Changes in High-Density Lipoprotein-Cholesterol Subfractions With Exercise Training May be Dependent on Cholesteryl Ester Transfer Protein (CETP) Genotype

Kenneth R. Wilund, Robert E. Ferrell, Dana A. Phares, Andrew P. Goldberg, and James M. Hagberg

We sought to determine if a cholesteryl ester transfer protein (CETP) gene locus variation contributes to the variability in the responses of plasma high-density lipoprotein-cholesterol (HDL-C) and its subfractions to endurance exercise training. Middle- to older-aged men and women with at least 1 lipoprotein-lipid risk factor underwent 6 months of endurance exercise training while on a low-fat diet. Plasma lipid levels were measured by nuclear magnetic resonance (NMR). Initial age, body composition, lipoprotein-lipid profiles, and $\dot{V}O_2$max did not differ between the 2 CETP genotype groups (B1B1, n = 16; B1B2, n = 14). With exercise training, $\dot{V}O_2$max increased, and body weight, total body fat, and computed tomographic (CT) intra-abdominal visceral fat decreased similarly in both CETP genotype groups. Plasma total cholesterol and low-density lipoprotein-cholesterol (LDL-C) levels did not change significantly with training in either genotype group. HDL_{2NMR}-C levels increased with exercise training in CETP B1B1 ($P < .05$), but did not change in CETP B1B2 genotype individuals. HDL_{3NMR}-C levels tended to decrease with training in CETP B1B1 persons and HDL_{4NMR}-C levels tended to increase with training somewhat more in CETP B1B2 individuals, but these differences were not significant. HDL_{5NMR}-C levels increased similarly with exercise training in the 2 groups. The integrated $HDL_{3\text{-}5NMR}$-C levels increased with exercise training in CETP B1B2 ($P < .05$), but did not change in CETP B1B1 genotype individuals. Apolipoprotein E (APO E) or lipoprotein lipase (LPL) *Pvu*II genotype did not associate with HDL-C subfraction changes with training. Thus, CETP genotype may contribute to the interindividual differences in plasma HDL-C subfraction changes occurring with endurance exercise training in sedentary middle- to older-aged men and women.

CHOLESTERYL ESTER transfer protein (CETP) catalyzes the exchange of triglycerides (TG) and cholesterol esters among plasma lipoproteins. CETP causes the net transfer of cholesterol from high-density lipoprotein (HDL) to very–low-density lipoprotein (VLDL), chylomicrons and low-density lipoprotein (LDL), in exchange for TG.[1] The resulting TG-rich HDL particles are then hydrolyzed by hepatic TG lipase to produce small, dense HDL particles that are relatively cholesterol-deficient. The importance of CETP activity in the metabolism and composition of HDL particles is clearly demonstrated in individuals with genetic CETP deficiency.[2] As a result of its involvement in these critical reactions, CETP clearly has a significant impact on plasma lipoprotein composition.

A Taq1B polymorphic variation in intron 1 of the CETP gene is relatively common in most populations studied, with B1 and B2 allele frequencies of approximately 0.57 and 0.43, respectively.[3-7] Though presumed to be nonfunctional, this variant associates with plasma CETP concentration, mass, and activity and with a variety of phenotypes related to plasma HDL-cholesterol (HDL-C) levels.[3-7] Furthermore, many studies report significant interactions between CETP Taq1B genotype and such environmental factors as smoking, alcohol ingestion, and obesity to affect plasma HDL-C levels.[3,4,7,8] Dullaart et al[9] also recently reported that CETP Taq1B genotype interacted with diet alterations to differentially affect plasma HDL-C level changes in a prospective study in type 1 diabetics.

Endurance exercise training is another lifestyle alteration that affects plasma HDL-C levels. Most training studies continued for longer than 12 weeks report at least a 5 mg/dL increase in plasma HDL-C levels.[10] However, there is substantial interindividual variability in plasma HDL-C responses to even highly standardized endurance exercise training programs.[11] This raises the possibility that genetic factors may affect the degree to which plasma HDL-C and its subfractions change in response to prolonged endurance exercise training. Therefore, because CETP is intimately involved in plasma HDL-C metabolism, we hypothesized that CETP Taq1B genotype would differentially affect the degree to which middle- to older-aged healthy individuals would alter their plasma HDL-C and HDL-C subfractions with prolonged endurance exercise training.

MATERIALS AND METHODS

Thirty-two healthy sedentary Caucasian men (n = 15) and women (n = 17) volunteered to participate in this study to assess the genetic determinants of plasma lipoprotein-lipid changes with endurance exercise training in middle- to older-aged individuals. Subjects responded to media advertisements and were initially screened via telephone to assess their interest in and suitability for the study. The study was approved by the Institutional Review Board at the University of Maryland, College Park and all subjects provided their written consent during their first laboratory visit. Subjects had to be sedentary, normotensive or with blood pressure (BP) controlled with medications not affecting plasma cholesterol levels, nondiabetic, nonsmoking, with no prior history of cardiovascular disease, and with a body mass index (BMI) less than 35 kg/m^2. All women were postmenopausal and

From the Department of Kinesiology, University of Maryland, College Park, MD; Department of Human Genetics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA; the Division of Geriatrics, University of Maryland School of Medicine, Baltimore, MD.

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Address reprint requests to James Hagberg, PhD, Department of Kinesiology, University of Maryland, College Park, MD 20742-2611.

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maintained their hormone-replacement therapy (HRT) regimen, either on or not on HRT, for the duration of the study.

Screening

Subjects' medical histories were reviewed on their first laboratory visit to ensure they met the study inclusion/exclusion criteria listed above. They also had height and weight measured to ensure they had BMI less than 35. Subjects had a blood sample drawn in the morning after an overnight fast and had to have at least one National Cholesterol Education Program lipid abnormality (cholesterol $>$ 200 mg/dL, HDL-C $<$ 35 mg/dL, TG $>$ 200 but $<$ 400 mg/dL). Each subject also had to have plasma cholesterol and LDL-C less than the 90th and plasma HDL-C greater than the 20th percentile for their age and sex to ensure they did not have familial hypercholesterolemia. Subjects had a fasting plasma glucose level determined and underwent a 2-hour 75-g oral glucose tolerance test. Those with fasting glucose greater than 126 mg/dL or 2-hour glucose greater than 200 mg/dL were excluded from the study. Subjects completed a maximal treadmill exercise test with BP and electrocardiographic monitoring to screen for cardiovascular disease. Subjects whose exercise test was terminated for cardiovascular signs or symptoms[12] were excluded from the study.

Dietary Stabilization

All qualified subjects then completed 6 weeks of instruction in the principles of an American Heart Association Step 1 diet, which consisted of less than 30% calories from fat, approximately 55% from carbohydrates, and 15% from protein with cholesterol intake less than 300 mg/d.[13] Subjects completed 7-day food records during this dietary program and had to adhere to the prescribed diet for more than 3 weeks prior to beginning baseline testing.

Baseline Testing

At the completion of the dietary program and prior to beginning exercise training, all subjects completed baseline testing that consisted of plasma lipoprotein-lipids, body composition, and $\dot{V}O_2$max assessments. Plasma lipoprotein-lipid profiles were measured on a blood sample drawn after an overnight fast and analyzed using nuclear magnetic resonance (NMR) techniques (LipoMed, Raleigh, NC) that were previously standardized and validated against plasma lipoprotein-lipid levels determined by more conventional methods of separation and analysis.[14] In NMR analyses of plasma lipoprotein-lipid levels, HDL_{1NMR}-C is roughly equivalent to HDL_{3c}-C determined by conventional separation and analysis methods; HDL_{2NMR}–C is roughly equivalent to HDL_{3b}-C; HDL_{3NMR}–C is roughly equivalent to HDL_{3a}-C; HDL_{4NMR}–C is roughly equivalent to HDL_{2a}-C; and HDL_{5NMR}–C is roughly equivalent to HDL_{2b}-C. Body composition was assessed by dual-energy x-ray absorptiometry (DPX-L; Lunar Corp, Madison, WI) and intraabdominal and subcutaneous fat were quantified at L4-L5 using a standardized CT protocol.[15] $\dot{V}O_2$max was measured during a modified treadmill protocol that was terminated when the subject was unable to continue.[16]

Genotyping

All subjects had DNA isolated from peripheral monocytes[17] and the DNA was typed at the CETP Taq1B locus for B1 and B2 allelic variants.[18] One man and one woman were CETP B2 homozygotes. Because of the low frequency of this genotype they were excluded from final statistical analyses, resulting in a final sample size of 30 subjects. Subjects were also typed at the apolipoprotein E (APO E) and lipoprotein lipase (LPL) *Pvu*II loci as we have previously shown that common allelic variants at these loci may affect the degree to which middle- to older-aged sedentary men increase their plasma HDL- and HDL_2-C levels with prolonged endurance exercise training.[19,20]

Exercise Training

Exercise training took place 3 days per week under the direct supervision of study personnel. All training sessions began and concluded with 10 to 15 minutes of stretching/warm-up and cool-down exercises, respectively. Training intensity was monitored with wrist heart rate monitors. Training started with 20 minutes of exercise per session at 50% $\dot{V}O_2$max. Training duration was increased by 5 minutes each week until 40 minutes of exercise at 50% $\dot{V}O_2$max was completed. Training intensity was then increased by 5% $\dot{V}O_2$max per week until a training intensity of 70% $\dot{V}O_2$max was achieved. After 12 wks of training, a lower intensity 45- to 60-minute walk at home on the weekend was incorporated into the training program. Only subjects who completed greater than 75% of training sessions at the prescribed intensity, duration, and frequency were included in the final data analyses. Subjects completed 7-day food records 2 to 3 times during the exercise training portion of the study to ensure they continued to adhere to the prescribed diet. Some subjects lost a moderate amount of weight during the exercise training portion of the study, but not as a result of an absolute caloric restriction as the amount of weight lost was less than that expected based on their total exercise training energy expenditure.

Final Testing

After training, all subjects completed the same plasma lipoprotein-lipid, body composition, and $\dot{V}O_2$max assessments as prior to training. The blood sample for plasma lipoprotein-lipid levels after training was drawn 24 to 36 hours after each subject's prior exercise training session.

Statistics

All data are presented as the mean $\pm$ SE. Initial subject characteristics and the different components of the plasma lipoprotein-lipid profile were compared between CETP B1B1 and B1B2 genotype groups using analysis of variance (ANOVA). Changes in the different variables from before to after exercise training were compared between CETP B1B1 and B1B2 genotype groups also using ANOVAs. A P value less than .05 was considered statistically significant.

RESULTS

There were somewhat more women in the CETP B1B1 genotype group and somewhat more men in the CETP B1B2 genotype group, but these differences were not significant (Table 1). All of the women in the CETP B1B2 genotype group were on HRT, while only half of the CETP B1B1 genotype women were on HRT (Table 1). Statistical analyses between CETP B1B1 genotype women on and not on HRT revealed no differences or trends towards differences in baseline variables or changes with exercise training. Therefore, HRT status was not considered further in the statistical analyses. There were no differences in exercise training-induced responses between men and women; therefore, their results are combined for all analyses.

Initial values for age, body weight, total body fat, CT intraabdominal and subcutaneous fat, and $\dot{V}O_2$max in L/min and mL/kg/min did not differ significantly between the 2 CETP genotype groups (Table 1). Initial plasma lipoprotein-lipid profiles also were not significantly different between the 2 CETP genotype groups (Table 2).

With exercise training, $\dot{V}O_2$max expressed both in terms of L/min and mL/kg/min increased significantly in the entire population, in both CETP genotype groups, and to the same

Table 1. Subject Characteristics and Their Changes With Exercise Training as a Function of CETP Genotype

Characteristic	CETP Genotype B1B1 (n = 16)	CETP Genotype B1B2 (n = 14)
Female/male	10/6	6/8
% females on HRT	50%	100%
Age (yr)	56 ± 1	56 ± 1
Weight (kg)		
Initial	84 ± 4	79 ± 4
Change with training	−0.8 ± 0.5	−1.2 ± 0.5*
Body fat (%)		
Initial	38 ± 2	34 ± 2
Change with training	−1.0 ± 0.4*	−0.9 ± 0.4*
CT intra-abdominal fat (cm^2)		
Initial	146 ± 10	128 ± 11
Change with training	−16 ± 6*	−19 ± 6*
CT subcutaneous Fat (cm^2)		
Initial	336 ± 31	284 ± 33
Change with training	−12 ± 7	1 ± 8
$\dot{V}o_2$max (L/min)		
Initial	2.1 ± 0.1	2.1 ± 0.2
Change with training	0.3 ± 0.1*	0.3 ± 0.1*
$\dot{V}o_2$max (mL/kg/min)		
Initial	25 ± 1	26 ± 1
Change with training	3.7 ± 0.6*	4.7 ± 0.6*

NOTE. Values are expressed as means ± SE. All baseline and change with training values are not significantly different between the 2 CETP genotype groups.

*Change with training within that genotype significant at $P<.05$.

extent in both CETP genotype groups (Table 2). Body weight decreased slightly, but significantly, in the entire group with exercise training. However, the body weight reductions with exercise training were significant and similar in the 2 CETP genotype groups. Total body fat and CT intra-abdominal fat also decreased significantly and to the same degree with exercise training in the 2 CETP genotype groups. CT subcutaneous fat did not change significantly with exercise training in the entire group and the changes with exercise training in the 2 CETP genotype groups also were not significantly different.

Plasma total cholesterol and LDL-C levels did not change significantly with exercise training in the entire group, in either CETP genotype group, or differently between the two CETP genotype groups (Table 2). HDL_{1NMR}-C was not evident in any of the subjects in the present study. HDL_{2NMR}-C levels increased significantly with exercise training in CETP B1B1 genotype individuals, but did not change significantly with exercise training in CETP B1B2 genotype individuals. Furthermore, HDL_{2NMR}-C responses to exercise training were significantly different between the 2 CETP genotype groups ($P < .05$). HDL_{3NMR}-C levels tended to decrease with exercise training in CETP B1B1 genotype individuals, and to not change with exercise training in CETP B1B2 genotype individuals. However, these differences between CETP genotype groups were not statistically significant. HDL_{4NMR}-C levels tended to increase with exercise training somewhat more in CETP B1B2 compared to B1B1 genotype individuals, although again the differences were not significant. HDL_{5NMR}-C levels tended to increase with exercise training and to the same extent in the 2 CETP genotype groups. The integrated $HDL_{3\text{-}5NMR}$-C levels increased with exercise training in CETP B1B2 genotype individuals, whereas they did not change in CETP B1B1 genotype individuals; the integrated $HDL_{3\text{-}5NMR}$-C response differences between the 2 CETP genotype groups were statistically significant.

Differential changes in plasma HDL-C subfractions with exercise training were not associated with APO E or LPL *Pvu*II genotype in these individuals (data not shown). Furthermore, the differential changes in HDL-C subfractions with exercise training as a function of CETP genotype in these individuals were not affected by APO E or LPL *Pvu*II allelic variants.

DISCUSSION

Endurance exercise training longer than 12 weeks in duration generally reduces cardiovascular disease risk by improving plasma lipoprotein-lipid profiles, specifically by increasing plasma HDL- and HDL_2-C levels.[10] However, interindividual plasma HDL- and HDL_2-C responses to even standardized exercise training interventions are highly variable[11] with a substantial number of individuals not eliciting increases in plasma HDL- and HDL_2-C levels. We found that a common Taq1B CETP locus polymorphic variation may account for some of the interindividual variability in plasma HDL-C sub-

Table 2. Initial Plasma Lipoprotein-Lipid Levels and Their Changes With Exercise Training as a Function of CETP Genotype

	CETP Genotype B1B1 (n = 16)	CETP Genotype B1B2 (n = 14)
$Cholesterol_{NMR}$		
Initial	216 ± 9	202 ± 9
Change with training	−2 ± 6	6 ± 7
LDL_{NMR}-C		
Initial	144 ± 7	133 ± 7
Change with training	−3 ± 6	4 ± 6
TG_{NMR}		
Initial	134 ± 15	145 ± 16
Change with training	−14 ± 12	−20 ± 12
HDL_{NMR}-C		
Initial	43 ± 3	38 ± 3
Change with training	2 ± 1†	5 ± 1†
HDL_{2NMR}-C		
Initial	12.1 ± 1.9	14.2 ± 2.0
Change with training	2.8 ± 1.4*†	−1.1 ± 1.5
HDL_{3NMR}-C		
Initial	15.0 ± 2.7	11.7 ± 2.9
Change with training	−4.5 ± 2.1†	0.2 ± 2.2
HDL_{4NMR}-C		
Initial	12.7 ± 1.7	10.2 ± 1.8
Change with training	2.6 ± 1.3†	4.7 ± 1.4†
HDL_{5NMR}-C		
Initial	3.2 ± 1.5	2.3 ± 1.6
Change with training	1.3 ± 0.8	1.4 ± 0.9
$HDL_{3\text{-}5NMR}$-C		
Initial	30.7 ± 4.3	24.2 ± 4.6
Change with training	−0.6 ± 2.0	6.2 ± 2.1*†

NOTE. All values are expressed as means ± SE in units of mg/dL.

*Difference between 2 CETP genotype groups significant at $P < .05$.

†Change with training within that genotype significant at $P < .05$.

fraction responses to prolonged, highly standardized endurance exercise training in healthy middle- to older-aged men and women. It is important to note that this genotype represents approximately 50% of Caucasian populations. Therefore, this polymorphic variation could have an impact on overall public health as it is relatively common. The association of this allelic variant with the plasma HDL-C subfraction responses to prolonged endurance exercise training was independent of 2 other common polymorphic variants we have previously found to associate with these responses.[19,20]

CETP catalyzes the exchange of TG and cholesterol esters between plasma lipoproteins and, therefore, has a significant impact on plasma lipoprotein composition. Plasma CETP activity transfers cholesterol from HDL to VLDL, chylomicrons and LDL, in exchange for TG.[1] The resulting TG-rich HDL particles are then hydrolyzed by hepatic TG lipase to produce small, dense HDL particles that are relatively cholesterol deficient. The importance of CETP activity in the metabolism and composition of HDL particles has been demonstrated in individuals with genetic CETP deficiency. In these individuals, reductions in CETP mass are associated with increased total HDL-C and HDL_2/HDL_3 ratios.[2] Polymorphic variation at the CETP locus also associates with plasma CETP mass and activity, with Taq 1B B1 homozygotes having the highest, heterozygotes intermediate, and B2 homozygotes the lowest levels.[5,6,21,22] As is the case with genetic CETP deficiency, individuals with the lowest CETP levels (B1 homozygotes) have the highest HDL-C concentration,[3,5-8,21,22] while those with the highest CETP levels (B2 homozygotes) have the lowest HDL-C and HDL_2/HDL_3 ratio.[7] While all of these outcome phenotypes clearly alter an individual's risk of developing cardiovascular disease, recently Kuivenhoven et al[22] also reported that CETP Taq1B genotype had a significant effect on coronary atherosclerosis progression with B1B1 individuals showing the greatest reduction, B1B2 heterozygotes an intermediate reduction, and B2B2 homozygotes the least reduction in coronary luminal diameter in the longitudinal Regression Growth Evaluation Statin Study (REGRESS) study. Thus, based on its relationship to cardiovascular disease risk factors and direct clinical measures of cardiovascular disease, CETP genotype would appear to be a putative cardiovascular disease risk factor.

Substantial evidence indicates that CETP Taq1B allelic variation interacts with a number of environmental factors to affect plasma HDL-C levels. Kondo et al reported that CETP genotype and plasma HDL-C level associations were evident in smokers, but not nonsmokers.[8] Vohl et al reported that the associations between CETP Taq1B genotype, plasma CETP activity, and HDL-C levels were evident only in men with abdominal obesity and some features of the insulin resistance syndrome.[4] Hannuksela et al found that the associations between CETP Taq1B genotype and plasma lipoprotein-lipid levels were affected by smoking and alcohol intake.[3] Freeman et al found that the effect of CETP Taq1B genotype on plasma HDL- and HDL_2-C levels was not evident in smokers and was diminished in obese individuals.[7] Thus, it is quite clear that this common CETP Taq1B locus allelic variation interacts with a number of environmental factors to affect plasma HDL-C levels and probably also HDL-C subfractions.

There is some evidence that CETP Taq1B genotype influences the change in critical clinical parameters with interventions in individuals at high risk for cardivascular disease. Dullaart et al[9] reported that plasma lipoprotein-lipid changes with a low-cholesterol diet were related to CETP Taq1B genotype in middle-aged type 1 diabetics. They found that VLDL-C and LDL-C levels decreased and HDL-C levels did not change with this diet in a small number of B1B1 homozygotes, whereas in a similar number of B1B2 heterozygotes VLDL-C and LDL-C did not change and HDL-C levels decreased with this diet. More recently, Kuivenhoven et al[22] reported that during the longitudinal REGRESS trial, pravastatin slowed the previously higher rate of coronary luminal diameter reduction in B1B1 homozygotes, but not in CETP B2B2 genotype patients, who initially had a slower rate of progression.

We observed an increase in HDL-C with exercise training in the total population and in both CETP Taq1B genotype groups. This increase tended to be somewhat greater in men and women with the CETP B1B2 genotype, although the difference did not achieve statistical significance. However, the changes in the subfractions that contributed to the overall increases in HDL-C levels with exercise training in the 2 CETP Taq1B genotype groups were clearly different. Those men and women with the CETP B1B1 genotype changed plasma HDL-C levels with exercise training by increasing plasma HDL_{2NMR}-C levels, while decreasing plasma HDL_{3NMR}-C levels – both of which changes appear to be proatherogenic.[23-25] They also increased their antiatherogenic plasma HDL_{4NMR}-C levels, but their increase was only approximately 50% of the increase evident in the B1B2 genotype men and women. On the other hand, CETP Taq1B B1B2 genotype men and women decreased plasma HDL_{2NMR}-C levels somewhat, did not change HDL_{3NMR}-C levels, and increased plasma HDL_{4NMR}-C levels substantially, with all of these changes being antiatherogenic compared to the changes in the CETP B1 homozygotes. Thus, despite the facts that both CETP genotype groups completed the same standardized exercise training intervention while maintaining the same low-fat diet and showed the same changes in other variables known to independently affect plasma lipoprotein-lipid levels, they had substantially different outcomes in the terms of HDL-C subfraction changes.

We found a significant association between CETP Taq1B genotype and the changes in HDL-C subfractions with prolonged endurance exercise training in a relatively small sample of subjects. However, our findings contribute important results for a number of reasons. First, the exercise training intervention was prolonged and highly standardized and a standardized diet was maintained throughout the study. Second, because this was a longitudinal intervention study, data for the subjects after their interventions were compared to their own baseline data, which is clearly a powerful study design as opposed to the cross-sectional nature of most of the previous studies of associations between CETP Taq1B genotype and plasma HDL-C levels. Finally, the study population was selected to be quite homogenous at the start of the study and numerous potential confounding variables that could independently affect plasma HDL-C levels were measured and found to not change differently with the intervention between CETP Taq1B genotype groups. Thus, we feel that these data provide some initial evidence that CETP Taq1B genotype may identify middle- to older-aged healthy sedentary men and women

who improve their plasma HDL-C subfractions the most with prolonged endurance exercise training. Unfortunately, because of the relatively small sample size we were unable to address the potential for gene-gene interactive effects with exercise training for other loci we have previously found to affect the plasma HDL-C changes with endurance exercise training.[19,20] However, the results indicate that the Taq1B CETP locus has a significant effect on these responses, independent of APO E and LPL *Pvu*II genotype.

One limitation of this study clearly is the relatively small sample size. Because of this limited statistical power it is possible that we may have rejected hypotheses that there were other significant genotype-dependent training adaptation differences (type 1 statistical error). On the other hand, it is also possible that if our relatively small sample size is not truly representative of the larger general population, we may have accepted our hypotheses when, in fact, they should have been rejected (type 2 statistical error). Post hoc statistical power calculations indicate that with our sample sizes of approximately 15 subjects per genotype group, we had 80% power to detect a difference between genotype groups that was roughly equal to the average SE for the 2 groups.

In summary, the present results provide some initial evidence that a common CETP locus polymorphic allelic variant appears to have a significant and independent effect on the degree to which middle- to older-aged individuals improve their plasma HDL-C subfractions with prolonged endurance exercise training. Future studies must determine if this is a robust putative marker that conveys significant information in populations of different ages and different ethnicity. It would also be important to determine whether this genotype interacts with other common polymorphic allelic variants related to plasma lipoprotein-lipid metabolism to further influence the changes in plasma HDL-C subfractions with prolonged endurance exercise training.

REFERENCES

1. Fielding CJ, Fielding PE: Molecular physiology of reverse cholesterol transport. J Lipid Res 36:211-228, 1995
2. Brown ML, Inazu A, Hesler CB, et al: Molecular basis of lipid transfer protein deficiency in a family with increased high-density lipoproteins. Nature 23:448-451, 1989
3. Hannuksela ML, Liinamaa MJ, Kesaniemi A, et al: Relation of polymorphisms in the cholesteryl ester transfer protein gene to transfer protein activity and plasma lipoprotein levels in alcohol drinkers. Atherosclerosis 110:35-44, 1994
4. Vohl MC, Lamarche B, Pascot A, et al: Contribution of the cholesteryl ester transfer protein gene TaqIB polymorphism to the reduced plasma HDL-cholesterol levels found in abdominal obese men with the features of the insulin resistance syndrome. Int J Obesity 23:918-925, 1999
5. Gudnason V, Kakko S, Nacaud V, et al: Cholesteryl ester transfer protein gene effect on CETP activity and plasma high-density lipoprotein in European populations. Eur J Clin Invest 29:116-128, 1999
6. Bernard S, Moulin P, Lagrost L, et al: Association between plasma HDL-cholesterol concentration and Taq1B CETP gene polymorphism in non-insulin-dependent diabetes mellitus. J Lipid Res 39:59-65, 1998
7. Freeman DJ, Griffin BA, Holmes AP, et al: Regulation of plasma HDL Cholesterol and subfraction distribution by genetic and environmental factors: associations between TaqI B RFLP in the CETP gene and smoking and obesity. Arterioscler Thromb 14:336-344, 1994
8. Kondo I, Berg K, Drayna D, et al: DNA polymorphism at the locus for human cholesteryl ester transfer protein (CETP) is associated with high density lipoprotein cholesterol and apolipoprotein levels. Clin Genet 35:49-56, 1989
9. Dullaart RPF, Hoogenberg K, Riemens SC, et al: Cholesteryl ester transfer protein gene polymorphism is a determinant of HDL cholesterol and of the lipoprotein response to a lipid-lowering diet in type 1 diabetes. Diabetes 46:2082-2087, 1997
10. Wood P, Stefanick M: Exercise, fitness, and atherosclerosis, in Bouchard C, Shephard R, Stephens T (eds): Exercise, Fitness, and Health. Chicago, IL, Human Kinetics, 1988, pp 409-423
11. Williams P, Stefanick M, Vranizan K, et al: Effects of weight loss by exercise or by dieting on plasma HDL levels in men with low, intermediate, and normal-to-high HDL at baseline. Metabolism 43:917-917, 1994
12. American College of Sports Medicine: Guidelines for Exercise Testing and Prescription. Baltimore, MD, Williams & Wilkens, 1991, pp 150-154
13. American Heart Association: Dietary guidelines for healthy American adults: A statement for physicians and health professionals by the nutrition committee. Circulation 77:721A-724A, 1988
14. Otvos JD, Jeyarajah EJ, Bennett DW, et al: Development of a proton nuclear magnetic resonance spectroscopic method for determining plasma lipoprotein concentrations and subspecies distributions from a single, rapid measurement. Clin Chem 38:1632-1638, 1992
15. Nicklas B, Rogus E, Colman E, et al: Visceral adiposity, increased adipocyte lipolysis, and metabolic dysfunction in obese postmenopausal women. Am J Physiol 270:E72-78, 1996
16. Dengel D, Hagberg J, Coon P, et al: Effects of weight loss by diet alone or combined with aerobic exercise on body composition in older obese men. Metabolism 43:867-871, 1994
17. Miller S, Dykes D, Polesky H: A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 16:1215-1218, 1988
18. Fumeron F, Betoulle D, Luc G: Alcohol intake modulates the effect of a polymorphism of the cholesteryl ester transfer protein gene on plasma high density lipoprotein and the risk of myocardial infarction. J Clin Invest 96:1664-1671, 1995
19. Hagberg JM, Ferrell RE, Katzel LI, et al: Apolipoprotein E genotype and exercise training-induced increases in plasma HDL- and HDL_2-cholesterol levels. Metabolism 48:943-945, 1999
20. Hagberg JM, Ferrell RE, Dengel DR, et al: Exercise training-induced blood pressure and plasma lipid improvements in hypertensives may be genotype dependent. Hypertension 34:18-23, 1999
21. Kuivenhoven JA, Knijff P, Boer JMA, et al: Heterogeneity at the CETP gene locus: influence on plasma CETP concentrations and HDL cholesterol levels. Arterioscler Thromb 17:560-568, 1997
22. Kuivenhoven JA, Jukema JW, Zwinderman AH, et al: The role of a common variant of the cholesteryl ester transfer protein gene in the progression of coronary atherosclerosis. N Engl J Med 338:86-93, 1998
23. Johansson J, Carlson LA, Landou C: High density lipoproteins and coronary atherosclerosis. A strong inverse relation with the largest particles is confirmed to normotriglyceridemic patients. Arterioscler Thromb Vasc Biol 11:174-182, 1991
24. Williams PT, Vranizan KM, Austin MA: Familial correlations of HDL subclasses based on gradient gel electrophoresis. Arterioscler Thromb Vasc Biol 12:1467-1474, 1992
25. Wilson HM, Patel JC, Russell D: Alterations in the concentration of an apolipoprotein E-containing subfraction of plasma high density lipoprotein in coronary heart disease. Clin Chim Acta 220:175-187, 1993