ApoE Polymorphism and Fish Oil Supplementation in Subjects With an Atherogenic Lipoprotein Phenotype

Anne M. Minihane, Syrah Khan, Elizabeth C. Leigh-Firbank, Philippa Talmud, John W. Wright, Margaret C. Murphy, Bruce A. Griffin, Christine M. Williams

Abstract—The study assessed the efficacy of fish oil supplementation in counteracting the classic dyslipidemia of the atherogenic lipoprotein phenotype (ALP). In addition, the impact of the common apolipoprotein E (apoE) polymorphism on the fasting and postprandial lipid profile and on responsiveness to the dietary intervention was established. Fifty-five ALP males (aged 34 to 69 years, body mass index 22 to 35 kg/m², triglyceride [TG] levels 1.5 to 4.0 mmol/L, high density lipoprotein cholesterol [HDL-C] <1.1 mmol/l, and percent low density lipoprotein [LDL]-3 >40% total LDL) completed a randomized placebo-controlled crossover trial of fish oil (3.0 g eicosapentaenoic acid/docosahexaenoic acid per day) and placebo (olive oil) capsules with the 6-week treatment arms separated by a 12-week washout period. In addition to fasting blood samples, at the end of each intervention arm, a postprandial assessment of lipid metabolism was carried out. Fish oil supplementation resulted in a reduction in fasting TG level of 35% (P<0.001), in postprandial TG response of 26% (TG area under the curve, P<0.001), and in percent LDL-3 of 26% (P<0.05). However, no change in HDL-C levels was evident (P=0.752). ANCOVA showed that baseline HDL-C levels were significantly lower in apoE4 carriers (P=0.035). The apoE genotype also had a striking impact on lipid responses to fish oil intervention. Individuals with an apoE2 allele displayed a marked reduction in postprandial incremental TG response (TG incremental area under the curve, P=0.023) and a trend toward an increase in lipoprotein lipase activity relative to non-E2 carriers. In apoE4 individuals, a significant increase in total cholesterol and a trend toward a reduction in HDL-C relative to the common homozygous E3/E3 profile was evident. Our data demonstrate the efficacy of fish oil fatty acids in counteracting the proatherogenic lipid profile of the ALP but also that the apoE genotype influences responsiveness to this dietary treatment. (Arterioscler Thromb Vasc Biol. 2000;20:1990-1997.)

Key Words: atherogenic lipoprotein phenotype ■ apoE genotype ■ fish oils ■ plasma lipids

The importance of hypertriglyceridemia as a risk factor for coronary heart disease (CHD) is now well established.1-5 In addition to the ability of triglyceride-rich lipoproteins to directly infiltrate and sequester cholesterol in the atheroma,6 raised circulating triglycerides (TG) have been implicated as a major metabolic component of an “atherogenic lipoprotein phenotype” (ALP),7,8 a term frequently used to describe a collection of proatherogenic lipoprotein abnormalities. The ALP lipid profile, which occurs in up to 25% of middle-aged males,9 is associated with a 3-fold increased CHD risk.10,11 It is characterized by a moderate fasting hypertriglyceridemia (1.5 to 4.0 mmol/L), exaggerated postprandial lipemic responses, low HDL cholesterol (HDL-C) levels (<1.1 mmol/L), and a predominance of the potentially atherogenic small dense LDL-3 particle (>40% of total LDL).8,12,13 The hypotriglyceridemic effect of fish oils is well documented, with a recent meta-analysis concluding that 3 to 4 g of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) per day resulted in a 25% and 34% decrease in fasting TG levels in normolipidemic and hyperlipidemic individuals, respectively.14 The efficacy of fish oil consumption in reducing the magnitude and duration of postprandial lipemic responses has also been demonstrated in a limited number of studies, although high levels of intake have often been used.12,15-19 Despite the potential benefits of fish oil supplementation in counteracting the characteristic fasting and postprandial dyslipidemia of the ALP, no study has yet investigated the efficacy of this dietary intervention in an ALP group.

Responsiveness of plasma lipids to dietary manipulations is highly variable, with diet-gene interactions thought to explain, in part, interindividual responses.20 In addition, polymorphisms at specific gene loci are thought to be significant determinants of fasting lipid levels21 and may also explain the highly heterogeneous nature of individuals’ postprandial responses to a standard fat load. ApoE is a functional and structural component of several classes of lipoproteins, including chylomicrons, VLDLs, and their remnants, and has

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a major influence on the metabolism and clearance of these particles by the liver. Three common isoforms of this gene loci exist, yielding apoE2, apoE3, and apoE4, with ~55% to 60% of the population homozygous for the E3 allele.

Population studies have shown that plasma cholesterol, LDL cholesterol (LDL-C), and apoB levels are highest in subjects with an E4 allele, intermediate in individuals homozygous for E3, and lowest in those with an E2 allele, with some evidence of greater responsiveness to cholesterol-lowering diets in subjects with an E4 allele. Data on the impact of apoE genotype on circulating TG levels are less consistent. In a meta-analysis published in 1992, Dallongeville et al concluded that although not observed in all studies, the apoE2 and apoE4 alleles result in moderately higher fasting TG levels in the general population. Although the association between the homozygous E2/E2 genotype and delayed postabsorptive triglyceride-rich lipoprotein clearance has been repeatedly demonstrated, this genotype is present in <1% of the population, and data on the impact of the more common apoE2/E3, apoE3/E4, and apoE4/E4 genotypes on lipemic responses have produced conflicting findings.

Although the effects of the apoE genotype on lipoprotein metabolism and responsiveness to dietary fat restriction have been extensively studied in various populations, no study has examined the association between this polymorphism and the lipid profile of the ALP or the responsiveness to fish oil supplementation. This is surprising in view of the central role of apoE in TG metabolism, the well-established defect in TG metabolism in an ALP, and the extensively studied TG-lowering actions of fish oils in normolipidemic and hyperlipidemic individuals.

The present study aims to examine the efficacy of fish oil supplementation in counteracting the dyslipidemia of the ALP. In addition, the impact of the apoE genotype on the baseline lipid profile and on lipoprotein responsiveness to the intervention treatment is investigated.

Methods

Study Subjects
Fifty-five healthy male volunteers, aged 30 to 70 years, were recruited through a database held at the Department of Clinical Pathology, Royal Berkshire Hospital, Reading, UK. All blood samples taken for lipid assessment in the West Berkshire Health District were analyzed at the Royal Berkshire Hospital, and the data were stored on computer for up to 5 years. Individuals considered to be at risk of an ALP, with a lipid profile of TG 1.5 to 4.0 mmol/L, total cholesterol (TC) 5.0 to 8.0 mmol/L, and HDL-C <1.1 mmol/L, were sent a letter (via their general practitioners) giving brief details of the objectives and protocol of the study. Those interested in participating attended the Hugh Sinclair Unit of Human Nutrition and completed a health and lifestyle questionnaire and provided a fasting screening blood sample. Exclusion criteria for participation in the study were as follows: diagnosed diabetes or fasting glucose >6.5 mmol/L, liver or other endocrine dysfunction, evidence of cardiovascular disease (including angina), smoking, hypolipidemic therapy or any other medication known to interfere with lipid metabolism, consumption of fatty acid supplements, weight-reducing diets, body mass index >35 kg/m2, blood pressure >160/95 mm Hg, and hemoglobin <130 g/L. The University of Reading and the West Berkshire Health Authority Ethics Committees approved the study protocol, and each individual gave written consent before participating. ApoE genotyping was performed on 50 individuals. Therefore, the data in the present study reflect 50 of the 55 individuals who completed the study.

Study Design

The study was a double-blind placebo-controlled crossover study with subjects consuming 6 g of fish oil (27.9% EPA and 22.3% DHA, Pikasol, Lube A/S) or 6 g of olive oil (placebo, Lube A/S) per day for 6 weeks. After a washout period of 12 weeks, subjects were placed on the opposite supplementation regime. The oils were provided as six 1-g oil capsules, with the fish oil supplements providing a total of 3.0 g of the long-chain n-3 fatty acids (EPA and DHA) per day. Fasting blood samples (30 mL) were collected at 0, 3, and 6 weeks for each treatment, and at the end of each supplementation period (6 weeks), a postprandial assessment was carried out. Compliance was monitored by examining platelet membrane fatty acid composition in a randomly chosen subgroup (n = 22).

Postprandial Protocol

After a 12-hour overnight fast, each participant completed a postprandial assessment. The previous day, no strenuous exercise or alcohol was permitted, and a standard evening meal containing <20 g fat was provided to standardize short-term fat intake. Before consuming the test meals, an indwelling cannula was inserted into the antecubital vein of the forearm, and a fasting blood sample (30 mL) was taken. A relatively high-fat breakfast providing 49 g fat, 109 g carbohydrate, and 18 g protein (start time, 0 minutes) and lunch providing 31 g fat, 63 g carbohydrate, and 15 g protein (330 minutes) were provided. Blood samples (11 mL) were collected at 0, 30, 60, 90, 150, 210, 270, 330, 360, 390, 420, and 480 minutes to assess postprandial TG and nonesterified fatty acids (NEFA). At 480 minutes, 100 IU/kg of heparin was administered intravenously, and a 5-mL blood sample was collected at 15 minutes into lithium heparin tubes to determine postheparin lipoprotein lipase (LPL) activity.

Biochemical Analysis

Fasting and postprandial venous blood samples were collected into 10-mL potassium EDTA tubes. All blood samples, except those collected for platelet phospholipid fatty acid composition, were centrifuged at 1600g for 10 minutes, and subsamples of plasma were stored at −20°C for TG, TC, and NEFA analysis. A 10-mL plasma sample was collected for determination of LDL subclass distribution; this sample was stored at 4°C and analyzed within 24 hours. The plasma collected for the determination of LPL activity was stored at −80°C. HDL-C was determined by measuring cholesterol in the supernatant after precipitation of the apoB-containing lipoproteins by use of dextran sulfate and magnesium chloride. LDL-C levels were computed by using the Friedewald formula.

Plasma samples were analyzed for TG, TC, HDL-C, and NEFA by using the Monarch Automatic Analyser (Instrumentation Laboratories Ltd). LDL activity was determined by using the method described by Nilsson-Ehle et al. LDL subclasses were separated by density-gradient ultracentrifugation, and the relative percentage of small dense LDL-3 was calculated by integrating the respective area under the LDL subclass profile, as previously described by Griffin et al. Postprandial TG responses were expressed as area under the curve (AUC, 0 to 480 minutes) or incremental area under the curve (IAUC, 0 to 480 minutes), calculated by use of the trapezoidal rule. Because of the shape of the postprandial NEFA response, NEFA AUC (0 to 480 minutes) is difficult to interpret, with circulating NEFA concentrations dropping below baseline levels in the early postprandial period; therefore, in the data analysis, the postprandial responses were represented as NEFA AUC (270 to 480 minutes).

Platelets were extracted from whole blood according to the methods of Indu and Ghafoorunissa and stored at −80°C for platelet phospholipid fatty acid analysis. Butylated hydroxytoluene was added to all solvents at a concentration of 50 mg/mL to minimize auto-oxidation during analysis. One hundred microliters of phosphatidylethanolamine diheptadecanoic acid (0.25 mg/mL in chloroform) was added as an internal standard to all samples. Lipids were extracted with chloroform/methanol (2:1 [vol/vol]) according to the method of Folch et al, and the phospholipid fraction was isolated.

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from the crude lipid by using a Sep-Pack C18 column (Waters Associates). The phospholipids were transmethylated by using a 1.5% sulfuric acid in methanol solution, and the fatty acids were quantified by gas liquid chromatography with use of a CPSil 88 column (Chrompak).36

### ApoE Genotyping

DNA was extracted from 10 mL of blood collected after an overnight fast into a potassium-EDTA tube. ApoE genotyping was performed by using the method of Bolla et al.39

### Statistical Analysis

Group results are expressed as mean ± SEM. The data were checked for normality, and skewed parameters were logarithmically transformed before statistical analysis. The significance of any impact of the apoE genotype on the fasting biochemical profile of the ALP participants was established by 1-way ANCOVA, with age as the covariate. Post hoc comparisons of the lipoprotein variables between the apoE genotype and age as the covariate. Significantly lower HDL-C was evident in the E4 carriers relative to noncarriers; however, these differences failed to reach significance when age was included as a covariate. Significantly lower HDL-C was evident in the E4 group (P = 0.035). Although not of statistical significance, lower TG AUC and IAUC and higher postheparin LPL activity were evident in the E3 group. Fasting and postprandial (270 to 480 minutes) NEFA concentrations were comparable in the 3 apoE subgroups (Table 1).

In the ALP group as a whole (n = 50), fish oil supplementation resulted in significant reductions of 35.3% (P < 0.000), 23.3% (P = 0.000), and 7.9% (P = 0.007) in fasting TG, TG AUC, and TG IAUC, respectively (Table 2, Figure 1). ApoE genotype had little impact on responsiveness of the fasting TG fraction; however, the apoE2 allele was associated with a greater reduction in postprandial responses after supplementation. TG IAUC, which represents the postprandial TG response minus the baseline TG levels, is more representative of postprandial clearance than is TG AUC, which represents fasting and postprandial TG metabolism. A significantly greater reduction in TG IAUC (P = 0.023) was evident in the

### Results

The mean ± SEM age, body mass index, lipid, and LPL activity profile of the group (n = 50) and of the apoE subgroups are given in Table 1. In accordance with the recruitment strategy, participants displayed an ALP blood lipid profile with group mean ± SEM fasting TG, HDL-C, and percent LDL-3 of 2.48 ± 0.12 mmol/L, 0.97 ± 0.12 mmol/L, and 61 ± 3%, respectively. Relative allele frequencies of 0.09 E2, 0.69 E3, and 0.23 E4 were observed. No individual expressed an E2/E2 genotype, and because the homozygous E4/E4 (n = 2) genotype sample size was small, individuals were classified into the following 3 phenotypes: (1) apoE2 group (n = 8), carrying the E2/E2 genotype; (2) apoE3 group (n = 22), carrying the most common E3/E3 phenotype; and (3) apoE4 group (n = 20), carrying either the E3/E4 or E4/E4 genotype. One individual with an apoE2/E4 genotype could not be assigned to any of the groups and was therefore excluded from the data analysis.

Age, body mass index, TG, and percent LDL-3 were comparable among the 3 apoE subgroups (Table 1). There was a trend toward higher TG, LDL-C, and TC/HDL-C ratio in E4 carriers relative to noncarriers; however, these differences failed to reach significance when age was included as a covariate. Significantly lower HDL-C was evident in the E4 group (P = 0.035). Although not of statistical significance, lower TG AUC and IAUC and higher postheparin LPL activity were evident in the E3 group. Fasting and postprandial (270 to 480 minutes) NEFA concentrations were comparable in the 3 apoE subgroups (Table 1).
apoE2 group (27.2%) relative to either the apoE3 group (2.7%) or the apoE4 group (5.5%; Table 2, Figure 2).

Fish oil supplementation resulted in a 7.1% increase in the LDL-C fraction in the overall group (P=0.054); however, little change in TC or HDL-C levels was evident (Table 2, Figure 1). The apoE4 group demonstrated a shift in the cholesterol profile relative to non-E4 carriers, with a 3.5% increase in TC (P=0.014), a 7.4% decrease in HDL-C (P=0.065) composition of platelet membrane phospholipids were similar at the beginning of each arm of the study (data not shown), indicating that the washout period.

A significant 7.8% decrease in fasting NEFA (P=0.012), a 7.4% decrease in NEFA AUC (270 to 480 minutes, P=0.002), and a 14.7% increase in postheparin LPL activity (P=0.065) were also observed in the overall group (Table 2).

Although there is a trend toward greater responsiveness of these outcome measures to fish oil supplementation in individuals with an E2 allele (Figure 2), large interindividual differences meant that differences failed to reach significance.

Compliance was monitored by using platelet membrane fatty acid composition. Fish oil supplementation resulted in a highly significant increase in platelet membrane EPA and DHA concentration, from 0.53% to 3.16% (P=0.000) and from 2.50% to 3.61%, respectively (P=0.000, Table 3).

Fasting TG (2.51 versus 2.55 mmol/L, P=0.329) and the EPA (0.53% versus 0.66%, P=0.227) and DHA (2.55% versus 2.58%, P=0.768) composition of platelet membrane phospholipids were similar at the beginning of each arm of the study, indicating that the washout period.
was sufficient to reverse the metabolic effects and tissue accumulation of EPA and DHA.

**Discussion**

The aim of the present investigation was to determine the efficacy of fish oil supplementation in counteracting the classical dyslipidemia of the ALP. The impact of the common apoE polymorphism on the fasting lipid and postprandial profile and on the responsiveness to the fish oil intervention was also investigated.

Forty percent of the ALP subjects in the study were either heterozygous or homozygous for the apoE4 allele, which is higher than the 25% to 27% prevalence reported in numerous population studies. Clinical studies have suggested a predisposing role for E4 in the development of atherosclerosis and cardiovascular disease, which is thought to reflect an adverse

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**Figure 2.** Impact of apoE genotype on postprandial TG (a through c) and NEFA (d through f) responses. Incremental TG response represents the total postprandial response minus the fasting levels.

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**TABLE 3.** Presupplementation and Postsupplementation Platelet Membrane PUFA Composition

<table>
<thead>
<tr>
<th></th>
<th>Olive Oil</th>
<th>Fish Oil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 wk</td>
<td>6 wk</td>
</tr>
<tr>
<td>C18:2</td>
<td>5.78±0.18</td>
<td>5.84±0.16</td>
</tr>
<tr>
<td>C20:4</td>
<td>24.31±0.54</td>
<td>24.86±0.33</td>
</tr>
<tr>
<td>C20:5</td>
<td>0.65±0.13</td>
<td>0.86±0.17</td>
</tr>
<tr>
<td>C22:6</td>
<td>2.64±0.13</td>
<td>2.72±0.17</td>
</tr>
</tbody>
</table>

Values are mean±SEM. C18:2 indicates linoleic acid; C20:4, arachadonic acid; C20:5, eicosapentaenoic acid; and C22:6, docosahexaenoic acid.

*The statistical significance of group (n=22) changes in fatty acid composition were calculated by repeated-measures ANOVA, with time and oil supplement (fish oil and olive oil) as the independent variables.

†Percent platelet membrane phospholipid fatty acids.
effect of this polymorphism on circulating LDL particle numbers that is due to the downregulation of LDL receptors. The role of apoE in lipoprotein metabolism and clearance has been extensively studied in recent years.

In present study, we have observed the expected trend in TC and LDL-C, with levels in E2 carriers lower and in E4 carriers higher than those observed in the homozygous E3/E3 subgroup. The intergroup differences were comparable with the 0.1- to 0.5-mmol/L differences reported in previous large-scale population studies. However, because of the relatively small sample size in the present study, the effect of apoE genotype on these outcome measures failed to reach statistical significance.

HDL-C levels were ≈10% lower in ALP subjects who were E4 carriers, and these intergroup differences were found to be significant. This finding is in agreement with the lower circulating HDL-C concentration reported in individuals with the E4/E3 genotype in 17 of 28 studies examined in a recent meta-analysis. Removal of HDL from the circulation occurs by a variety of pathways, including an apoE-dependent receptor–mediated pathway and a hepatic lipase catabolic pathway. Although the precise biochemical origin of the low HDL-C in E4 individuals remains to be established, the previously reported preferential association of the E4 protein with VLDL rather than transfer of a large portion back to HDL, lower total apoE concentrations in E4 individuals, or altered lipase activities associated with apoE genotype may be involved.

In the present study, we observed no relationship between apoE polymorphism and baseline fasting or postprandial TG levels in subjects with an ALP profile. Divergent results are reported in the literature regarding the impact of the apoE genotype on the responsiveness of this pathway. Notably, in TG IAUC in these subgroups. However, in E2 carriers, a 28% reduction in the postprandial increase in circulating TG levels (TG IAUC) was evident after fish oil supplementation in addition to the 31% reduction in fasting TG levels. An associated 47% increase in LPL activity was observed in this apoE subgroup, which was higher than that in other subgroups.

In the group as a whole, the fish oil intervention resulted in a borderline significant 15% increase in LPL activity. A limited number of human studies have generally failed to show an increased postheparin LPL activity with high fish oil diets, although 2 recent reports have found significant increases. Zampelas et al have shown elevated postheparin LPL activity 9 hours after meals enriched with n-3 PUFA compared with saturated fatty acid, and Harris et al observed a 62% increase in endogenous LPL activity in healthy volunteers after 3 weeks of fish oil supplementation (5 g/d). Several mechanisms may be responsible for this observed increase in LPL activity, including changes in LPL gene expression, transport of newly synthesized LPL to the vascular wall, or a change in NEFA metabolism. Circulating NEFA is a potent inhibitor of LPL, with a buildup of released NEFA at the capillary endothelium, resulting in the detachment of LPL from the vascular walls, thereby losing its hydrolytic activity. In the present study, there was a trend toward a greater reduction in fasting and postprandial NEFA concentrations in the apoE2 subgroup, indicative of more effective NEFA removal from the circulation, which may have contributed to the greater increase in LPL activity in this subgroup.

In addition to the impact on the TG profile, fish oil intervention also had a marked influence on TC and LDL-C levels and on the LDL density profile. Because LDL is derived from VLDL catabolism, reductions in VLDL might be expected to lower LDL-C. However, in agreement with previous studies, an increase (7%) in levels was observed in the group as a whole. In addition to suppressing VLDL production, n-3 PUFA is also known to influence VLDL composition, with a shift in the distribution of VLDL subclasses toward the smaller VLDL particles. Because smaller VLDL particles represent the primary precursor of LDL, this qualitative change in VLDL may result in a greater rate of conversion to LDL. The adverse effect of fish oils on LDL-C was strongest in E4 carriers, in whom a 16% increase was observed. ApoE4 is known to selectively associate with VLDL, which may enhance its catabolism to LDL (via the apoE-dependent catabolic pathway) and, in combination with the downregulated state of the LDL receptor in this subgroup, may explain the greater increase in LDL-C levels. This potentially proatherogenic increase in LDL concentrations, particularly in the apoE4 carriers, may be offset by the significant reduction in the percentage of LDL as LDL-3. Caution is required in drawing conclusions regarding the
atherogenic consequences of these 2 opposing changes, because lack of LDL compositional data means that it is not possible to calculate the absolute concentration of cholesterol in the LDL subfractions, which may be the relevant measure. Although strong correlations between TG and LDL–3 concentrations have been observed in a recent study of ours (data not shown)65 and other studies,11,12 early work investigating the impact of n-3 PUFAs on the LDL profile failed to observe any beneficial changes in LDL composition changes.5,6,7,8,9 However, these studies used indirect measures of LDL particle size and composition, because density gradient ultracentrifugation techniques used in the present study were not available. More recent studies are in agreement with our findings,67,68 although Homma et al99 actually found decreases in LDL particle size after n-3 PUFAs supplementation, and Patti et al100 observed no change in LDL composition in patients with non–insulin-dependent diabetes mellitus after fish oil treatment.

In conclusion, the presence of an apoE4 allele exaggerates the HDL abnormalities of the ALP. Fish oil supplementation is effective in correcting fasting and postprandial ALP dyslipidemia. However, apoE genotype is an important determinant of responsiveness to this dietary intervention. The greatest benefits were evident in apoE2 carriers, in whom the observed reduction in fasting and postabsorptive TG levels, a decrease in the atherogenic LDL–3, and a trend toward higher HDL–C levels would be expected to be associated with a clinically meaningful reduction in CHD risk. In apoE4 carriers, the hypotriglyceridemic benefits may be counteracted by a potential proatherogenic shift in the cholesterol profile.

Acknowledgments

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