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PRELIMINARY REPORT

# Apolipoprotein E Genotype and Exercise Training–Induced Increases in Plasma High-Density Lipoprotein (HDL)- and $HDL_2$-Cholesterol Levels in Overweight Men

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**We determined if the apolipoprotein E (APO E) genotype affects the exercise training–induced increase in plasma high-density lipoprotein cholesterol (HDL-C) and $HDL_2$-C. Sedentary overweight men on an American Heart Association (AHA) step I diet had plasma lipoprotein-lipids measured before and after 9 months of endurance exercise training. APO E2 (n = 6), E3 (n = 33), and E4 (n = 12) groups were similar at baseline in terms of age, body weight and composition, and plasma lipoprotein-lipid profiles. APO E2 men had a larger increase in plasma HDL-C and $HDL_2$-C with exercise training than APO E3 and E4 men (HDL-C, 8 ± 4 *v* 3 ± 1 *v* 2 ± 1 mg/dL; $HDL_2$-C, 5 ± 3 *v* 1 ± 1 *v* −1 ± 1 mg/dL; mean ± SE, all $P < .01$). After adjusting for body weight changes, the increases in plasma HDL-C and $HDL_2$-C remained greater in APO E2 versus E3 and E4 men (all $P < .03$). These results indicate that APO E2 men may have greater plasma HDL-C and $HDL_2$-C increases with endurance exercise training.**


PLASMA HIGH-DENSITY lipoprotein cholesterol (HDL-C) and $HDL_2$-C levels generally increase with endurance exercise training, but in many individuals there are no changes, and in some, actual decreases in plasma HDL-C and $HDL_2$-C occur with exercise training.[1] Because the apolipoprotein E (APO E) genotype is known to influence plasma lipoprotein-lipid levels, we sought to determine if APO E genotype affects plasma lipoprotein-lipid changes resulting from endurance exercise training.

## SUBJECTS AND METHODS

The subjects were from two previous identical exercise training studies,[2,3] and the data from these studies were combined. The original and follow-up studies were approved by the Johns Hopkins and University of Maryland Schools of Medicine, University of Maryland College Park, and University of Pittsburgh Institutional Review Boards, and subjects provided consent to participate. The subjects were healthy, nonsmoking, nondiabetic, sedentary men 45 to 80 years of age.[2,3] They were also overweight, with a body fat content of greater than 25% as measured by hydrodensitometry.[2] The subjects had plasma triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) levels less than the 90th percentile for age and blood pressure less than 160/95 mm Hg, and were not on medications affecting glucose or lipid metabolism. Subjects were excluded if they had evidence of coronary artery disease during a maximal treadmill test.

The subjects were first stabilized for 8 weeks on an American Heart Association (AHA) step I diet. They were also provided an AHA step I diet for 3 days prior to blood sampling after a 12-hour overnight fast for lipid levels. Maximal $O_2$ consumption ($Vo_2max$) also was measured.[2] After baseline studies, the subjects completed 9 months of endurance exercise training including cycle ergometry and treadmill walking and jogging, with all sessions supervised by study personnel. For the last 2 to 4 months, subjects exercised 3 d/wk for 45 minutes at 70% to 80% $\dot{V}o_2max$; training intensities were verified with heart rate monitors. Adherence to the training program was assessed by inspection of daily training logs. After training, diet and weight were stabilized before

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blood sampling for plasma lipoprotein-lipid levels, with samples drawn 24 to 36 hours after an exercise session. Plasma lipoprotein-lipid levels are the average of two samples from different days and were measured as previously described.[4-6]

APO E gene locus phenotyping using immunochemical techniques[7] was performed for 33 subjects. For 18 subjects, APO E genotyping was performed using standard procedures.[8] Subjects were categorized as APO E2 if they had at least one APO E2 allele, APO E4 if they had at least one APO E4 allele, and APO E3 if they had two APO E3 alleles. The final subject pool consisted of six APO E2 subjects (one APO E2/2 and five APO E2/3), 33 APO E3 subjects, and 12 APO E4 subjects (all APO E3/4).

Results are expressed as the mean ± SE. Baseline characteristics were compared among genotype groups using ANOVA. Changes in the different variables with exercise training were compared using ANOVA after adjusting for the baseline level of the analyzed variable. A $P$ level less than .05 was accepted as significant.

## RESULTS

The genotype groups were initially similar in terms of age, body weight and composition, $\dot{V}O_2$max, and plasma lipoprotein-lipid profiles. With training, the APO E3 group had a larger reduction in body weight than the E4 group. Body fat changes did not differ significantly among groups. However, the APO E4 group showed a larger increase in $\dot{V}O_2$max with training than the APO E2 group (Table 1).

APO E3 men had a greater decrease in plasma total cholesterol than APO E4 men. Plasma LDL-C reductions were greater, but not significantly, in APO E2 and E3 groups. However, plasma HDL-C levels increased twofold to threefold more with training in the APO E2 group versus APO E3 and E4 groups. Similarly, plasma $HDL_2$-C levels increased substantially more with training in the APO E2 group versus the APO E3 and E4 groups. Plasma $HDL_3$-C levels increased similarly in all groups. Plasma TG decreased more with training in APO E2 and E3 versus E4 men.

After controlling for body weight changes, plasma total cholesterol and LDL-C changes did not differ among genotype groups. However, the increase in plasma HDL-C remained greater in APO E2 versus E3 ($P$ = .009) and E4 ($P$ = .03) men. The plasma $HDL_2$-C increase also remained greater in APO E2 versus APO E3 ($P$ = .006) and E4 ($P$ = .004) men. Plasma TG reductions were somewhat greater in APO E2 versus E4 men ($P$ = .09).

**Table 1. Baseline Values and Changes With Exercise Training in the Three APO E Groups**

| Variable | APO E Genotype E2 (n = 6) | E3 (n = 33) | E4 (n = 12) |
|---|---|---|---|
| Age (yr) | 61 ± 3 | 59 ± 1 | 58 ± 2 |
| Weight (kg) | | | |
| Baseline | 89 ± 6 | 92 ± 2 | 93 ± 3 |
| Change with training | −2 ± 2 | −2 ± 1† | 0 ± 1 |
| Body fat (%) | | | |
| Baseline | 30 ± 3 | 32 ± 1 | 29 ± 1 |
| Change with training | −2 ± 2 | −2 ± 1 | 0 ± 1 |
| $\dot{V}O_2$max (mL/kg/min) | | | |
| Baseline | 27 ± 2 | 28 ± 1 | 27 ± 2 |
| Change with training | 3 ± 1† | 5 ± 1 | 7 ± 1 |
| Cholesterol (mg/dL) | | | |
| Baseline | 187 ± 15 | 183 ± 6 | 190 ± 9 |
| Change with training | −7 ± 11 | −12 ± 4 | 0 ± 5 |
| LDL-C (mg/dL) | | | |
| Baseline | 125 ± 11 | 121 ± 5 | 132 ± 9 |
| Change with training | −11 ± 10 | −9 ± 4 | −2 ± 4 |
| HDL-C (mg/dL) | | | |
| Baseline | 36 ± 4 | 33 ± 1 | 32 ± 2 |
| Change with training | 8 ± 4*‡ | 3 ± 1 | 2 ± 1 |
| $HDL_2$-C (mg/dL) | | | |
| Baseline | 2.5 ± 0.7 | 2.5 ± 0.7 | 2.2 ± 0.7 |
| Change with training | 5 ± 3*‡ | 1 ± 1 | −1 ± 1 |
| $HDL_3$-C (mg/dL) | | | |
| Baseline | 33 ± 3 | 31 ± 1 | 30 ± 2 |
| Change with training | 3 ± 1 | 2 ± 1 | 3 ± 1 |
| TG (mg/dL) | | | |
| Baseline | 137 ± 23 | 145 ± 20 | 132 ± 14 |
| Change with training | −32 ± 15† | −23 ± 8* | 1 ± 11 |

NOTE. Values are the mean ± SE.
*$P$ < .01, †$P$ < .05 $v$ APO E4 group.
‡$P$ < .01 $v$ APO E3 group.

## DISCUSSION

Endurance exercise training generally results in increased plasma HDL-C and $HDL_2$-C and decreased plasma TG levels. However, individual changes with exercise training are highly variable. Our results suggest that the APO E genotype provides insight into the anticipated training-induced plasma HDL-C and $HDL_2$-C increases in overweight sedentary middle-aged and older men. Training increased plasma HDL-C levels twofold more in APO E2 men versus APO E3 men and threefold more versus APO E4 men. The plasma $HDL_2$-C increases were sixfold higher in APO E2 versus E3 men, with E4 men actually showing a small decrease with training. Plasma TG changes were the mirror image of those for plasma HDL-C, suggesting that the differences may be related to the action of lipoprotein and/or hepatic lipase.

In a 1-year training study in middle-aged men,[1] the average plasma HDL-C and $HDL_2$-C increases were 4.2 and 2.9 mg/dL, respectively. However, individual plasma HDL-C changes ranged from a 20-mg/dL increase to an 8-mg/dL decrease. Similarly, plasma $HDL_2$-C changes ranged from an 18-mg/dL increase to a 5-mg/dL decrease. Our results suggest that APO E genotype may account for a portion of these differences among individuals.

One study has assessed whether APO E genotype interacts with physical activity levels to affect plasma lipoprotein-lipid profiles.[9] In Finnish males 9 to 24 years of age, questionnaire-assessed physical activity levels were not related to plasma lipoprotein-lipid levels in APO E4/4 males. However, in APO E3/4 or E3/3 males, higher physical activity levels were associated with lower plasma total cholesterol and LDL-C levels and a higher HDL-C to total cholesterol ratio. In APO E3/2 males, higher physical activity levels were more closely associated with these same plasma lipoprotein-lipid levels. Our study extends these findings because we used a longitudinal intervention design, standardized the subjects' diets, used a vigorous and standardized exercise training stimulus, and studied individuals at high risk for cardiovascular disease.

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