The effect of apolipoprotein E genotype on serum lipoprotein particle response to exercise

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Received 16 June 2004; received in revised form 30 March 2005; accepted 1 June 2005
Available online 13 July 2006

Abstract

Exercise affects lipoprotein metabolism and apolipoprotein E (Apo E) genotype may alter changes in lipoprotein subclasses that occur with exercise. The present study examined the effects of Apo E genotype (APOE) on the response of lipoprotein subclass concentrations to long-term exercise. A prospective longitudinal study, conducted at seven centers, genetically screened 566 individuals to create three cohorts of healthy adults, equal for gender and the most common APOE variants: E2/3 (n = 35), E3/3 (n = 40), and E3/4 (n = 31). Subjects with body mass index (BMI) ≥31 or evidence of dyslipidemia or metabolic disease were excluded. All subjects exercised aerobically at 75% of maximal heart rate for 40 min, four times weekly for 6 months. Fasting lipoprotein subpopulations were measured before and after exercise training using proton nuclear magnetic resonance spectroscopy. Serum lipids for the entire cohort did not change with exercise training, but the LDL subpopulation response varied by APOE. Small-sized LDL particles decreased only in the APOE3 homozygotes whereas medium-sized LDL particles increased only in this group. These changes were directionally different from the responses in the E2/3 and E3/4 subjects (p < 0.05).

Neither exercise nor APOE variant affected overall LDL or HDL size or cholesterol concentration, but exercise decreased VLDL diameter by 3.5 nm (p < 0.001) attributable to decreases in large VLDL in each APOE group. In conclusion, APOE variants influence the serum LDL subpopulation response to exercise training in normolipidemic subjects. Subjects homozygous for APOE3 experienced the most beneficial lipid effects from exercise training.

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Keywords: Apo E; Lipoproteins; Particle size; Aerobic exercise; Lipid metabolism

1. Introduction

Lipoprotein subclass levels and particle size distributions convey information about cardiovascular disease (CVD) risk not provided by traditional blood lipid measures [1–4]. Nuclear magnetic resonance (NMR) analysis offers a rapid
and efficient means of assessing the concentrations of 15 lipoprotein subclasses of varying size, as well as the overall average particle sizes of very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL) [5]. Small LDL particles indicate increased CVD risk [6].

Apolipoprotein E (Apo E) facilitates triglyceride clearance by mediating the binding of triglyceride-rich particles to hepatic receptors [7], and common Apo E genotype (APOE) variants (E2/3, E3/3, and E4/3) modulate LDL metabolism [8]. APOE genotype is hypothesized to differentially affect the formation of small, medium, and large LDL particles [9], at least in part through the unique structural and biophysical properties that distinguish the three most common allelic isoforms of Apo E (E2, E3, and E4). These characteristics differentially affect the binding affinity of Apo E to hepatic receptors [10], the activation of hepatic lipase by Apo E [11], and the strength of Apo E interactions with heparan sulfate proteoglycans [12], all of which are involved in the conversion of triglyceride-rich particles to LDL particles [9].

We have recently shown that common APOE variants affect the lipid response to 6 months of aerobic exercise [13]. Exercise decreased the LDL-cholesterol to HDL-cholesterol ratio in subjects with the APOE3/3 genotype (the most common APOE genotype [14]), but did not alter the LDL/HDL-cholesterol ratio in APOE2/3 or 4/3 subjects [13]. Others have demonstrated that exercise can decrease small LDL-cholesterol and/or increase overall LDL size [15–19], but genotype or phenotype analysis of Apo E was not performed and these studies cannot determine whether the APOE variants affect the lipoprotein particle response to long-term exercise training. We used NMR spectroscopy to obtain a detailed analysis of lipoprotein particle subpopulations and to examine further the effects of the most common APOE variants on the lipoprotein particle cholesterol responses to exercise training [13].

Approximately 10% of the population have the APOE2/3 genotype whereas 20% have APOE4/3 [14]. The focused study of APOE2/3 and 4/3 individuals through random sampling of the population yields few APOE2/3 or 4/3 subjects thereby increasing the number of subjects required to obtain sufficient sample sizes of the less frequent genotypes. This is a major problem for exercise training studies, which are labor intensive for both the subjects and investigators. Consequently, as described previously [13], we recruited subjects based on APOE genotype to create a study cohort in which the APOE2/3 and 4/3 genotypes were over-represented.

2. Methods

2.1. Study overview

This study was conducted by the Exercise and Genetics Collaborative Research Group, a consortium of investigators at seven institutions*. Informed consent was obtained from 566 individuals screened for APOE genotype. Screening ceased when 50–60 subjects each with the less common APOE2/3 and 4/3 genotypes – enough to statistically power the study – were identified. Fifty-seven, 60, and 57 subjects representing the APOE2/3, 3/3, and 3/4 genotypes, respectively, entered the study. Of these, 120 completed the 6-month exercise program. In 14 subjects, samples were not obtained either at the pre- or post-training timepoint, leaving complete NMR-lipoprotein data for 106 subjects.

2.2. Subjects

Subjects were recruited if they were: healthy and without orthopedic problems, non-smokers, physically inactive, between 18 and 70 years of age, had a body mass index (BMI) ≤ 31, and consumed less than two alcoholic beverages daily. Subjects were considered physically inactive if they participated in vigorous activity less than four times/month for the prior 6 months. Subjects underwent a medical history, physical exam, and a maximal exercise test to detect unreported abnormalities and occult coronary artery disease. They were reimbursed US$ 250 at the end of the study.

2.3. APOE genotype determination

DNA was extracted from leukocytes and APOE variants determined using standard techniques [20].

2.4. Serum lipoprotein measurements

Serum was obtained after a 12 h fast before the start and after 6 months of exercise training. Post-training samples were obtained within 24 h of the penultimate and final exercise training session. Lipid levels in women before and after training were obtained within 10 days of the onset of menses to avoid variations in lipoprotein values [21]. Lipoprotein subclass population levels and mean particle size were determined by NMR spectroscopy as previously described [1]. Concentrations of six VLDL subclasses (V1–V6), intermediate density lipoproteins (IDL), three LDL subclasses (L1–L3), and five HDL subclasses (H1–H5) were determined. The L1–L3 subclasses were designated small, medium, and large LDL, respectively. Large VLDL was the sum of the V5 + V6 fractions; medium VLDL, the sum of V3 + V4; small VLDL, the sum of V1 + V2. Similarly, H1 + H2 were summed to give small HDL-cholesterol and the sum of H3–H5 was taken as large HDL-cholesterol. The lipid results in the present report differ slightly from our prior report [13] which determined lipids by enzymatic techniques. The present report presents only NMR-derived lipid values. Total serum triglycerides are determined enzymatically in both reports [13].

2.5. Anthropometric measurements

Body weight and height were measured using balance beam scales and wall mounted tape measures. Waist and hip
girth measurements were taken using a cloth tape measure [22].

2.6. Maximal exercise capacity

Subjects underwent two pre- and one post-training maximal treadmill exercise tests. The first pre-training test was designed to detect occult ischemia and to familiarize subjects with the measurement protocol, but was not used in data analysis. The second pre-training test and the post-test used the modified Astrand protocol [23]. Blood pressure and 12-lead electrocardiogram, as well as expired oxygen, carbon dioxide, and ventilatory volume were measured. Each test site used its own metabolic measurement system for cardiorespiratory measurements and followed manufacturers’ calibration procedures. Maximal oxygen uptake was defined as the average of the two highest consecutive 30-s values at peak exercise.

2.7. Dietary control procedures

Subjects were asked to maintain their usual dietary composition throughout the study. Dietary calories and composition were assessed by random, 24-h dietary recall [24]. Trained dieticians called the subjects by telephone on 1 weekday and 1 weekend day before the start and during the last month of exercise training. Results from the two calls were averaged to estimate dietary intake.

2.8. Exercise program

Subjects underwent a 6-month, progressive, supervised exercise program. Exercise session duration was increased from 15 to 40 min during the first 4 weeks. Subjects exercised between 60 and 85% of their maximal exercise capacity based on pre-training maximal heart rate. Once subjects could perform 40 min of exercise, they continued this duration of exercise 4 days a week for an additional 5 months. Subjects also participated in 5 min of warm-up and cool-down so that each workout required 50 min. Subjects used a variety of exercise modalities including treadmills, stationary cycles, cross-country ski machines, stair steppers, and rowing machines.

2.9. Exercise energy expenditure

Weekly exercise energy expenditure expressed as kilocalories per week was estimated from the average heart rates recorded for exercise sessions of that week. From individual, pre-training maximal exercise test data plots of oxygen uptake (VO2) versus heart rate, we estimated the VO2 corresponding to the exercise HR intensity and multiplied that VO2 by bout duration (in minutes) to obtain total oxygen consumption for each bout. Each liter of oxygen was assumed to represent 5 kcal of energy expenditure.

2.10. Data analysis

The main purpose of the study was to investigate whether APOE affects LDL and HDL subpopulation responses to exercise. Of secondary interest were gender interactive effects. To test for these effects, 3 (genotype) × 2 (gender) analyses of variance (ANOVA) were used for variables that passed Levene’s test for equality of variances. In the absence of a gender effect, the APOE genotype effect on change scores was analyzed using analysis of covariance was employed using baseline concentrations and change in triglycerides as covariates (p ≤ 0.1). Post hoc tests (Fisher’s L.S.D.) were employed when F ratios were significant. For hypothesis testing, significance levels were two-sided with alpha = 0.05.

3. Results

3.1. Baseline values

The numbers of men and women were similar across genotypes (Table 1). There were no differences in baseline anthropometric or exercise performance parameters among the three APOE genotype groups [13]. Pre-training LDL-cholesterol concentrations were higher in the APOE3/3 compared with the APOE2/3 subjects (Table 2). When adjusted

<table>
<thead>
<tr>
<th>Variable</th>
<th>APOE genotype</th>
</tr>
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<tbody>
<tr>
<td>N, male/female</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td></td>
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<tr>
<td>VO2 max (mL/(kg min))</td>
<td></td>
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<tr>
<td>Changes with training</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td></td>
</tr>
<tr>
<td>VO2 max (mL/(kg min))</td>
<td></td>
</tr>
</tbody>
</table>

Table 1
Subject characteristics by APOE group
for the significant confounding effects of waist-to-hip ratio, triglycerides, and percent body fat, baseline LDL-C levels in Apo E2/3, E3/3, and E4/3 were 118.7 ± 5.0, 136.2 ± 4.8, and 138.0 ± 5.2 mg/dL, respectively (p < 0.05, 2/3 versus 3/3 or 4/3). There were no other baseline differences in serum lipids, lipoprotein classes, or particle size (Tables 2 and 3).

### 3.2. Effects of exercise training

VO₂ max increased 10.1% with exercise in the 106 subjects. As presented in detail elsewhere [13], the increase in VO₂ max was significantly less in the APOE3/3 subjects than in the other two APOE groups. Exercise energy expenditure averaged 14.5 ± 1 kcal/kg per week during the last 2 weeks of training and was not different across groups. In the 106 subjects studied presently, body weight decreased 1.0 ± 0.3 kg (p < 0.001), BMI fell 0.3 ± 0.1 units (p < 0.003), and waist circumference fell 0.63 ± 0.19 in. (p < 0.055) overall as before [13]. There were no other significant changes in anthropometric, exercise, or dietary parameters with exercise training and no differences in anthropometric changes among the Apo E genotype groups.

Serum lipids for the entire cohort were altered little by exercise training, although triglycerides in the 106 studied here decreased 14% (136.0 ± 89.9–118.9 ± 7.9 mg/dL) (p < 0.0003). LDL particle subpopulations changed significantly with exercise training and the changes were dependent on APOE genotype (Fig. 1). Large VLDL decreased with exercise in all subjects (F ratio = 9.22, p < 0.01) with no genotype effect for any VLDL subclass response (Fig. 1, Panel A). Large VLDL also decreased in men (p < 0.05, not shown), and tended to decrease in women (p < 0.17, not shown). Medium-sized LDL increased whereas small-sized LDL-cholesterol decreased in APOE3 homozygotes. These changes were directionally different from responses in the APOE2/3 and 3/4 subjects (Fig. 1, Panel B) and statistically significantly different from APOE2/3 (p < 0.01) and 3/4 for medium LDL (p < 0.05), and from APOE2/3 and 3/4 for small LDL (p < 0.05) (Fig. 1, Panel B). The training change in large HDL was directionally different in APOE3/3 versus APOE2/3 and 3/4 but this was not statistically significant (Fig. 1, Panel C, p < 0.18).

The change for each LDL subpopulation was significantly related to the respective baseline concentration (−0.41 to −0.48, p < 0.00001), but poorly related to changes in BMI, waist circumference, and percent body fat (Table 4). Baseline values for BMI, waist circumference, and percent body fat were unrelated to LDL subclasses (not shown). Fig. 1 presents estimated means statistically adjusted for the baseline small, medium, or large LDL concentration and the change in log triglycerides. The adjusted means (± S.E.M.) for APOE2/3, 3/3, and 4/3 groups were 9.9 ± 6.4, 7.3 ± 6.0, and 8.4 ± 6.7 mg/dL, respectively, for large LDL-cholesterol (APOE group effect, F ratio = 0.05, p NS); −14.9 ± 4.8, 9.0 ± 4.5, and −6.8 ± 5.1 mg/dL for medium LDL (F ratio = 6.91, p < 0.002); 5.0 ± 4.7, −8.4 ± 4.3, and 6.6 ± 4.9 mg/dL for small LDL (F ratio = 3.35, p < 0.039).

The APOE effect on LDL particle subclasses was generally similar across gender (data not shown). Neither training nor APOE affected overall LDL or HDL diameter (Table 3). Training decreased VLDL diameter by 3.5 nm overall (p < 0.01) due entirely to decreases in large VLDL in each group (Fig. 1, Panel A).
4. Discussion

The present study is to our knowledge the first to demonstrate that the effect of aerobic exercise training on lipoprotein subpopulations varies by common APOE variant. Specifically, exercise training in APOE3/3 subjects decreased small LDL particle cholesterol and raised medium LDL particle cholesterol concentrations, whereas the opposite changes in these subfractions were observed in the APOE2/3 and 4/3 subjects. This response was true for the entire cohort and the pattern existed in both men and women.

Several studies have examined the effect of exercise on LDL particle size but without regard to APOE variant. Williams et al. [15] used analytic ultracentrifugation to demonstrate lower small LDL and higher large HDL mass in runners compared to sedentary men. In another study, LDL mean particle size decreased slightly in 46 previously sedentary men after 1 year of exercise training and the decrease in small LDL was inversely related to running mileage [17]. Using NMR spectroscopy to measure LDL small, medium and large subpopulations, Kraus et al. [18] and Kang et al. [19] confirmed that exercise increased the mean diameter of LDL by decreasing the small LDL subclass concentration [18,19].

Small dense LDL particles appear more atherogenic than other LDL subpopulations [25]. Though the seven subclasses of LDL determined by gradient gel electrophoresis (GGE) do not directly correspond to the LDL subpopulations measured by NMR spectroscopy, it is reasonable to assume both methods measure cholesterol native to atherogenic small LDL particles. Both NMR spectroscopy and GGE detect clinically relevant changes in LDL subpopulations in response to pharmacologic treatments [26].

How APOE influences the LDL subpopulation response to exercise training is unclear, but must result from differences in clearance and/or production of the individual particles. Apo E is found on both triglyceride-rich and HDL particles. The Apo E2, E3 and E4 isoforms differentially affect the rate of hepatic clearance of Apo E-containing chylomicrons, VLDL, and IDL, through their interactions with the LDL family of receptors [7]. Apo E has 299 amino acids with a binding region between amino acids 140 and 160. Apo E3, the most common or “wild-type” Apo E, contains a cysteine at amino acid 112 and an arginine within the binding region at amino acid 158 [10]. The E4 variant contains an arginine at the 112 site and has normal or enhanced binding to the LDL (B/E) receptor. The E2 variant contains a cysteine substitution within the binding region at amino acid 158 and has only 1–2% of normal binding capacity reducing clearance of Apo E2 containing particles [10]. Apo E3 and E4 protein iso-
forms also bind with higher affinity to the lipoprotein receptor like protein than does Apo E2 [27]. The higher affinity of E3 and E4 and their more rapid clearance increases the hepatic cholesterol pool and downregulates the hepatic receptor population, producing higher fasting LDL-cholesterol concentrations in E3 and E4 compared to E2 [14]. In addition, the in vivo clearance of E4 is greater than E3 [28] due to the preferential association of E4 with VLDL over HDL [29]. The clearance of VLDL-cholesterol by this mechanism is thought to further downregulate LDL receptors in E4 carriers [28] and explain the 5–10% higher LDL concentrations in Apo E4/3 subjects compared to Apo E3/3 [14]. A similar pattern, though not statistically significant, could be seen in the present study. Correction of baseline LDL-C for the confounding effects of age and log-transformed triglycerides lowered LDL-C to 136.2 ± 4.8 in APOE3/3 and raised LDL-C to 138.0 ± 5.0 mg/dL in 4/3.

Exercise training reduces serum triglycerides in part by accelerating the lipolysis of VLDL [30]. In the present study, exercise significantly decreased large VLDL by 5–20 mg/dL across genotypes, consistent with increased delipidation due to lipoprotein lipase activity [31] and increasing lipoprotein precursor for LDL and LDL formation.

We can only speculate as to how small LDL increased with exercise training in both APOE4 and 2 allele variants in the present study. In the absence of exercise, kinetic studies have shown that the rate of VLDL to LDL conversion is increased and the LDL catabolic rate is decreased in Apo E4/3 [8]. Consequently, with exercise VLDL lipolysis increases, and we speculate that for APOE4, the increased production and the extended residence time of LDL permits greater formation of small, dense LDL from medium LDL [25,32].

In APOE2 subjects, the conversion rate of VLDL to LDL is compromised [8] and another explanation for the increase in small LDL is required. The rise in small LDL may be a consequence of both the low affinity of Apo E2 for hepatic receptors [7] and the increased lipid transfer between VLDL and LDL particles leading to the formation of small dense LDL [33]. In the present study, APOE2/3 had slightly higher baseline VLDL triglycerides (Table 2) and slightly smaller VLDL particles (Table 3), consistent with an increase in overall VLDL particle number. Increased VLDL favors formation of small dense LDL through the combined actions of cholesteryl ester transfer protein (CETP) and hepatic lipase. CETP facilitates the exchange of VLDL triglycerides to LDL and LDL-cholesteryl esters to VLDL, and hepatic lipase lipolyzes LDL-triglycerides, reducing LDL size [33]. The increased plasma VLDL residence time in Apo E2 subjects [18] provides more time for the modification of LDL particle composition and the formation of small LDL. Although very little of the total plasma Apo E is found in LDL [21], the smallest, most dense LDL fraction is enriched in Apo E [34]. By increasing lipolysis, exercise might accelerate the production and subsequent accumulation of these poorly cleared small LDL-Apo E2. Finally, some small LDL derive directly from specific precursors [35] and direct conversion of small VLDL to small LDL may be preferred in VLDL-Apo E2-containing particles, but this is speculative.

We have previously reported increases in HDL-cholesterol (determined enzymatically) with exercise training only in the APOE3/3 subjects [13]. NMR determined changes in total HDL-cholesterol and HDL particle distribution were not significantly different among the genotype groups in the present analysis. Nevertheless, the present results suggest that these

### Table 4

Correlations between changes in LDL subpopulations and their respective baseline concentrations and with exercise-associated changes in factors known to affect LDL size

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change in LDL size (nm)</th>
<th>Change in LDL subpopulation (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Large</td>
<td>Medium</td>
</tr>
<tr>
<td><strong>Baseline value</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.407&lt;sup&gt;‡‡&lt;/sup&gt;</td>
<td>−0.408&lt;sup&gt;‡‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age</td>
<td>0.031</td>
<td>−0.007</td>
</tr>
<tr>
<td>Change, log TG</td>
<td>−0.420&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>−0.367&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>Change, weight</td>
<td>0.001</td>
<td>0.160&lt;sup&gt;o&lt;/sup&gt;</td>
</tr>
<tr>
<td>Change, %fat</td>
<td>−0.050</td>
<td>0.006</td>
</tr>
<tr>
<td>Change, waist circumference</td>
<td>−0.111</td>
<td>0.024</td>
</tr>
<tr>
<td>Change, BMI</td>
<td>−0.005</td>
<td>0.138</td>
</tr>
</tbody>
</table>

**Partial correlations** (effect of baseline value removed)

| Age                             | −0.021                  | −0.014                             | −0.012              |
| Change, log TG                  | −0.352<sup>‡</sup>      | −0.312<sup>‡</sup>                 | 0.149               |
| Change, weight                  | 0.060                   | 0.196<sup>o</sup>                  | −0.058              |
| Change, %fat                    | −0.053                  | −0.005                             | −0.085              |
| Change, waist circumference     | −0.100                  | 0.036                              | −0.007              |
| Change, BMI                     | 0.057                   | 0.182<sup>o</sup>                  | −0.069              |

**Note:** The partial correlation coefficients demonstrate that correcting for baseline particle size does not importantly affect the results.

<sup>a</sup> Baseline LDL medium and LDL small concentrations were normalized using log([1/1 + baseline value]) transformation.

<sup>o</sup> <i>p</i> < 0.07.

<sup>‡</sup> <i>p</i> < 0.05.

<sup>‡‡</sup> <i>p</i> < 0.01.

<sup>‡‡‡</sup> <i>p</i> < 0.00001.
changes are produced by increases in large HDL particles in the APOE3/3 and decreases in large HDL particles in the APOE2/3 and 4/3 subjects. Changes in serum lipids for the entire cohort in the present and prior report are indeed small compared to those expected from exercise training. A meta-analysis of 52 exercise training trials of >12 weeks duration including 4700 subjects demonstrated an average increase in HDL-cholesterol levels of 4.6% and reductions in triglycerides and LDL-cholesterol concentrations of 3.7 and 5.0%, respectively [36]. In the present study NMR analysis indicated a non-significant change in HDL-cholesterol of −1.0% for the entire cohort whereas triglycerides decreased 4.9% and LDL-cholesterol increased 3.6%. The paucity of change in the present report is undoubtedly due in part to the composition of the study population. APOE2/3, 3/3, and 4/3 subjects comprise 10, 62, and 22% of the general population, respectively [14]. The present study was designed to include equal numbers of these three genotypes. Consequently, differences in the response among the APOE groups magnified or diminished the response for the entire cohort. For example, HDL-cholesterol increased 2.1 mg/dL or 4.2% in APOE3/3, a response similar to the 4.6% observed in unselected subjects [37] but decreased 0.4 and 0.5 mg/dL, or 0.8 and 1.1%, respectively, in the APOE heterozygotes. The heterozygous subjects exerted a larger effect on the average HDL-cholesterol response than normally observed in unselected population-based studies because they were intentionally over-represented in the present sample. This may also explain the increase in total cholesterol with exercise training in the whole cohort.

There are several limitations to the present study. First, we purposely sought carriers of the APOE2 or 4 alleles in order to enlarge the APOE2/3 and 4/3 groups, following the premise that functional differences in the protein products of the APOE2, 3, and 4 alleles affect lipid metabolic responses. That Apo E protein variants display many profoundly different and physiologically meaningful biochemical behaviors justifies our approach. Nevertheless, we cannot exclude explanations related to possible underlying but unknown genetic differences. Grouping subjects by APOE variants does not guarantee genetic homogeneity within the 2/3, 3/3, and 4/3 groupings, because coding specificity does not generate identical APOE haplotypes [32,33,38]. In fact, within the classical APOE2, 3, and 4 alleles, 18 additional sites of variation exist at other exons or introns [34,39] that may obscure or override some metabolic tendencies associated with the functionality of the Apo E2, E3, and E4 proteins.

Perhaps even more importantly, there is no guarantee of equivalent genetic heterogeneity elsewhere in the genome, across the APOE groupings. There may be different degrees of linkage disequilibrium between the individual APOE2, 3, and 4 alleles and other gene variants [40] to explain the present findings. A more encompassing genomic analytic strategy, based on genome-wide haplotyping that simultaneously accounts for genetic variation both within and without the APOE alleles studied here, is evolving [41] and may demonstrate differences within the commonly accepted APOE variants. As genes that determine variation in the exercise response become known, genetic variability may be found that outweighs the physiological consequences of the polymorphisms studied here.

Other factors limit the generalizability of our results. The study population consisted of relatively healthy adults. Subjects with BMI > 31 were excluded, as were individuals with hyperlipidemia. It is possible that in metabolic disease states such as metabolic syndrome, the ability of common APOE variants to affect exercise-associated LDL size changes is different.

In summary, we have demonstrated an APOE allele-specific LDL subpopulation response to exercise in healthy subjects free of metabolic disease. In APOE3/3 homozygotes, medium LDL particles increased in concentration and small LDL particles decreased. The opposite was observed in APOE2/3 and 4/3 heterozygotes, suggesting that exercise training produces the potentially most beneficial changes in LDL particle size only in APOE3/3 individuals. The NMR findings extend our previous observation that the LDL-to-HDL-cholesterol ratio improves most with exercise in APOE3/3 subjects [13]. These findings are clinically relevant since they help explain the variability in lipid and lipoprotein responses induced by exercise training [42]. The results also demonstrate that the lipid response to exercise, like the response to pharmacologic therapies, differs by genetic composition. Consequently, exercise genetic profiling or “exercise genomics” may ultimately help predict population subgroups most likely to reduce their cardiovascular risk with exercise training.

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