Exercise Training Decreases Plasma Cholesteryl Ester Transfer Protein


To assess the effect of exercise on the plasma concentration of cholesterol ester transfer protein (CETP) and its possible influence in mediating the exercise-associated redistribution of cholesterol among plasma lipoproteins, we measured plasma CETP in 57 healthy normolipidemic men and women before and after 9 to 12 months of exercise training. The training protocol resulted in significant changes in VO₂ max (mean±SD, +5.3±3.5 mL · kg⁻¹ · min⁻¹), body weight (-2.5±3.5 kg), plasma triglycerides (-25.7±36.3 mg/dL), high-density lipoprotein cholesterol (HDL-C) (+2.6±6.2 mg/dL), and ratios of total cholesterol to HDL-C (-0.0±0.0) and low-density lipoprotein cholesterol (LDL-C) to HDL-C (-0.18±0.45), but no change in lipoprotein(a). CETP concentration fell significantly in response to training in both men (n=28, 2.47±0.66 to 2.12±0.43; % A=14.2%; P<.005) and women (n=29, 2.72±1.01 to 2.66±0.76; % A=13.2%; P<.005). The CETP change was observed both in subjects who lost weight (n=28, Δ mean weight=-5.0 kg; Δ CETP=-0.42±0.79; % A=15.4%; P<.009) and in those who were weight stable (n=29, Δ mean weight=-0.12 kg; Δ CETP=-0.29±0.78; % A=10.4%; P<.055). Pretraining plasma CETP concentration predicted training-associated changes in HDL-C (r= -.27, P<.02) and ratio of LDL-C to HDL-C (r=+.40, P<.002). In a smaller study of 15 men, exercise training was associated with a decrease in levels of CETP, an increase in plasma postheparin lipoprotein lipase (LPL) activity, and a decrease in hepatic triglyceride lipase (HTGL) activity. Overall, the data suggest that basal plasma CETP concentrations, in addition to LPL and HTGL activities, may contribute to determining the extent to which exercise redistributes cholesterol among plasma lipoproteins. (Arterioscler Thromb. 1993;13:1359-1367.)

KEY WORDS • body composition • percent body fat • maximal oxygen uptake • exercise training • lipoprotein(a) • insulin • glucose tolerance • apolipoproteins

Long-term exercise training affects numerous metabolic and body compositional parameters. Lipid metabolic changes include a reduction of plasma triglycerides and the redistribution of plasma total cholesterol from the very-low-density lipoprotein (VLDL) fraction to the high-density lipoprotein (HDL) fraction. The processes responsible for the redistribution of plasma cholesterol to give higher HDL cholesterol (HDL-C) levels are not fully understood. Several enzymes, including lipoprotein lipase (LPL), hepatic triglyceride lipase (HTGL), lecithin: cholesterol acyltransferase (LCAT), and the cholesterol ester transfer protein (CETP), modify plasma lipoprotein particles and may play a physiological role in HDL metabolism. In relation to exercise, an increase in plasma LPL activity and a decrease in HTGL activity probably contribute to the rise in HDL-C. On the other hand, exercise has no effect on LCAT mass and only a small and temporary effect on LCAT activity. The effect of exercise on plasma CETP mass or activity is not known.

CETP catalyzes the net flux of esterified cholesterol from cholesterol ester–rich particles (ie, HDL) to larger, triglyceride-rich acceptor plasma particles (ie, VLDL and chylomicrons) and to low-density lipoprotein (LDL). In humans, CETP deficiency is associated with extremely high HDL-C levels, low LDL-C levels, and a low ratio of plasma total cholesterol to HDL-C. Tissue sources of CETP include the liver, intestine, fat, and muscle. Dietary cholesterol intake increases plasma CETP mass and activity, but there are few other data to provide insight into factors associated with fluctuations in CETP mass in humans. Because exercise increases HDL-C, we hypothesized that exercise may also decrease CETP mass. We therefore compared plasma CETP concentrations in adult men and women before and after exercise training. In addition, before and after exercise training, we related plasma CETP concentration to parameters such as body composition, plasma lipid and apolipoprotein levels, glucose tolerance and insulin responses to an oral glucose load, and maximal oxygen uptake (VO₂ max), many of which are altered by exercise training.

Methods

Subjects

In the main study, 57 previously sedentary men (n=28) and women (n=29) 60 to 72 years old were
TABLE 1. Baseline Characteristics of Men and Women in Exercise Study

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>Age (y)</td>
<td>63.8±12.8</td>
<td>64.1±12.1</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>166±45</td>
<td>128±46</td>
</tr>
<tr>
<td>Sum of skinfolds (mm)</td>
<td>37.8±4.7</td>
<td>28.6±6.5</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>45.0±8.0</td>
<td>58.4±5.6</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>22.4±3.2</td>
<td>24.3±9.0</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>67.3±12.8</td>
<td>81.9±12.1</td>
</tr>
<tr>
<td>Ratio of fat-free mass to fat mass</td>
<td>1.69±0.38</td>
<td>2.65±0.75</td>
</tr>
<tr>
<td>VO2max (mL·kg⁻¹·min⁻¹)</td>
<td>22.4±3.2</td>
<td>24.3±9.0</td>
</tr>
<tr>
<td>VO2max (L/min)</td>
<td>1.53±0.29</td>
<td>2.27±0.32</td>
</tr>
</tbody>
</table>

Values are mean±SD. VO2max indicates maximal oxygen uptake.

Exercise Training

In the main study of 57 subjects, the subjects were studied. All had given informed consent to participate in studies of exercise training effects approved by the Human Studies Committee of the Washington University School of Medicine. The subjects were healthy nonsmokers who normally were active but had not engaged in exercise training (defined as 30 minutes of aerobic activity at least 2 days per week). Health status was evaluated from the following screening procedures: medical history, physical examination, SMA-12, chest radiograph, resting electrocardiogram (ECG), and a Bruce treadmill exercise test with ECG and blood pressure monitoring. Subjects were excluded from the study if they had medical problems that could interfere with interpretation of the results and/or performance of vigorous exercise. Those with evidence of impaired glucose tolerance (2-hour oral glucose-tolerance test plasma glucose level between 140 and 200 mg/dL) were excluded. Four of the women received estrogen replacement therapy throughout the study period. Subject characteristics at baseline are shown in Table 1. In a follow-up experiment to evaluate exercise-related changes in plasma CETP, postheparin plasma lipase activities, and plasma lipoproteins, 15 healthy men were studied before and after short-term training. Five young normolipidemic men (age range, 26 to 40 years; percent body fat [%BF]=15.9±5.4%; VO2max=56.4±4.7 mL·kg⁻¹·min⁻¹) and 10 healthy older men (age range, 56 to 72 years; %BF=27.9±4.0%; VO2max=27.6±2.1 mL·kg⁻¹·min⁻¹) participated in this study. Of the older men, 4 had fasting plasma triglyceride levels of the 90th percentile or higher, and 2 had HDL-C levels in the fifth percentile or lower. The others were normolipidemic.

Exercise Energy Expenditure

Exercise energy expenditure rates were estimated from walking velocities, running velocities, and cycle power outputs recorded for 4 weeks near the end of exercise training, using formulas published by the American College of Sports Medicine. One liter of oxygen consumption was assumed to require 5 kcal of energy expenditure.

Dietary Monitoring

Subjects completed 7-day food records on four occasions, twice before beginning the endurance training program and then once at the midpoint and once at the completion of the training program. Foods were weighed by the subjects and recorded in household measures, and the registered dietician who instructed the subjects on how to record food intake also conducted an interview to assess the accuracy of the portions that were recorded. The food intake records were analyzed using the DATADIET NUTRIENT ANALYSIS program (IPC Datadiet, Camarillo, Calif).

Blood-Sampling Procedure

Blood was sampled before and after the training period from a subcutaneous arm vein with the subject seated or in a supine position after an overnight fast and 16 hours after the most recent exercise bout. Plasma was separated from cells via centrifugation (1000g×20 minutes) at 4°C. Plasma samples were frozen at −70°C for later analysis.

Plasma Lipid, Lipoprotein, and Apolipoprotein Measurements

Lipoproteins were measured in the Washington University Lipid Research Clinic Core Laboratory, which participates in the lipid standardization program of the Centers for Disease Control and Prevention. Total HDL-C, HDL-C, and HDL-C were determined after selective precipitation of whole plasma using the heparin-manganese procedure. CETP mass was measured with solid-phase competition radioimmunoassay using recombinant CETP derived from transfected mammalian cells to coat the wells and a calibrated plasma pool as the standard. For any given subject, pretraining and postraining samples were analyzed in the same assay. Three assays were used to assay all the samples. The mean intra-assay coefficient of variation was 6.3%. Apolipoproteins A1, B, and E were measured by enzyme-linked immunosorbent assay (ELISA) as previously described. Lipoprotein(a) [Lp(a)] was determined by ELISA using the Macra Lp(a) immunoassay kit (Terumo Medical Corporation, Elkton, Md).

Postheparin Plasma Lipase Activity Measurements (Follow-up Study Only)

Plasma samples for lipase activity analysis were collected 15 minutes after administration of 60 U heparin/kg body wt IV. Pretraining and postraining samples were stored at −70°C before being assayed for lipase activity in triplicate in the same assay, as described...
Percent Body Fat

Skinfold Measurements

Skinfold thicknesses were assessed by one of two experienced technicians (intrarater reliability coeffi-
cient, r=.99) using Lange calipers. Sites measured included pectoral, subcapular, midaxillary, umbilical, suprailiac, and thigh. All measurements were performed in duplicate. If values differed by more than 1.0 mm, additional measurements were taken. Outlying values (more than 4.0 mm) for a site were eliminated, and the remaining values were averaged.

Table 2. Plasma Lipid and Lipoprotein Changes With Training

<table>
<thead>
<tr>
<th></th>
<th>Pretraining</th>
<th>Posttraining</th>
<th>Δ</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>127.4±52.9</td>
<td>101.7±38.3</td>
<td>-25.7±36.3</td>
<td>.0001*</td>
</tr>
<tr>
<td>HDL triglycerides</td>
<td>85.9±49.4</td>
<td>61.2±34.9</td>
<td>-24.8±34.9</td>
<td>.0001*</td>
</tr>
<tr>
<td>LDL+HDL triglycerides</td>
<td>44.1±8.9</td>
<td>44.2±7.7</td>
<td>-0.87±5.22</td>
<td>.265</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>201.8±27.1</td>
<td>193.7±29.8</td>
<td>-8.1±22.6</td>
<td>.009*</td>
</tr>
<tr>
<td>HDL-C</td>
<td>17.1±12.7</td>
<td>14.5±20.3</td>
<td>-2.7±21.3</td>
<td>.349</td>
</tr>
<tr>
<td>LDL-C</td>
<td>129.0±24.7</td>
<td>124.1±28.6</td>
<td>-4.9±22.0</td>
<td>.049*</td>
</tr>
<tr>
<td>HDL-C</td>
<td>52.8±13.9</td>
<td>55.3±15.5</td>
<td>+2.6±6.2</td>
<td>.003*</td>
</tr>
<tr>
<td>HDL2-C (n=39)</td>
<td>17.4±9.8</td>
<td>17.7±11.0</td>
<td>+0.3±5.3</td>
<td>.766</td>
</tr>
<tr>
<td>HDL3-C (n=39)</td>
<td>32.9±6.7</td>
<td>34.4±6.2</td>
<td>+1.5±5.5</td>
<td>.092</td>
</tr>
</tbody>
</table>

VLDL indicates very-low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; C, cholesterol. Δ, Change between pretraining and posttraining.

Values in mg/dL, mean±SD. n=57 unless otherwise indicated.

*Significant difference from pretraining to posttraining.

V02max was measured during a graded treadmill walking and jogging protocol designed to increment exercise intensity by 3 to 4 mL O2 • kg^-1 • min^-1 and elicit fatigue within 6 to 12 minutes.24 Cardiorespiratory data were collected at 30-second intervals using a computerized system that included a Parkinson-Cowan CD-4 dry gas meter, O2 (Applied Electrochemistry S3-A) and CO2 (Beckman LB-2) gas analyzers, and a 5-L mixing chamber. V02max was taken as the highest V02 recorded over two consecutive 30-second periods. To ensure that V02max had been attained, at least two of the following criteria had to be satisfied: plateau in V02, heart rate within 10 beats per minute of age-predicted maximum heart rate, and respiratory exchange ratio of more than 1.10.

Percent Body Fat

Percent body fat was estimated from underwater weight taken at partial exhalation.23 Lung residual volume was measured outside the hydrostatic weighing tank using the oxygen dilution procedure.20 Body density was converted to percent body fat using the equation of Brozek et al.27 The method became available in time to test the last 17 women and 24 men entering the study.

SkINFold Measurements

Skinfold thicknesses were assessed by one of two experienced technicians (intrarater reliability coeffi- cient, r=.99) using Lange calipers. Sites measured included pectoral, subcapular, midaxillary, umbilical, suprailiac, and thigh. All measurements were performed in duplicate. If values differed by more than 1.0 mm, additional measurements were taken. Outlying values (more than 4.0 mm) for a site were eliminated, and the remaining values were averaged.

Oral Glucose-Tolerance Test

After an overnight fast, subjects ingested 75 g glucose. Plasma samples obtained at 0, 30, 60, 90, 120, and 180 minutes were enzymatically analyzed for glucose (model 23A glucose analyzer; Yellow Springs Instruments, Yellow Springs, Ohio), and insulin was analyzed by radioimmunoassay.29 Areas under the plasma glucose and insulin concentration curves were determined using the trapezoidal rule.

Statistical Analysis

Student's paired t test was used to test for differences before and after training. For nonnormally distributed variables, the Wilcoxon nonparametric sign test was used. Pearson's correlations and partial correlations were computed using SAS statistical software (SAS Institute, Cary, NC).

Results

During the last 4 weeks of the training period, training bouts required 1196±343 kcal/wk for women and 1814±669 kcal/wk for men. Expressed relative to body weight, energy expenditure was 18.8±6.6 kcal • kg^-1 • wk^-1 for women and 24.2±8.9 kcal • kg^-1 • wk^-1 for men. Exercise intensity, expressed as percent of maximal heart rate, was similar for both men and women (81±4% in women and 82±6% in men). Basal V02max values are given in Table 1. As reported previously,24 training increased V02max by 4.2 mL O2 • kg^-1 • min^-1 (18.8%) (P<.0001) in women and 6.3 mL O2 • kg^-1 • min^-1 (22.3%) (P<.0001) in men. The respective changes expressed as liters per minute were 0.22 (13.7%) and 0.41 (18.1%) (P<.0001). Mean body weight decreased by 2.4±3.9 kg (P<.002) in women and 2.6±3.3 kg (P<.003) in men. Body composition analyses of a subset of 17 women and 24 men indicated that fat loss accounted for 71% of the weight loss in women and 92% of the weight loss in men.
Plasma Lipoprotein Lipid Changes

For the group as a whole, exercise significantly decreased plasma triglycerides by 20.2%, VLDL triglycerides by 28.8%, and plasma total cholesterol by 4.0% (Table 2). HDL-C increased significantly by 4.9%, and LDL-C decreased by 4.6%. In subjects with complete pretraining and posttraining measurements of HDL subfractions, the increase in HDL₃-C (1.5 mg/dL) accounted for most of the increase in total HDL-C (1.8 mg/dL). Patterns of response were identical for men and women; for example, mean triglycerides decreased by 30.5 mg/dL in women and 22.5 mg/dL in men. The respective changes in women and men were -8.4 and -8.6 for total cholesterol, -6.2 and -6.1 for LDL-C, and +3.3 and +2.2 for HDL-C (all in mg/dL).

Plasma CETP, Lp(a), and Apolipoprotein Changes

Training significantly affected plasma CETP concentration (Fig 1 and Table 3) as well as plasma apolipoprotein B concentration (Table 3). CETP concentration decreased by 13.5% (P<.001), and apolipoprotein B concentration decreased by 17.3% (P<.0001). However, Lp(a) and apolipoproteins E and AI did not change significantly.

Effects of Sex and Weight Loss on Plasma CETP Change

Mean levels of CETP decreased significantly in both men (from 2.47±0.66 to 2.12±0.43 mg/dL; 14.2%; P=.005) and women (from 2.72±1.01 to 2.36±0.72 mg/dL; 13.2%; P=.012) (Fig 1). Because weight changes within the subjects ranged from +2.7 to -17.9 kg (mean±SD change, -2.5±3.5 kg), CETP data were further analyzed according to weight loss. Fifteen women and 14 men were weight stable (ie, lost less than 2.1 kg and had mean±SD change of -0.12±1.30 kg). In 20 of these 29 subjects, mean fat mass decreased by 0.5 kg and lean mass increased by 0.2 kg according to body composition analyses. The mean CETP level decreased in these 29 subjects from 2.80±0.87 to 2.54±0.73 mg/dL (9.3%) (Fig 2). Fourteen women and 14 men lost more than 2.1 kg (mean±SD change, -4.98±3.43 kg). Body composition analyses performed in 21 of these 28 subjects showed that fat mass decreased by 3.9 kg. Mean CETP levels also decreased in this group, from 2.72±1.15 to 2.16±0.41 mg/dL (20.6%) (Fig 2). Thus, neither weight loss nor sex affected the exercise-related CETP response. Lp(a) was unaffected by exercise regardless of sex.

Plasma Lipoprotein Lipid Distribution and Composition

Exercise training changed the distribution of plasma total cholesterol among the major lipoproteins as well as the compositions of some lipoproteins (Table 4). The ratios of total plasma cholesterol to HDL-C and of LDL to HDL decreased by -8.0% and -7.4%, respectively, but the ratio of VLDL-C to HDL-C remained unchanged. In a subset of 39 subjects in whom the HDL subfractions were quantified, training decreased the ratio of VLDL-C to HDL₃-C by 36% and the ratio of VLDL-C to HDL₁-C by 31%, but the ratio of HDL₃-C to HDL₄-C was unaffected. Relative to apolipoprotein B content, VLDL and LDL contained less cholesterol after training (Table 4, bottom). In addition, the ratio of HDL-C to apolipoprotein AI was increased after training.

Triglyceride distribution also was affected by training (Table 4). The depletion of VLDL triglycerides was greater than the depletion of non-VLDL triglycerides, resulting in a decrease of the ratio of VLDL triglycerides to non-VLDL triglycerides by 22.9% and of the ratio of VLDL triglycerides to plasma triglycerides by 9.6%. Although the depletion of plasma triglycerides

<table>
<thead>
<tr>
<th>Table 3. Apolipoprotein Changes With Training</th>
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<tr>
<td>Apo E</td>
</tr>
<tr>
<td>Apo B</td>
</tr>
<tr>
<td>Apo AI</td>
</tr>
<tr>
<td>Lp(a)</td>
</tr>
<tr>
<td>CETP</td>
</tr>
</tbody>
</table>

Apo indicates apolipoprotein; Lp(a), lipoprotein(a); and CETP, cholesterol ester transfer protein. Values in mg/dL except CETP, which is µg/mL; mean±SD. n=57. See Table 2 for explanation of Δ and *.
FIG 2.  Bar graph of lack of effect of weight loss on decrease in plasma cholesterol ester transfer protein (CETP) mass concentration associated with exercise. *Significant difference from pretraining to posttraining.

was larger than that of plasma cholesterol after training, the ratios of triglyceride to cholesterol in both the $d<1.006$ (VLDL) and the $d>1.006$ (LDL+HDL) fractions were not affected.

Correlations Between Plasma CETP Concentration and Other Parameters

The directions (— or +) of the correlation coefficients ($r$) were the same before (Fig 3A) and after (Fig 3B) training for the significant correlations. Percent body fat was positively correlated with CETP after training ($r=.386, P<.009$), and lean body mass was negatively correlated before training. However, there were no significant correlations between either basal CETP or $\Delta$ CETP and $\Delta$ % fat mass or $\Delta$ lean body mass ($\Delta$ indicates change between before and after training). This was true even in the subgroup that lost more than 2.1 kg. The sum of skinfold measurements was not correlated with CETP. $V_{O_{2\text{max}}}$ was inversely related to plasma CETP after training ($r=-.291, P<.03$). Plasma total cholesterol was correlated to plasma CETP after training ($r=.262, P<.05$). None of the measured apolipoproteins or triglyceride parameters were significantly related to plasma CETP concentrations ($-.04<r+.13$, data not shown). Of the plasma cholesterol ratios, none were significantly related to plasma CETP at either time point ($-.20<r+.20$). Insulin response to an oral glucose load was not significantly correlated to plasma CETP either before ($r=.209, P<.13$) or after ($r=.255, P<.07$) training.

Prediction of Plasma Cholesterol Redistribution From Plasma CETP Concentration

Of particular interest to us were the exercise-induced changes in the distribution of plasma cholesterol with training (eg, $\Delta$ [LDL-C/HDL-C]) and their possible relationship to CETP concentration (Fig 4 and Table 5). Basal (ie, pretraining) CETP levels, which ranged from 1.20 to 5.18 mg/L, were negatively correlated with the exercise-associated change in HDL-C ($r=-.267, P<.04$) (Fig 4A) and positively correlated with the change in the ratio of LDL-C to HDL-C ($r=.396, P<.002$) (Fig 4B). Removing the effects of basal and training-associated changes in cholesterol and triglycerides through partial correlations strengthened each of these relationships with basal CETP (Table 5). Thus, removing the effects of $\Delta$ triglycerides and $\Delta$ total cholesterol changed the correlation between basal CETP and $\Delta$ HDL-C from −0.267 to −0.335. The $r$ value for $\Delta$ LDL-C/HDL-C changed from +0.396 to +0.418, and the $r$ value for $\Delta$ total cholesterol/HDL-C increased from +0.241 to +0.390.

Correlations between pretraining vs posttraining changes for $\Delta$ CETP, $\Delta$ HDL-C, $\Delta$ total cholesterol/ HDL-C, and $\Delta$ triglycerides ranged from −.196 to +.340. For example, $\Delta$ triglycerides vs $\Delta$ HDL-C was −.048 ($P=NS$). The only significant correlation was $r=.340 (P<.010)$, for $\Delta$ triglycerides vs $\Delta$ total choles-

### Table 4. Changes in Plasma Cholesterol and Triglyceride Distribution and Lipoprotein Composition With Training

<table>
<thead>
<tr>
<th></th>
<th>Pretraining</th>
<th>Posttraining</th>
<th>$\Delta$</th>
<th>$P$</th>
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</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol/HDL</td>
<td>4.03±1.00</td>
<td>3.73±1.03</td>
<td>-0.299±0.520</td>
<td>.0001*</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>2.58±0.77</td>
<td>2.40±0.88</td>
<td>-0.181±0.453</td>
<td>.004*</td>
</tr>
<tr>
<td>VLDL/HDL</td>
<td>0.38±0.39</td>
<td>0.30±0.41</td>
<td>-0.077±0.426</td>
<td>.180</td>
</tr>
<tr>
<td>VLDL/HDL$_1$ (n=39)</td>
<td>1.89±2.69</td>
<td>1.22±1.45</td>
<td>-0.675±1.781</td>
<td>.024*</td>
</tr>
<tr>
<td>VLDL/HDL$_2$ (n=39)</td>
<td>0.61±0.50</td>
<td>0.42±0.38</td>
<td>-0.188±0.333</td>
<td>.001*</td>
</tr>
<tr>
<td>HDL$_2$/HDL$_3$ (n=39)</td>
<td>0.52±0.24</td>
<td>0.50±0.28</td>
<td>-0.018±0.241</td>
<td>.631</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL/plasma</td>
<td>0.64±0.12</td>
<td>0.57±0.11</td>
<td>-0.068±0.094</td>
<td>.0001*</td>
</tr>
<tr>
<td>VLDL/non-VLDL (n=46)</td>
<td>2.00±1.34</td>
<td>1.38±0.76</td>
<td>-0.618±0.967</td>
<td>.0001*</td>
</tr>
<tr>
<td>Compositions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL:triglycerides/C</td>
<td>5.72±1.57</td>
<td>5.71±1.68</td>
<td>-0.006±1.93</td>
<td>.981</td>
</tr>
<tr>
<td>Non-VLDL:triglycerides/C (n=46)</td>
<td>0.24±0.06</td>
<td>0.25±0.06</td>
<td>0.006±0.045</td>
<td>.385</td>
</tr>
<tr>
<td>(VLDL-C+LDL-C)/apo B</td>
<td>2.10±0.75</td>
<td>1.98±0.77</td>
<td>-0.122±0.385</td>
<td>.020*</td>
</tr>
<tr>
<td>HDL-C/apo AI</td>
<td>0.42±0.09</td>
<td>0.44±0.11</td>
<td>0.020±0.049</td>
<td>.0003*</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; C, cholesterol; and apo, apolipoprotein.

Values are mean±SD of mass ratios. n=57 unless otherwise indicated. See Table 2 for explanation of $\Delta$ and *.
terol/HDL-C. The respective r values for Δ CETP vs Δ HDL-C, Δ total cholesterol/HDL-C, and Δ LDL-C/HDL-C were +.229 (P=.090), +.184 (P=.174), and -.008 (P=.952). For percent Δ CETP vs percent Δ HDL-C, r=.104 (P=.446).

**Results of Follow-up Study**

Given the correlation between basal CETP and Δ HDL in the original 57 subjects, we wanted to compare basal CETP with changes in plasma lipase activities as factors contributing to the exercise-induced increase in HDL-C. Therefore, an additional study was conducted in which the responses of five runners (running at least 20 miles per week) who stopped training for 2 weeks were combined with the responses of 10 healthy sedentary men who exercised for 10 to 13 consecutive days for more than 1 hour per day at 60% to 70% of maximal capacity. The results were consistent with those found in the original 57 subjects. For example, exercise training decreased plasma CETP from 2.59 to 2.13 mg/L (17.8%) (P<.008). Also, plasma triglycerides decreased by 46 mg/dL (P<.07) (percent change, 15.5%; P<.0007), HDL-C increased by 4.0 mg/dL (P<.018), HDL-C increased by 1.6 mg/dL (P<.008), LPL activity increased by 2.67 μmol free fatty

**Fig 3.** Graphs of Pearson's correlations between plasma cholesterol ester transfer protein mass concentration and various laboratory measurements before (A) and after (B) training (n=57 except where noted in parentheses). *P<.05. WT indicates weight; LBM, lean body mass; BF, body fat; SK, skinfold measurements; TC, total cholesterol; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; C, cholesterol; and INS, insulin.

**Fig 4.** Scatterplots showing the relationship of plasma cholesterol ester transfer protein (CETP) mass concentration before training to exercise-associated changes in plasma high-density lipoprotein cholesterol (HDL-C) concentration (A) and plasma ratio of low-density lipoprotein cholesterol (LDL-C)/HDL-C (B).
women. In concordance with the findings of many other studies, the increase in HDL-C following exercise training performed under supervision four or five times weekly at an intensity of 81±5% maximum heart rate by healthy nondiabetic persons is known to increase HDL-C by 2.6 mg/dL and decrease triglycerides by 20.2%, with the directions and magnitudes of changes similar for men and women.

Although plasma volume was not measured in the present study, it is possible that part of the decrease in CETP is attributable to plasma volume expansion. Exercise training expands plasma volume, with the magnitude of the expansion depending on a number of factors, including rate and amount of energy expenditure. The plasma volume response of subjects 60 to 70 years old is not known, but in younger men (mean age, 32 to 37 years), comparable long-term training at a higher absolute intensity or requiring a twofold greater weekly caloric expenditure expanded plasma volume by 6% to 8% (and increased $V_{\text{O2max}}$ by 18% to 26%). If older subjects (ages, 60 to 70 years) respond similarly, the 15.9% increase in plasma volume observed in the present study makes it reasonable to assume a plasma volume expansion of 5% in the present subjects. If such a change in plasma volume had occurred, it would increase the total plasma CETP concentration following training by 5% ($[2.24 \mu g/mL] \times [1.05 L] = 2.37$), leaving a net 8.8% decrease in plasma CETP due to exercise.

Plasma CETP concentrations decreased in a subset of subjects whose weight remained stable (mean change, $-0.11 \text{ kg}$) as well as in subjects who lost weight (mean change, $-5.0 \text{ kg}$). The absence of a significant correlation between A CETP and A lean body mass or A percent body fat, even in the subgroup that lost more than 2.1 kg, suggests that depletion of adipocyte triglyceride per se may not affect CETP production. Thus, the lowering of CETP concentration through exercise occurred independently of weight change or sex. Previous reports have shown that plasma CETP concentration increases in response to a high-fat, high-cholesterol diet,

### Table 6. Results of Follow-up Study of 15 Men Showing Correlations Between Changes in Plasma HDL-C Parameters and Factors That May Influence Response of HDL-C to Exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\Delta$ LPL activity (%)</th>
<th>$\Delta$ HTGL activity (%)</th>
<th>Baseline CETP</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$ Plasma triglycerides</td>
<td>$-0.77$ ($P&lt;.001$)</td>
<td>$0.24$</td>
<td>$-0.24$</td>
</tr>
<tr>
<td>$\Delta$ HDL-C</td>
<td>$-0.08$</td>
<td>$0.35$ ($P&lt;.20$)</td>
<td>$-0.12$</td>
</tr>
<tr>
<td>$\Delta$ HDL$_2$C (n=12)</td>
<td>$-0.10$</td>
<td>$-0.01$</td>
<td>$-0.38$ ($P&lt;.24$)</td>
</tr>
<tr>
<td>$\Delta$ HDL$_2$C (n=12)</td>
<td>$-0.03$</td>
<td>$0.19$</td>
<td>$0.34$ ($P&lt;.28$)</td>
</tr>
<tr>
<td>$\Delta$ HDL$_2$C/HDLC$_2$-C (n=12)</td>
<td>$-0.09$</td>
<td>$-0.06$</td>
<td>$-0.47$ ($P&lt;.12$)</td>
</tr>
<tr>
<td>$\Delta$ Plasma total cholesterol/LDL-C</td>
<td>$0.04$</td>
<td>$0.03$</td>
<td>$-0.05$</td>
</tr>
<tr>
<td>$\Delta$ LDL-C/HDLC</td>
<td>$-0.04$</td>
<td>$0.18$</td>
<td>$-0.11$</td>
</tr>
</tbody>
</table>

LPL indicates lipoprotein lipase; HTGL, hepatic triglyceride lipase; CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and C, cholesterol. See Table 2 for explanation of $\Delta$ and *.
most Americans (not shown) and remained constant during training. That CETP decreased during exercise regardless of sex, weight change, and reported dietary status argues for a specific effect of exercise on plasma CETP levels.

Percent body fat was weakly positively and lean body mass was weakly negatively correlated with CETP before and after exercise training ($r$ range, $-0.3$ to $0.4$). In mammals, fat tissue contains mRNA for CETP and synthesis of CETP by fat tissue has been postulated. The present data advance the idea that fat mass may be an important determinant of human plasma CETP. We subsequently have examined the relationship between percent body fat and plasma CETP levels in 28 men who varied in body fat (range, 6% to 34% of body weight) and found a significant correlation ($r = -0.44$, $P < 0.04$) (unpublished data), further supporting this hypothesis. By contrast, the sum of skinfold measurements, which is an index of subcutaneous fat deposition, was not related to CETP either before or after exercise training. That overall body fatness but not subcutaneous fat is related to plasma CETP concentration may mean that intra-abdominally deposited fat is the more important determinant of plasma CETP concentration.

Exercise significantly reduced the insulin response to a glucose challenge. Such a response is consistent with a reduction in peripheral insulin resistance. It is tempting to link the decrease in CETP to an exercise-related decrease in peripheral insulin resistance, perhaps at the adipose tissue level. However, this speculation must be tempered by the weakness of the correlations among CETP, adipose tissue, and insulin resistance. Clearly, more definitive studies are required.

The exercise-induced increase in HDL-C has been attributed to changes in plasma lipase activities. In highly fit runners, whose plasma HDL-C levels generally are high, a significant portion of the variance in HDL-C levels is explained by variance in hepatic lipase activity. In sedentary adults, negative correlations between hepatic lipase activity and HDL-C levels were found. In particular, HDL-C levels were often stronger than LPL activity vs HDL-C relationships. Exercise intervention increases hepatic plasma LPL activity, may decrease HTGL activity, and increases plasma HDL-C. Significant correlations between Delta HDL-C and exercise-associated changes in lipase activities have not been demonstrated. The highest correlations ($r = 0.33$, $P = 0.04$) between changes in HDL-C and LPL activity have been reported by Peltonen et al. The results of our follow-up study agree with results of these previous studies. We detected significant increases in plasma triglycerides, HDL-C, and LPL activity and a decrease in HTGL activity, but lipase changes were not correlated with HDL-C changes.

We hypothesized that plasma CETP concentration may be an additional factor related to the exercise-associated increase in plasma HDL-C. In our sample of 57 healthy men and women, we found that basal CETP concentrations were negatively and significantly correlated with the exercise-associated changes in HDL-C ($r = -0.27$, $P < 0.04$) and the ratio of LDL-C to HDL-C ($r = -0.40$, $P < 0.002$). These negative correlations are consistent with the physiological role of CETP in the redistribution of cholesterol esters from HDL to larger triglyceride-rich particles. Removing the effects of baseline cholesterol and of the change in triglycerides through statistical means further strengthened the relationships of HDL-C, LDL-C to HDL-C, and total cholesterol to HDL-C with basal CETP mass. In the additional study of 15 men, the plasma CETP decrease with training seen in the main study was confirmed, and the correlations between Delta HDL-C and Delta LDL-C to HDL-C with baseline CETP were in the same direction as those found in 57 subjects. Given the difficulty of detecting significant correlations between Delta HDL-C and lipase activity changes, it is not surprising to see only trends between either Delta HDL-C or Delta LDL-C and baseline CETP in our follow-up study.

The predictive value of basal CETP concentration on the HDL-C and ratio of LDL-C to HDL-C responses may reflect the exponential relationship between plasma CETP concentration and HDL-C, as defined by human genetic CETP deficiency. This relationship predicts that equal reductions in CETP will have a much larger effect on HDL-C when baseline CETP levels are lower. Based on these observations, we speculate that a high basal CETP level predisposes to a small exercise-induced increase in HDL-C and a small decrease in LDL-C to HDL-C. Alternatively, with a low basal plasma CETP level, a wider range of plasma cholesterol distribution responses is possible, including a large increase in HDL-C, which may depend on the extent to which plasma LPL activity increases. Obviously, these speculations need to be tested.

In summary, long-term exercise decreased plasma CETP levels in both men and women, independent of weight change. Positive relationships between plasma CETP and LDL-C and between plasma CETP and total cholesterol, observed both before and after exercise training, support the link between CETP and cholesterol metabolism. We also reported a positive correlation between body fat and plasma CETP concentration, which may be evidence that adipose tissue in humans is an important source of CETP. With respect to the increase in HDL-C associated with exercise, low basal plasma CETP concentration, but not change in CETP, was found to be a significant predictor of the HDL-C increase associated with exercise and a stronger predictor of the decrease in the ratio of LDL-C to HDL-C. Because the mechanism of exercise-induced HDL-C increase remains incompletely understood, the role of CETP in exercise-induced changes of lipoprotein cholesterol distribution warrants further study.

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References


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