Apolipoprotein E Polymorphisms and Postprandial Triglyceridemia Before and After Fenofibrate Treatment in the Genetics of Lipid Lowering and Diet Network (GOLDN) Study

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Background—Although much is known about the effect of Apolipoprotein E (APOE) alleles on fasting lipid concentrations, less is known about the effect of APOE alleles on postprandial triglyceridemia or the triglyceride response to fenofibrate.

Methods and Results—We evaluated the effects of the APOE locus on fasting and postprandial triglyceride concentrations as part of the Genetics of Lipid Lowering and Diet Network (GOLDN) study. Participants were evaluated after a high-fat meal challenge before (n=1072) and after 3 weeks of daily treatment with 160 mg of fenofibrate (n=738). Mixed models adjusted for sex, age, waist circumference, and family relationship were used to examine the association of the ε4 carrier and ε2 carrier status versus ε3 homozygotes with fasting triglycerides and the area under the curve (AUC) for triglycerides during the high-fat meal challenge. Compared with the ε3/ε3 genotype, ε2 carriers had on average higher fasting triglyceride concentrations (130.5 mg/dL versus 109.3 mg/dL, P<0.001). After fenofibrate treatment, the APOE genotype differences persisted in the fasting state (ε2 carriers: 85.1 mg/dL versus ε3/ε3: 75.9 mg/dL, P<0.05). Carriers of the ε4 allele had significantly higher fasting triglyceride concentrations only prefenofibrate (120.9 mg/dL versus 109.3 mg/dL, P=0.008). APOE alleles did not have an effect on response to fenofibrate. Postprandial triglycerides were significantly higher for ε2 carriers versus ε3 homozygotes (but not ε4 carriers) both before and after fenofibrate treatment (P=0.01 and P=0.005, respectively).

Conclusions—APOE polymorphisms are important determinants of triglyceride concentrations, especially in the fasting state. (Circ Cardiovasc Genet. 2010;3:462-467.)

Key Words: apolipoproteins ■ lipids ■ genetics

Elevated plasma triglyceride concentrations contribute to increased risk of cardiovascular disease (CVD) directly. Additionally, hypertriglyceridemia is often associated with other CVD risk factors such as obesity, metabolic syndrome, proinflammatory biomarkers, and type 2 diabetes mellitus.1

After a meal, >90% of the circulating triglycerides are broken down and absorbed in intestinal cells, where they are subsequently reprocessed, packaged, and secreted in chylomicrons.2 Additionally, fatty acids synthesized by the liver are converted to triglycerides and transported to the blood via very-low-density lipoprotein (VLDL) particles.2 The Apolipoprotein E (APOE) gene is a key mediator of both triglyceride and cholesterol metabolism. APOE binds to receptors on the liver to help mediate clearance of chylomicrons and VLDLs (triglyceride-rich lipoproteins, or TRLs) from the bloodstream.3–5 There have been >30 APOE variants characterized, of which many are associated with rare forms of hyperlipoproteinemia.6 In the present study, we focus on 3 common APOE protein isoforms (ε2, ε3, and ε4) caused by 2 functional polymorphisms that differ in physiological structure and affect the efficiency of TRL clearance.3 The APOE ε2 allele is associated with higher fasting concentrations of triglycerides, whereas the ε4 allele has been linked to hypercholesterolemia and elevated levels of low-density lipoprotein (LDL).7,8 The APOE ε4 allele has also been associated with increased risk for myocardial infarction or other coronary risk in some9–11 studies.12 Although much is known about the effect of APOE polymorphisms on fasting cholesterol and triglyceride concentrations,13 much less is known about the APOE gene effect in the postprandial state, particularly postprandial triglyceridemia. For example, one study found that among obese women, the APOE ε4 polymorphism...
did not affect postprandial triglyceridemia, but the sample size was limited (n = 93).14

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A few studies have reported the association between APOE alleles and response to fenofibrate treatment, though with conflicting results.15–17 Whether APOE alleles would modify the effect of fenofibrate therapy on postprandial triglyceridemia has not been reported. In this large study, we propose to test whether APOE genotypes are associated with postprandial triglyceridemia before and after treatment with fenofibrate. The effect of the interaction between APOE genotypes and fenofibrate concentration on postprandial triglyceridemia will be considered. We hypothesize APOE e2 and e4 carriers compared with e3 homozygotes will have larger responses to fenofibrate and have higher postprandial triglyceridemia. A secondary hypothesis is postprandial triglyceride response to fenofibrate will be modified by APOE genotypes.

Methods

Study Population

The Genetics of Lipid Lowering and Diet Network (GOLDN) study was designed to identify genes that determine response of lipids to 2 interventions: 1 to raise lipids (ingestion of high-fat meal, referred to as postprandial lipemia challenge, or PPL) and 1 to lower lipids (fenofibrate treatment 160 mg/d for 3 weeks). The GOLDN Study ascertained and recruited families from the National Heart, Lung, and Blood Institute Family Heart Study from 2 genetically homogenous centers, Minneapolis, Minn, and Salt Lake City, Utah, who were self-reported to be white. In each case, only families with at least 2 siblings were recruited, and only participants who did not take lipid-lowering agents (pharmaceuticals or nutraceuticals) for at least 4 weeks before the initial visit were included. To meet the sample size goals and increase relative pairs, participants were offered the option of doing either part of the protocol, high-fat meal and/or fenofibrate (TriCor, Abbott Laboratories, Abbott Park, Ill) treatment. The fenofibrate treatment protocol included a second PPL challenge after treatment. For the prefenofibrate and postfenofibrate analyses, the number of participants with complete data on triglyceride concentrations, APOE genotype, and demographics were 1072 and 738, respectively. Detailed design and methodology of the study have been published.18

In brief, the PPL challenge protocol included an 8-hour fast and 24-hour abstinence from alcohol followed by ingestion of a high-fat meal formulated according to the protocol of Patsch et al.19 Specifically, participants were given 700 kilocalories/m² of body surface area in the form of a high-fat milk shake with protein, carbohydrate, and fat content in the ratios of 3%, 14%, and 83%, respectively. Participants were instructed to consume the shake within 15 minutes. Blood samples were drawn immediately before fasting and 3.5 and 6 hours after ingestion of the high-fat meal. The study protocol was approved by the Institutional Review Board for human studies at the University of Minnesota, University of Utah, and Tufts University/New England Medical Center. Informed consent was obtained on all participants.

Biochemical Measurements

Triglycerides were measured using a glycerol blanked enzymatic method (Trig/GB, Roche Diagnostics Corp, Indianapolis, Ind) on the Roche/Hitachi 911 Automatic analyzer. Fenofibric acid, the active moiety of fenofibrate, was measured by high-performance liquid chromatography.20

Genotyping

Genomic DNA was extracted from blood samples and purified using commercial Puregene reagents (Gentra System, Inc, Minneapolis, Minn), following the manufacturer’s instructions. APOE genotyping was completed using the 5′-nuclease allelic discrimination TaqMan assay with ABI 7900HT system (Applied Biosystems, Foster City, Calif) for the C130R (rs429358) and R176C (rs7412) polymorphisms under the manufacturer’s suggested conditions. APOE genotypes were then called on the basis of the guidelines of Hixson and Vernier.21

Statistical Methods

Hardy-Weinberg equilibrium testing was completed for each single nucleotide polymorphism among a sample, including 1 participant chosen at random from each of 200 families in GOLDN. One-way ANOVA and χ² tests were used to examine differences in characteristics of the study population for continuous and categorical traits by APOE genotype group. APOE was coded as a categorical variable with values e3/e3, e2 carrier, and e4 carrier. Persons with the e2/e4 genotype were excluded from the analysis to distinguish the distinct role of each allele and also because of the low frequency of this allele combination (n = 48). Using the freely available software Quanto, we had >80% power (α = 0.05) to see an effect size of at least R² = 0.01 under a dominant model for either the e3 or e2 alleles (reference e3/e3) on postprandial triglycerides in our postfenofibrate treatment analysis (n = 738).22 R² represents the marginal proportion of Y (postprandial triglycerides), explained by the genetic effect.

The difference in fasting triglyceride concentration (FTG) was calculated for all participants who completed both the prefenofibrate and postfenofibrate PPL challenge, and the average percent change in FTG was calculated and compared by genotype group at the univariate and multivariable levels. All outcome variables were log-transformed to meet the assumption of normality of residuals for linear modeling, and outliers (defined as >4 standard deviations from the mean) were removed. A constant was added to percent change in FTG to make all values positive for the log transformation. Mixed models were used to test the association of APOE genotype group with FTG, percent change in FTG, and area under the curve (AUC) for triglycerides during the PPL challenge (measurements at 0, 3.5, and 6 hours) calculated using the trapezoidal rule. These models were adjusted for fixed effects including age, sex, and waist circumference, with family ID included as a random variable. Including family as a random variable in the model induces a compound symmetry covariance structure. The method has been validated and has improved type 1 error rate compared with within-cluster resampling methods.23 We thought that adjustment for family was sufficient to control for potential allele frequency differences between groups, and we did not adjust for population substructure in our analysis. The potential for sex differences in triglyceride response was examined by including a sex-by-genotype interaction term in the mixed models. We examined AUC triglycerides with and without adjustment for FTG concentration (0-hour measurement). The model for postfenofibrate AUC triglycerides was additionally adjusted for area under the serum fenofibric acid concentration curve measured at 0, 3.5, and 6 hours after the dose of fenofibrate taken immediately before the second PPL challenge. Finally, an APOE genotype by AUC for serum fenofibric acid concentration interaction term was modeled to test if APOE alleles would modify the effect of fenofibrate therapy on postprandial triglyceridemia. Statistical analysis as carried out in SAS (Version 9.1.2, Cary, NC). The least square means statement within the mixed model procedure was used to estimate mean triglyceride concentrations and AUC triglycerides by genotype group adjusted for the covariates discussed above. These means are presented in the tables and Figure.

Results

The 2 polymorphisms in APOE, C130R and R176C that determined e2, e3, and e4 allele genotypes were in Hardy-Weinberg equilibrium, with P = 0.15 and P = 0.35, respectively. The genotyping rate for each variant was >99%. Among the GOLDN study population participating in the prefenofibrate treatment PPL challenge, age, sex, and waist circumference were
not different by *APOE* genotype group after univariate comparisons, whereas FTG concentrations were significantly different, with *P*=0.02 (Table 1). The same comparisons yielded similar results for the participants in the postfenofibrate treatment PPL challenge group; however, differences in FTG concentrations by genotype group were no longer present. Additionally, AUC for serum fenofibric acid concentration curve was not different by genotype group.

FTG decreased on average 34.4% after 3 weeks of fenofibrate treatment for the *ε3/ε3* genotype group. FTG decreased on average −35.2%, −33.0%, and −38.1% for *ε3/ε4* carriers, and *ε2* carriers, respectively. This difference was not statistically significant between any of the genotype groups. Estimated average FTG concentration by *APOE* genotype after adjustment for covariates both before and after fenofibrate treatment is shown in Table 2. Compared with the *ε3/ε3* genotype reference group, *ε2* carriers had, on average, higher FTG concentrations both before and after fenofibrate treatment. The difference in FTG between *ε2* carriers and *ε3* homozygotes was more marked and more statistically significant before fenofibrate treatment (*P*=0.0008 versus *P*=0.04), though fewer participants are included in the postfenofibrate treatment estimates. Treatment with fenofibrate attenuated the *APOE* *ε4* genotypic effects on FTG: Carriers of the *ε4* allele had significantly higher FTG-only prefenofibrate (*P*=0.008, Table 2). The effect of *APOE* alleles on FTG before and after fenofibrate was not modified by sex.

Average triglyceride concentrations estimated at 0, 3.5, and 6 hours after the high-fat meal by genotype group both before and after fenofibrate treatment are depicted in the Figure. The 95% confidence intervals show the most variation for the *ε2* carriers, adjusting for age, sex, waist circumference, baseline FTG, and family relationship, the percent change in FTG after fenofibrate treatment was −35.2%, −33.0%, and −38.1% for *ε3/ε3*, *ε4* carriers, and *ε2* carriers, respectively. This difference was not statistically significant between any of the genotype groups.

### Table 1. Characteristics of the GOLDN Study Population That Participated in the Postprandial Lipemia Challenge Before and After Treatment With Fenofibrate 160 mg/d by *APOE* Genotype Group

<table>
<thead>
<tr>
<th>Genotype Group Before and After Treatment With Fenofibrate 160 mg/d</th>
<th>ε3/ε3</th>
<th>ε4 Carrier</th>
<th>ε2 Carrier</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefenofibrate PPL</td>
<td>n=666</td>
<td>n=289</td>
<td>n=117</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>49.2±17</td>
<td>46.9±15</td>
<td>48.4±16</td>
<td>0.12</td>
</tr>
<tr>
<td>Sex, % women</td>
<td>52%</td>
<td>54%</td>
<td>41%</td>
<td>0.06</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>96.1±16</td>
<td>96.6±18</td>
<td>98.8±13</td>
<td>0.24</td>
</tr>
<tr>
<td>FTG, mg/dL</td>
<td>131.0±34</td>
<td>124.1±32</td>
<td>128.9±45</td>
<td>0.02</td>
</tr>
<tr>
<td>Postfenofibrate PPL</td>
<td>n=454</td>
<td>n=203</td>
<td>n=81</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>49.7±17</td>
<td>47.5±15</td>
<td>49.0±16</td>
<td>0.27</td>
</tr>
<tr>
<td>Sex, % women</td>
<td>50%</td>
<td>55%</td>
<td>40%</td>
<td>0.06</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>96.8±16</td>
<td>97.2±17</td>
<td>97.4±13</td>
<td>0.31</td>
</tr>
<tr>
<td>FTG, mg/dL</td>
<td>85.5±51</td>
<td>91.7±50</td>
<td>97.2±48</td>
<td>0.09</td>
</tr>
<tr>
<td>Average % change in FTG</td>
<td>−29.0%</td>
<td>−26.4%</td>
<td>−34.4%</td>
<td>0.05</td>
</tr>
<tr>
<td>Fenofibric acid AUC†</td>
<td>69.5±33</td>
<td>67.0±31</td>
<td>74.8±34</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*GOLDN participants were given the option to participate in the PPL challenge without fenofibrate or in the PPL challenge before and after 3 weeks of daily treatment with 160 mg of fenofibrate. Thus, samples in the prefenofibrate PPL study overlap with those in the postfenofibrate PPL study but are not exactly the same.

†Area under the serum fenofibric acid concentration curve measured at 0, 3.5, and 6 hours after the dose of fenofibrate taken immediately before the PPL challenge was calculated using the trapezoidal rule; unit is arbitrary.

### Table 2. Adjusted Fasting Triglyceride Concentrations by *APOE* Genotype Group Before and After Fenofibrate Treatment (160 mg/d)

<table>
<thead>
<tr>
<th>Genotype Group Before and After Fenofibrate Treatment (160 mg/d)</th>
<th>ε3/ε3</th>
<th>ε4 Carrier</th>
<th>ε2 Carrier</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>n=666</td>
<td>n=289</td>
<td>n=117</td>
<td></td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>FTG, mg/dL</td>
<td>109.3 (104, 115)</td>
<td>120.9 (113, 129)*</td>
<td>130.5 (118, 144)*</td>
</tr>
<tr>
<td>After</td>
<td>n=454</td>
<td>n=203</td>
<td>n=81</td>
<td></td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>FTG, mg/dL</td>
<td>75.9 (72, 80)</td>
<td>81.9 (76, 88)</td>
<td>85.1 (77, 95)*</td>
</tr>
</tbody>
</table>

*Values are least-squares means (95% confidence intervals) adjusted for age, sex, waist circumference, and family relationship.

†Additionally adjusted for area under the serum fenofibric acid curve.

‡Significantly higher FTG concentration when compared with the reference genotype (*ε3/ε3*). Superscripts a, b, and c signify *P*<0.05, *P*<0.01, and *P*<0.001, respectively.
**Table 3. Area Under the Curve for Triglycerides Measured at 0, 3.5, and 6 Hours After the Postprandial Lipemia Challenge by APOE Genotype Group Before and After 3 Weeks of Fenofibrate Treatment (160 mg/d)**

<table>
<thead>
<tr>
<th></th>
<th>ε3/ε3</th>
<th>ε4 Carrier</th>
<th>ε2 Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before fenofibrate</td>
<td>n=666</td>
<td>n=289</td>
<td>n=117</td>
</tr>
<tr>
<td>AUC*</td>
<td>1077.7 (1022, 1136)</td>
<td>1210.3 (1127, 1299)§</td>
<td>1340.5 (1211, 1484)§</td>
</tr>
<tr>
<td>AUC†</td>
<td>1095.1 (1072, 1119)</td>
<td>1127.7 (1095, 1162)</td>
<td>1161.9 (1112, 1214)§</td>
</tr>
<tr>
<td>After fenofibrate</td>
<td>n=454</td>
<td>n=203</td>
<td>n=81</td>
</tr>
<tr>
<td>AUC†</td>
<td>727.3 (689, 767)</td>
<td>798.3 (742, 858)§</td>
<td>866.2 (778, 965)§</td>
</tr>
<tr>
<td>AUC††</td>
<td>738.7 (720, 757)</td>
<td>754.6 (730, 779)</td>
<td>793.9 (756, 832)§</td>
</tr>
</tbody>
</table>

*Values are least-squares means (95% confidence intervals) with arbitrary unit adjusted for age, sex, waist circumference, and family relationship.
†Additionally adjusted for area under the serum fenofibric acid curve.
§Significantly higher AUC when compared with the reference genotype (ε3/ε3). Superscripts d, e, and f signify P<0.05, P<0.005, and P<0.0001, respectively.

A finding most likely due to the smaller sample size of that group (see Table 1). The Figure depicts that postprandial triglyceride concentrations peak at the 3.5-hour measurement and start to decline by hour 6. At the sixth hour, on average, the concentrations remain greater than fasting concentrations. Estimated AUC for triglycerides during the PPL challenge before and after fenofibrate treatment by genotype group is presented in Table 3. We present models both adjusted and unadjusted for FTG. When our mixed models were unadjusted for FTG, carrier status for both the ε2 and ε4 allele was associated with higher AUC triglycerides before and after fenofibrate treatment with P<0.05. However, inclusion of FTG concentration in our models attenuated the effect of APOE alleles. Specifically, after adjustment for fasting triglycerides, carrying the APOE ε2 allele was still associated with higher postprandial triglycerides (P=0.01 and P=0.0047 before and after fenofibrate treatment, respectively), but the effect of the APOE ε4 allele was removed. Like FTG concentration, the effect of APOE alleles on postprandial triglycerides before and after fenofibrate was not modified by sex. Finally, we report no interaction between APOE alleles and AUC serum fenofibric acid concentration on postprandial triglycerides when we include adjustment for fasting triglycerides.

**Discussion**

It could be argued that studies of the nonfasting state are most relevant to human health, as most humans spend more hours in the nonfasting state (up to 8 hours after the last meal) than in the fasting state (more than 8 hours after the last meal).24 We report persons carrying the APOE ε2 allele are exposed to significantly higher triglyceride concentrations regardless of the metabolic state compared with persons with the most common ε3/ε3 genotype. Elevated triglyceride concentration is diagnosed in the fasting state, and the Adult Treatment Panel III of the National Cholesterol Education Program has suggested fasting triglyceride strata in the context of assessment of risk for cardiovascular disease: normal (<150 mg/dL), borderline high (150 to 199 mg/dL), high (200 to 499 mg/dL), and very high (≥500 mg/dL). Treatment is suggested for fasting triglycerides ≥150 mg/dL.25 On average, before fenofibrate treatment, ε2 carriers from GOLDN come the closest to having borderline high triglycerides with adjusted fasting mean 130.5 mg/dL (95% confidence interval, 118 to 144) and have a greater postprandial response to a high-fat meal (Figure). Exposure to elevated triglyceride concentrations is clinically important. Growing evidence links excess circulating remnant TRL particles (the products of lipolytic degradation of TRLS) to oxidative stress and subsequent atherosclerosis.26–28 These results suggest that screening for the APOE ε2 allele may provide useful information for targeting dietary fat restrictions for future prevention of CVD, especially in high-risk populations such as those with a family history of CVD.

Our results agree with other studies of fasting and nonfasting triglycerides. Several studies report increased triglyceride concentrations in the fasting state for ε2 and ε4 carriers,11,13,29,30 and another large study (n=9060) of a Danish population reports similar results for the nonfasting state.24 A meta-analysis of 45 populations in 17 countries reported the ε2/ε2, ε2/ε3, and ε3/ε4 genotypes but not the ε4/ε4 genotype (in reference to the ε3/ε3 genotype) were associated with higher plasma triglyceride concentrations.13 Though the association of the ε2 allele with higher FTG concentrations is consistent in the literature, results vary more for ε4. In the Turkish Heart study, the ε2 allele but not the ε4 allele was associated with higher FTG concentrations in men, but no association of either allele was found in women.31 Another study reported lower FTG concentrations with the ε4/ε4 genotype.32

There are fewer and mostly small studies (n<100) of postprandial triglycerides, especially among healthy individuals. In a study of 66 nondiabetic patients with the metabolic syndrome who consumed a 60 g fat load, carriers of ε2 or ε4 had a 6.2 greater odds (95% confidence interval, 1.4 to 16; P=0.01) of postprandial hypertriglyceridemia at 4 hours compared with ε3/ε3 homozygotes.33 In 2 other studies of the postprandial state, the ε4 allele was associated with higher triglyceride concentrations in patients with a form of hyperlipidemia34,35; however, the ε2 and ε4 alleles were not related to higher postprandial triglycerides in patients with non–insulin-dependent diabetes mellitus.36 Finally, in the largest study (n=407), carrying the ε2 allele and to a lesser extent carrying the ε4 allele was associated with 21.2% and 11.5% higher postprandial triglyceride concentrations at 6 hours (P<0.01 and P=0.05, respectively) in healthy young male adults from the European Atherosclerosis Research Study with and without a family history of myocardial infarction.37
All of the studies of postprandial triglycerides we have mentioned adjusted for FTG; however, results presented were not for AUC outcomes. In our study of AUC for triglycerides, we present models both adjusted and unadjusted for FTG concentration (Table 3). Whereas the postprandial AUC measurement incorporates the FTG in the calculation, the magnitude of the AUC is determined by both the FTG and the physiological response to the high-fat meal. We and others have shown APOE alleles are associated with FTG measures, and we wanted to focus on the postprandial state. Thus, to reach this end, we concluded it necessary to adjust for the effects of baseline and focus on those results. We show that the effect of APOE alleles on AUC for triglycerides is greatly attenuated after adjustment for FTG concentration, and we conclude that differences before adjustment are largely driven by baseline effects (Table 3).

The GOLDN study is different from other studies of fasting and postprandial triglycerides in that plasma was measured before and after 3 weeks of fenofibrate treatment. We report no difference in percent change in FTG concentration after fenofibrate treatment by APOE genotype group. This result has been reported previously in the GOLDN study.38 The effect of APOE allele status on response to fibrates varies in the literature. A study among hypertriglyceridemic patients (n = 292) treated with fenofibrate for 3 months reported e2 allele carriers have a better response to fenofibrate on all lipid parameters than e3 or e4 carriers.15 Another study among patients with primary hypertriglyceridemia or mixed hyperlipidemia (n = 136) reported the reduction in fasting triglyceride concentration after fenofibrate treatment (200 mg/d for 6 months) for e3, e4, and e2, allele carriers was 36%, 33%, and 53%, respectively (P = 0.033).16 Conversely, the APOE genotype was not associated with plasma triglyceride response to at least 3 years of fenofibrate treatment (200 mg/d) among type 2 diabetics from the Diabetes Atherosclerosis Intervention Study (n = 155).17 The first study mentioned did not adjust for baseline measures, whereas our study and the latter studies did. We consider it important to adjust for baseline FTG in these models because it has been noted in the literature that change in triglyceride concentration after fibrates is dependent on baseline levels.39–41 Differing results even after adjustment for baseline measures may be due to variability in the underlying study populations and/or small sample size.

Finally, in the GOLDN population we were able to examine whether APOE genotypes modify the effect of fenofibrate treatment on postprandial triglyceridemia. There was no difference in the association of AUC serum fenofibrate acid concentration with AUC postprandial triglycerides for e2 carriers or e4 carriers versus e3 homozygotes when our model was adjusted for fasting triglyceride concentration. Future larger studies may consider the same interactive effect as our sample may have been small to identify the interaction (n = 738).

The current study strengthens the evidence that the APOE e2 allele is associated with higher triglyceride concentrations. This effect is consistent across different physiological states, for example, fasting and after ingesting a high-fat meal. These observations are consistent with reports that the e2 allele is associated with defective clearance of the e2-containing remnant lipoproteins that are triglyceride-rich as the result of defective interaction with the VLDL/cholesteromic cell receptor.5,42 The effect of the e4 allele on triglyceride concentrations is not as strong as the e2 allele, although we report it is associated with higher fasting triglyceride concentrations. In conclusion, APOE polymorphisms are important determinants of triglyceride concentrations in the fasting state. Because hypertriglyceridemia is an important risk factor for CVD and e2 alleles are associated with higher triglyceride concentrations, future studies should determine if APOE genotype is useful for the prevention of this lipid disorder.

Acknowledgments

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Disclosures

None.

References

Elevated plasma triglyceride concentrations have been associated with an increased risk of cardiovascular disease. A key mediator of triglyceride metabolism is the apolipoprotein E (APOE) gene. Although much is known about the association of APOE alleles (ε2, ε3, and ε4) with fasting triglyceride concentrations, much less is known about the association of these alleles with postprandial blood triglyceride concentrations. We evaluated the effects of the APOE locus on postprandial triglyceride concentrations as part of the Genetics of Lipid Lowering and Diet Network (GOLDN) study. This population is unique, as participants were evaluated after a high-fat meal challenge before (n = 1072) and after 3 weeks of daily treatment with 160 mg of fenofibrate (n = 738). We report that APOE polymorphisms are important correlates of triglyceride concentrations. Importantly, APOE ε2 alleles are associated with higher triglycerides in the fasting and postprandial state before and after treatment with fenofibrate. Exposure to elevated triglyceride concentrations is clinically important because growing evidence links excess circulating triglyceride rich lipoprotein remnant particles to oxidative stress and subsequent atherosclerosis. Future studies should determine if the APOE genotype is useful for the early prevention of hypertriglyceridemia, especially among high-risk groups such as those with a family history of cardiovascular disease.
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