating the B,E receptor, resulting in an increased catabolism of LDL (1).

In contrast to our observations in the group with the apoE2 isoform, the body fatness variables were predominantly correlated to LDL-cholesterol and LDL-apoB rather than LDL-TG in women with the apoE4 isoform. These results are in accordance with the role of apoE4 in down-regulating B,E receptors, resulting in higher concentrations of LDL-cholesterol and LDL-apoB. The poor association observed between body fat indices and VLDL in this group is quite striking and suggests that important changes in VLDL metabolism are associated with the apoE4 isoform. These results are in agreement with enhanced clearance of radiolabeled apoE4 in kinetic studies (34) and also the lower concentration of apoE in subjects with the E4 isoprotein. It has been suggested that the rapid metabolism of apoE4 is due to its higher in vivo affinity for apoE and/or apoB,E receptors. It should also be noted that there was a lack of significant correlation between body fat variables and HDL-cholesterol or HDL-apoA-I in this group, in contrast to significant negative correlations noted in apoE2 and apoE3 groups. As there is an inverse relationship between VLDL-TG and HDL-cholesterol level (5), the lack of correlation between body fatness indices and VLDL observed in the group of women with apoE4 isoform may explain why body fatness variables were not associated with HDL-cholesterol concentration in this group.

Although the present study does not bring any further insights into the mechanisms by which apoE polymorphism affects plasma lipoprotein levels, the results clearly demonstrate that the various associations between body fat indices and concentrations of VLDL, LDL, and HDL components described in previous studies (4–9) are prevalent in the group of women with apoE3 isoform, and that these associations are altered and are more specific in the groups of women with apoE2 and E4 isoforms. Body fat variables are predominantly associated with VLDL components and TG metabolism in the former, whereas they are predominantly associated with LDL-cholesterol and LDL-apoB in the latter. To our knowledge, our study is the first to report that apoE polymorphism modifies the well-documented associations between obesity, fat distribution, and plasma lipoprotein levels. These findings may help to account for some of the inconsistent results in the literature about the relationships between body fat, fat topography, and blood lipids and lipoproteins.

This work was supported by the Quebec Heart Foundation, the Canadian Fitness and Lifestyle Research Institute, NSERC of Canada, by FRSQ-Quebec, and by Merck Frosst Canada. M. C. Pouliot is the recipient of an FRSQ fellowship; J-P. Després is an FRSQ research scholar.

Manuscript received 25 August 1989 and in revised form 13 November 1989.

REFERENCES


