Effects of Endurance Exercise Training on Plasma HDL Cholesterol Levels Depend on Levels of Triglycerides

Evidence From Men of the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study

Charles Couillard, Jean-Pierre Després, Benoît Lamarche, Jean Bergeron, Jacques Gagnon, Arthur S. Leon, D.C. Rao, James S. Skinner, Jack H. Wilmore, Claude Bouchard

Abstract—High density lipoprotein (HDL) cholesterol concentrations have been shown to increase with regular endurance exercise and, therefore, can contribute to a lower risk of coronary heart disease in physically active individuals compared with sedentary subjects. Although low HDL cholesterol levels are frequently observed in combination with hypertriglyceridemia, some individuals may be characterized by isolated hypoalphalipoproteinemia, ie, low HDL cholesterol levels in the absence of elevated triglyceride (TG) concentrations. The present study compared the responses of numerous lipoprotein-lipid variables to a 20-week endurance exercise training program in men categorized on the basis of baseline TG and HDL cholesterol concentrations: (1) low TG and high HDL cholesterol (normolipidemia), (2) low TG and low HDL cholesterol (isolated low HDL cholesterol), (3) high TG and high HDL cholesterol (isolated high TGs), and (4) high TGs and low HDL cholesterol (high TG/low HDL cholesterol). A series of physical and metabolic variables was measured before and after the training program in a sample of 200 men enrolled in the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study. At baseline, men with high TG/low HDL cholesterol had more visceral adipose tissue than did men with isolated low HDL cholesterol and men with normolipidemia. The 0.4% (not significant) exercise-induced increase in HDL cholesterol levels in men with isolated low HDL cholesterol suggests that they did not benefit from the "HDL-raising" effect of exercise. In contrast, men with high TG/low HDL cholesterol showed a significant increase in HDL cholesterol levels (4.9%, $P<0.005$). Whereas both subgroups of men with elevated TG levels showed reductions in plasma TGs ($\approx -15.0\%$, $P<0.005$), only those with high TG/low HDL cholesterol showed significantly reduced apolipoprotein B levels at the end of the study (-6.0%, $P<0.005$). Multiple regression analyses revealed that the exercise-induced change in abdominal subcutaneous adipose tissue (10.6%, $P<0.01$) was the only significant correlate of the increase in plasma HDL cholesterol with training in men with high TG/low HDL cholesterol. Results of the present study suggest that regular endurance exercise training may be particularly helpful in men with low HDL cholesterol, elevated TGs, and abdominal obesity. **(*Arterioscler Thromb Vasc Biol*. 2001;21:1226-1232.)**

Key Words: HDL cholesterol ■ triglycerides ■ exercise training ■ coronary heart disease

Regular endurance exercise is a widely recognized modality to raise plasma HDL cholesterol levels,[1–3] which is one of the metabolic adaptations contributing to the reduced risk of coronary heart disease (CHD) observed among physically active and fit individuals.[4–6] Although a low plasma HDL cholesterol concentration is often accompanied by an elevated triglyceride (TG) level associated with abdominal obesity and an insulin resistance-hyperinsulinemic state,[7,8] some individuals are characterized by low HDL cholesterol levels without obesity or hypertriglyceridemia, a condition that has been referred to as isolated hypoalphalipoproteinemia.[9–11] Previous studies from our laboratory have shown that subjects with isolated low HDL cholesterol were neither characterized by hyperinsulinemia nor by visceral obesity.[12] Although studies have suggested that patients with isolated low HDL cholesterol syndrome may be at increased CHD risk,[9,10,13,14] it appears very difficult to increase HDL cholesterol levels in these individuals by diet, weight loss, or pharmacotherapy.[15]

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From the Lipid Research Center (C.C., J.-P.D., B.L., J.B.) and the Laboratory of Molecular Endocrinology (J.G.), Laval University Medical Research Center, CHUL Pavilion, Sainte-Foy, Québec, Canada; the Physical Activity Sciences Laboratory (J.G.), Department of Kinesiology, and the Department of Food Sciences and Nutrition (J.-P.D., B.L.), Laval University, Sainte-Foy, Québec, Canada; the Québec Heart Institute (J.-P.D.), Laval Hospital Research Center, Sainte-Foy, Québec, Canada; the School of Kinesiology and Leisure Studies (A.S.L.), University of Minnesota, Minneapolis; the Division of Biostatistics (D.C.R.), Washington University Medical School, St. Louis, Mo; the Department of Kinesiology (J.S.S.), Indiana University, Bloomington; the Department of Health and Kinesiology (J.H.W.), Texas A&M University, College Station; and the Pennington Biomedical Research Center (C.B.), Louisiana State University, Baton Rouge.

Correspondence to Jean-Pierre Després, PhD, Québec Heart Institute, Pavilion Mallet, 2nd Floor, 2725 chemin Sainte-Foy, Sainte-Foy, Québec, Canada G1V 4G5. E-mail Jean-Pierre.Despres@crchul.ulaval.ca

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Because subjects with isolated low HDL cholesterol have normal body weight and fat content, we have hypothesized that they may be less responsive to endurance exercise–induced improvements of the lipoprotein-lipid profile than are subjects with low HDL cholesterol, elevated TG concentrations, abdominal obesity, and hyperinsulinemia. Therefore, the aim of the present study was to compare the lipoprotein-lipid responses to a 20-week endurance exercise training program in men with low HDL cholesterol levels but with or without high TG concentration.

Methods

Subjects

The Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study cohort has been previously described.[16] Briefly, the HERITAGE subjects came from families that included the natural mother and father (aged ≤65 years) and 3 adult offspring. The present study describes the results of baseline and follow-up data from 200 white men (79 fathers and 121 sons). Subjects were healthy and sedentary and met a number of inclusion and exclusion criteria.[16] The study protocol had been previously approved by the Institutional Review Board at each of the 4 clinical centers. Informed consent was obtained from each subject.

Endurance Exercise Training Program

The training program has already been extensively described.[16–18] Participants trained under supervision in the clinical centers on a cycle ergometer (Universal Aerobicycle) for 60 sessions by using the same standardized training protocol. They were required to complete the 60 sessions within 21 weeks. They could not exercise >1 session per day, >4 sessions per week, or <1 session per week. As well, they could not get ahead by >2 sessions or fall behind by >2 sessions. Participants who knew that they might miss a few sessions were encouraged to train 4 times per week for 2 weeks to build up a reserve. Program adherence was monitored several times per week. Participants were contacted when they appeared to be falling behind, and a plan was developed to bring them back on schedule as soon as possible. To determine each person's training intensity, heart rate (HR), power output, and oxygen intake (VO_2) obtained during the 3 baseline cycle ergometer tests were plotted to determine the average HR and power output associated with 55%, 65%, 70%, and 75% of his/her maximum VO_2 (VO_2max) before training. These HR and power output values were then used throughout the training program. Training sessions during the first 2 weeks began at an HR associated with 55% VO_2max for 30 minutes. Either duration or intensity was then increased each 2 weeks until the 14th week of training, when participants exercised at the HR associated with 75% of their initial VO_2max for 50 minutes. This was then maintained for the next 6 weeks.

Anthropometry, Body Composition, and Fat Distribution

Body weight, height, and waist and hip circumferences were measured according to standardized procedures,[19] and the waist-to-hip ratio was calculated. Body density was measured by the hydrostatic weighing technique,[20] and percent body fat was calculated as already described.[17,21] Fat mass was obtained by multiplying body weight by percent body fat. These measurements are highly reproducible, with no difference between clinical centers and no drift over time.[21] Visceral adipose tissue (AT) accumulation was assessed by computed tomography with the use of previously described procedures.[22]

Plasma Lipid, Lipoprotein, and Apolipoprotein Measurements

Blood sampling was obtained in the morning after a 12-hour overnight fast. Both pretraining and posttraining data are means of 2 separate measurements. Posttraining plasma samples were collected 24 hours after the last exercise session, and lipoprotein-lipid levels were adjusted for plasma volume changes, as already described.[23] Blood was drawn locally at each clinical center and then shipped to the core laboratory in Québec City. Cholesterol and TG levels were determined by enzymatic methods by using the Technicon RA-500 analyzer (Bayer Corp Inc,), as previously described.[24] Plasma VLDLs (density <1.006 g/mL) were isolated by ultracentrifugation, and the HDL fraction was obtained after precipitation of LDL in the infranatant (density >1.006 g/mL) with heparin and $MnCl_2$.[25] The cholesterol and TG contents of the infranatant fraction were measured before and after the precipitation step. ApoA-I (infranatant) and apoB (plasma) levels were measured by the rocket immunoelectrophoretic method of Laurell, as previously described by Avogaro et al.[26] The lyophilized serum standards for apolipoprotein measurements were prepared in the core laboratory at the Lipid Research Center of Laval University Medical Center and calibrated with reference standards obtained from the Centers for Disease Control. The cholesterol content of HDL_2 and HDL_3 subfractions was also determined after further precipitation of HDL_2 with dextran sulfate.[27] Reproducibility of all lipid-lipoprotein measurements has been examined and is excellent.[28]

Plasma Insulin Concentrations

Plasma insulin levels were measured by radioimmunoassay after polyethylene glycol separation, as described by Desbuquois and Aurbach.[29] Polyclonal antibodies that cross-react >90% with proinsulin (and, presumably, with its conversion intermediates) were used.[30] Therefore, in the present study, insulin refers to immunoreactive insulin (defined as the sum of insulin, proinsulin, and split proinsulin).

Postheparin Plasma Lipase Activities

Postheparin lipoprotein lipase (PH-LPL) and postheparin hepatic lipase (PH-HL) activities were also measured on 1 occasion before training and again after the training program in subjects after a 12-hour overnight fast, 10 minutes after an intravenous injection of heparin (60 IU/kg body mass). The postheparin plasma lipase activities were measured as previously described.[31] The 2 lipolytic enzyme activities were expressed as nanomoles of oleic acid released per milliliter of plasma per minute. These measures are also highly reproducible.[28]

Statistical Analyses

Pearson product moment correlation coefficients were used to quantify associations between variables. Men were divided into 4 subgroups according to baseline fasting plasma TG and HDL cholesterol concentrations: (1) normolipidemia (n=62), (2) isolated low HDL cholesterol (n=38), (3) isolated high TGs (n=38), and (4) high TG/low HDL cholesterol (n=62). Cutoff values were 1.34 and 0.92 mmol/L for TG and HDL cholesterol, respectively, which corresponded to the 50th percentiles of their respective distributions. Interestingly, the 50th percentile of the sample distribution for HDL cholesterol (0.92 mmol/L) was found to be near the value of 0.90 mmol/L recommended by the Canadian Working Group on Hypercholesterolemia and Other Dyslipidemia.[32] On the other hand, the 1.34 mmol/L value for TGs is well below the upper limit of 2.0 mmol/L recommended by the working group. By using the 50th percentile value of the TG distribution, our intent is not to define a new cut point for hypertriglyceridemia but to examine the metabolic response to exercise training among subjects with low HDL cholesterol levels but with varying TG concentrations. Therefore, our definition of "high" and "low" is limited to the classification of subjects above and below the 0.92 and 1.34 mmol/L arbitrary cut points for HDL cholesterol and TGs, respectively. Differences among men with various baseline fasting lipoprotein-lipid phenotypes were tested for significance by using ANOVA with the Duncan multiple range test. Paired *t* tests were used to examine the significance of the changes in physical and metabolic variables within each subgroup of men. In all analyses, $P<0.05$ was considered significant. Analyses were conducted with the SAS statistical package (SAS Institute).

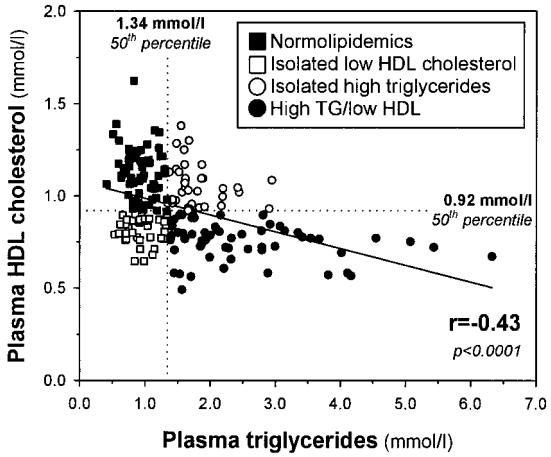

Figure 1. Association between baseline fasting plasma TG and HDL cholesterol concentrations. Using the 50th percentiles of the TG (1.34 mmol/L) and HDL cholesterol (0.92 mmol/L) distribution, we identified 4 different fasting lipoprotein phenotypes: normolipidemic men (n=62, solid squares), men with isolated low HDL cholesterol (n=38, open squares), men with isolated high TGs (n=38, open circles), and men with high TG/low HDL cholesterol (n=62, solid circles).

Results

Figure 1 shows the relationship between baseline plasma HDL cholesterol levels and TG concentrations from which we categorized men into 3 distinct dyslipidemic groups and 1 reference group of normolipidemic men who had high HDL cholesterol levels (above the 50th percentile) and low TG concentrations (below the 50th percentile).

Table 1 shows the baseline pretraining plasma lipoprotein profile of the 4 subgroups of men. Although men with high TG/low HDL cholesterol had higher plasma TG (by design), cholesterol, and apoB concentrations than did normolipidemic men, men with isolated low HDL cholesterol levels had lower plasma cholesterol and apoA-I levels but similar apoB levels compared with the levels in normolipidemic men. Thus, the higher total cholesterol/HDL cholesterol ratio noted among subjects with isolated low HDL cholesterol resulted solely from the very low HDL cholesterol concentrations. However, high plasma cholesterol and low HDL cholesterol levels contributed to the high total cholesterol/HDL cholesterol ratio observed in men with high TG/low HDL cholesterol compared with normolipidemic men. Men with high TG/low HDL cholesterol were also clearly hyperinsulinemic and, presumably, more insulin resistant at baseline than were the other subgroups of subjects.

Table 2 shows the baseline physical characteristics of the 4 groups of men. Men with high TG/low HDL cholesterol had the highest body mass index and body fat mass values of the 4 groups. Furthermore, men with high TG/low HDL cholesterol were characterized by a larger waist circumference and by higher levels of abdominal visceral and subcutaneous AT than were subjects with isolated low HDL cholesterol, which were neither characterized by obesity nor by a higher accumulation of abdominal fat compared with normolipidemic subjects.

Table 3 shows the responses of body composition and of abdominal fat accumulation indices to the standardized endurance exercise training program. It is important to point out that maximal aerobic power increased significantly and comparably in all subgroups of men (≈0.5 L/min, $P<0.001$). Thus, there were no differences in the fitness gains between dyslipidemic and normolipidemic subjects. All groups showed a small but significant reduction in body fat mass and increase in fat-free mass. These changes were accompanied by small but significant reductions in abdominal AT areas (subcutaneous and visceral), with the exception of the change in visceral AT in subjects with isolated low HDL cholesterol and in individuals with isolated high TGs. The greatest reduction in visceral AT levels with exercise training was observed among men with high TG/low HDL cholesterol ($P<0.0001$).

TABLE 1. Baseline Plasma Lipid Profile of Participants According to Baseline Dyslipidemic Phenotype

Variables	Normolipidemia	Isolated Low HDL Cholesterol	Isolated High TGs	High TG/Low HDL
Subjects, n	62	38	38	62
TGs, mmol/L	0.94±0.22	0.93±0.22	1.77±0.39*†	2.45±1.09*†‡
HDL cholesterol, mmol/L	1.12±0.14	0.81±0.07**	1.05±0.12*†	0.75±0.10*†‡
Cholesterol, mmol/L	4.20±0.80	3.70±0.80*	5.30±0.80*†	5.00±1.00*†
LDL cholesterol, mmol/L	2.80±0.70	2.60±0.80	3.60±0.80*†	3.30±0.90*†‡
HDL_2 cholesterol, mmol/L	0.36±0.10	0.22±0.06*	0.29±0.09*†	0.18±0.07*†‡
HDL_3 cholesterol, mmol/L	0.76±0.10	0.59±0.06*	0.76±0.10†	0.58±0.08*
Total/HDL cholesterol	3.80±0.80	4.60±0.90*	5.10±1.00*†	6.80±1.40*†‡
ApoA-1, g/L	1.23±0.12	1.01±0.10*	1.28±0.12*†	1.07±0.12*†‡
ApoB, g/L	0.77±0.20	0.73±0.19	1.05±0.20*†	1.06±0.22*†
Insulin, pmol/L	52.0±32.7	58.1±33.5	73.8±48.1*	94.6±70.6*†‡
Postheparin plasma lipase activities, nmol/mL per min				
LPL	57.1±27.9	47.0±28.6	48.2±22.9	28.7±21.2*
HL	241.4±62.9	252.1±59.4	255.4±54.2	238.7±65.1
HL/LPL ratio	5.6±3.5	12.1±19.0*	10.2±21.3	10.3±11.2

LPL indicates lipoprotein lipase; HL, hepatic lipase. Values are mean±SD.
*$P<0.05$ vs normolipidemic men; †$P<0.05$ vs men with isolated low HDL cholesterol; and ‡$P<0.05$ vs men with isolated high TGs.

TABLE 2. Baseline Physical Characteristics of Participants According to Baseline Dyslipidemic Phenotype

Variables	Normolipidemia	Isolated Low HDL Cholesterol	Isolated High TGs	High TG/ Low HDL
Subjects, n	62	38	38	62
Age, y	33±14	30±14	40±14*†	42±14*†
Weight, kg	78.4±14.3	78.5±11.6	85.1±16.5*†	90.8±13.9*†
Body mass index, kg/m^2	24.3±3.9	25.2±4.1	27.4±4.4*†	28.8±4.2*†
Body fat, %	18.7±9.2	19.3±8.5	25.4±6.1*†	27.5±7.1*†
Fat mass, kg	15.5±9.7	15.8±8.8	22.4±9.6*†	25.6±9.9*†
Fat-free mass, kg	62.9±8.1	62.7±6.7	62.8±8.5	65.2±7.2
Waist girth, cm	88.0±12.1	89.4±11.9	96.3±11.9*†	101.5±10.9*†‡
Abdominal AT areas, cm^2				
Visceral	82±48	83±56	120±62*†	136±56*†
Subcutaneous	170±114	182±117	255±121*†	289±117*†
VO_2max, mL/kg per min	41.3±8.8	41.4±9.1	34.2±6.9*†	32.6±6.7*†

Values are mean±SD.

*$P<0.05$ vs normolipidemic men; †$P<0.05$ vs men with isolated low HDL cholesterol; and ‡$P<0.05$ vs men with isolated high TGs.

The responses of plasma lipoproteins and lipids to the exercise program in the 4 groups of men are shown in Figure 2. First, subjects with isolated low HDL cholesterol did not appear to benefit from the expected "HDL-raising" effect of exercise, whereas men with high TG/low HDL cholesterol showed increases in HDL cholesterol and apoA-I levels (4.9% and 3.7%, respectively) that were significantly higher ($P<0.05$) than the marginal increases of both variables (HDL cholesterol 0.4%, apoA-I 1.5%) noted in those with isolated low HDL cholesterol. Furthermore, the increase in HDL cholesterol in men with high TG/low HDL cholesterol was mostly the result of the important rise in HDL_2 cholesterol levels. Thus, among subjects with isolated low HDL cholesterol, failure of HDL cholesterol to increase with exercise largely explained the lack of a favorable impact of the exercise program on the total/HDL cholesterol ratio in this group. However, the increase in HDL cholesterol levels noted in response to the exercise program in men with high TG/low HDL cholesterol was accompanied by a significant reduction (9.0%) in the ratio of total/HDL cholesterol, which was greater than in all other groups. Although both groups of subjects with high TG levels showed similar reductions ($\approx -15.0\%$, $P<0.005$) in plasma TGs, only men with high TG/low HDL cholesterol showed a significant reduction in apoB (-6.0%, $P<0.005$) in response to the exercise program. Because markedly hypertriglyceridemic individuals within men with high TG/low HDL cholesterol may have affected the change in apoB over the training period, we have also adjusted the change in apoB for baseline TG levels. The adjustment procedure had no effect on the change in apoB, which remained highly significant ($P<0.005$). Furthermore, PH-LPL increased in all groups, whereas PH-HL activity decreased significantly only in the normolipidemic group ($P<0.001$) and in individuals with isolated high TGs ($P<0.005$).

Finally, multivariate analyses revealed that change in abdominal subcutaneous AT (10.6%, $P<0.01$) was the only variable that was significantly associated with the increase in

TABLE 3. Exercise-Induced Changes in Physical Characteristics of Participants According to Their Baseline Dyslipidemic Phenotypes

Variables	Normolipidemia	Isolated Low HDL Cholesterol	Isolated High TGs	High TG/ Low HDL
Subjects, n	62	38	38	62
Weight, kg	−0.3±2.4	0.0±1.9	−0.2±1.8	−0.7±2.1§
Body mass index, kg/m^2	−0.1±0.7	0.1±0.6	−0.1±0.6	−0.3±0.6*
Body fat, %	−0.8±1.9*	−0.9±2.1§	−0.8±1.3†	−1.1±1.6†
Fat mass, kg	−0.8±2.1*	−0.7±4.1§	−0.7±1.4*	−1.1±1.9†
Fat-free mass, kg	0.5±1.1†	0.7±1.3*	0.5±1.2‡	0.4±1.2‡
Waist girth, cm	−0.9±2.6‡	−0.3±1.8	−0.9±2.2§	−1.2±2.3†
Abdominal AT areas, cm^2				
Visceral	−6.8±18.4*	−4.7±13.0	−5.0±17.2	−10.8±21.1†
Subcutaneous	−9.8±25.1*	−5.9±20.4§	−11.2±19.7†	−12.7±22.9†
VO_2 max, l/min	0.5±0.3†	0.4±0.2†	0.5±0.2†	0.5±0.2†

Values are mean±SD.

*$P<0.005$, †$P<0.001$, ‡$P<0.01$, and §$P<0.05$ vs pretraining values.

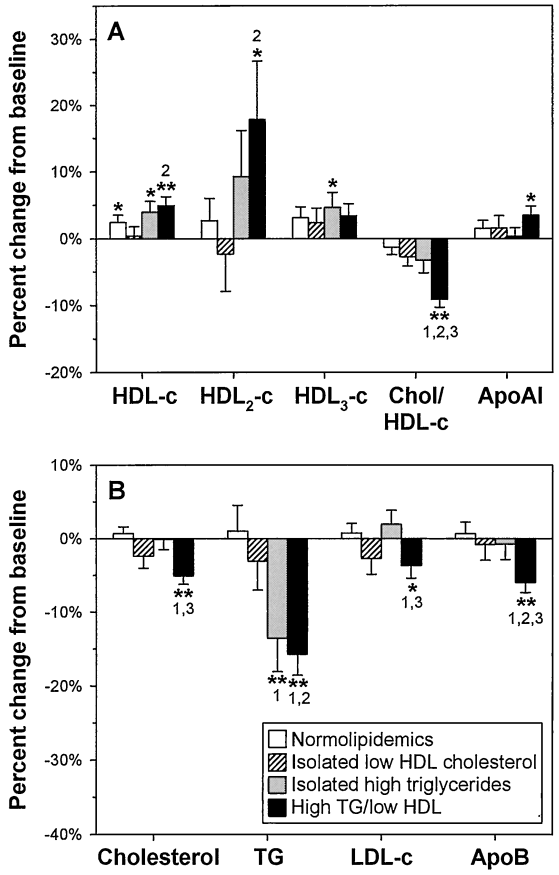

Figure 2. Exercise-induced changes (expressed in percentage from baseline) in HDL cholesterol (HDL-c) concentrations and related variables (A) and other lipid profile parameters (B) induced by the exercise training program according to the different fasting plasma lipoprotein phenotypes at baseline. *$P<0.05$ and **$P<0.005$ for statistically significant change. Numbers indicate the following: 1, significantly different from the normolipidemic men; 2, significantly different from men with isolated low HDL cholesterol; and 3, significantly different from men with isolated high TGs.

plasma HDL cholesterol with training among men with high TG/low HDL cholesterol (Table 4). As for the total/HDL cholesterol ratio, change in fasting TG explained 14.6% ($P<0.005$) of the response of this ratio. On the other hand, none of the selected variables appeared to significantly contribute to the changes in HDL cholesterol and the total/HDL cholesterol ratio in subjects with isolated low HDL cholesterol.

Discussion

It is well established that low plasma HDL cholesterol levels are associated with an increased risk of CHD.[33,34] Indeed, a low HDL cholesterol concentration has been shown to be the most prevalent abnormality of the lipoprotein-lipid profile reported among men with documented CHD.[35] In this regard, the recently published results of the Veterans Affairs High-Density Lipoprotein Intervention Trail (VA-HIT) Study[36] clearly show that pharmacotherapy aimed at increasing plasma HDL cholesterol levels reduces the risk of CHD, even in the absence of any change in plasma LDL cholesterol levels; this latter finding is commonly observed when CHD patients with low HDL cholesterol levels are treated with a fibrate such as gemfibrozil.

It is now fairly well recognized that endurance exercise training can increase plasma HDL cholesterol levels[1–3] if the exercise training stimulus is sufficient. Furthermore, several studies have suggested that the HDL-raising effect of endurance exercise training could be largely explained by the concomitant loss of body mass or fat.[37] Therefore, among high-risk overweight dyslipidemic patients with insulin resistance, hyperinsulinemia, hypertriglyceridemia, and low HDL cholesterol levels, the net increase in the daily energy expenditure produced by regular endurance exercise may eventually induce mobilization of body fat and weight loss. In turn, this may ultimately reduce the amount of abdominal fat, improve insulin action, lower TG levels, and increase plasma HDL cholesterol concentrations.[38] These favorable metabolic improvements explain why regular endurance exercise of moderate intensity but of long duration is advocated for the management of obesity and of its related high TG/low HDL cholesterol dyslipidemia.

However, low plasma HDL cholesterol is a heterogeneous condition. Apart from rare monogenic disorders,[39–41] it is not uncommon to find individuals with low HDL cholesterol levels in the absence of abdominal obesity, insulin resistance, or hypertriglyceridemia. For instance, in the present study, 38 men of the total sample of 200 men (19% of the sample) had plasma HDL cholesterol levels <0.92 mmol/L, while simultaneously having plasma TG levels <1.34 mmol/L. This group with isolated low HDL cholesterol had very low

TABLE 4. Multivariate Regression Analyses Showing Independent Contributions of Physical and Metabolic Characteristics to Change in HDL Cholesterol Levels and in Total/HDL Cholesterol Ratio

Dependent Variable	Independent Variable	Partial ($R^2\times100$)	P
Men with high TG/low HDL cholesterol			
HDL cholesterol	Abdominal subcutaneous AT	10.6	0.0095
Total/HDL cholesterol	TGs	14.6	0.0022
Men with isolated HDL cholesterol			
HDL cholesterol	...	NS	NS
Total/HDL cholesterol	...	NS	NS

NS indicates that no variable met the 0.05 significance/level. Independent variables included were the changes in fat mass, waist circumference, abdominal subcutaneous and visceral AT and plasma TG levels, PH-LPL, and PH-HL activities.

average plasma cholesterol as well as LDL cholesterol, apoB, and apoA-I levels. Furthermore, they were not obese and did not differ from normolipidemic subjects for abdominal fat accumulation. It also seems important to point out that men with isolated low HDL cholesterol had a VO_2max at baseline as high as that of normolipidemic men, suggesting that they were as physically fit as normolipidemic men. These results are consistent with our previously published study in which we reported that patients with isolated hypoalphalipoproteinemia were not characterized by abdominal obesity or by the features of insulin resistance.[12] Because these patients were neither overweight nor hyperinsulinemic, we hypothesized that they might show a specific response pattern to a standardized endurance exercise training program. Indeed, men with high TG/low HDL cholesterol displayed the expected favorable changes in the lipoprotein profile in response to the standardized exercise training program (eg, decrease in plasma TG, cholesterol, LDL cholesterol, and apoB levels and an increase in apoA-I and HDL cholesterol). Furthermore, the concomitant increases in HDL_2 cholesterol and apoA-I in men with high TG/low HDL cholesterol suggest simultaneous effects of exercise training on the density and number of HDL particles. On the other hand, exercise training was unsuccessful in raising plasma HDL cholesterol levels in subjects with isolated low HDL cholesterol. The lack of response in subjects with isolated low HDL cholesterol could not be attributed to differences in the compliance to the training program or to difference in cardiorespiratory adaptations, inasmuch as the absolute and relative increase in VO_2max was similar among all study groups. Furthermore, all groups displayed similar favorable changes in the PH-HL/PH-LPL ratio, which we have previously shown to be a significant correlate of plasma HDL cholesterol levels.[28]

Zmuda et al[42] have already shown that the ability to increase HDL cholesterol levels through endurance exercise training was limited in subjects with low initial HDL cholesterol. Failure to improve TG metabolism in these subjects was proposed as a possible explanation. Our results are concordant with those previous observations, because among our subjects with low HDL cholesterol levels, only those with concomitantly elevated baseline TG concentrations showed an increase in HDL cholesterol after the training program. It is noteworthy that these individuals also showed a decrease in fasting TGs in response to the training program. On the other hand, Williams et al[43] found the largest increase in HDL cholesterol with exercise in men with high baseline HDL cholesterol levels. These results may appear at first glance to be at variance with our own observations. However, Williams et al[43] also reported a significant and positive association between baseline HDL cholesterol levels and the subjects' running mileage during the trial, which led them to suggest that greater distances and a more important weight loss may have accounted, at least in part, for the larger increase in HDL cholesterol levels in these individuals.

Inasmuch as multivariate analyses revealed that changes in TG levels and abdominal subcutaneous AT were significant predictors of the response of the total/HDL cholesterol ratio and of HDL cholesterol levels, respectively, the lack of response among subjects with isolated low HDL cholesterol may be due to the fact that they were nonobese, normotriglyceridemic, and insulin sensitive and, thus, could not get the benefits associated with weight loss and from the exercise training–induced improvement in insulin sensitivity.[38] Indeed, because fasting insulin is often used a crude index of insulin resistance, the significantly lower baseline insulin levels compared with the levels in men with high TG/low HDL cholesterol suggest that men with isolated low HDL cholesterol were more insulin sensitive, whereas men with high TG and low HDL cholesterol concentrations appeared to be more insulin resistant.

In intervention studies, the regression to the mean phenomenon is always a factor that needs to be considered. Indeed, in situations in which several measurements are made, values will tend to regress to the mean of the entire group because of measurement error. This phenomenon will translate into a negative relationship between a baseline measurement and the difference between the baseline and follow-up measurements of a variable. In the present study, however, there was no association between baseline HDL cholesterol and changes in HDL cholesterol levels ($r=0.05$, $P=0.53$). Furthermore, apoA-I data give further support to our finding that there was a true metabolic basis for the heterogeneity of HDL cholesterol response, because the largest increase in apoA-I was found among men with high TG/low HDL cholesterol. Because apoA-I and HDL cholesterol measurement errors are independent of each other, a regression to the mean phenomenon is unlikely to be a major contributor to the HDL-raising effect of exercise noted in men with high TG/low HDL cholesterol.

Finally, 2 additional points need to be emphasized. First, subjects with isolated low HDL cholesterol could still benefit from regular endurance exercise through metabolic adaptations that are beyond body mass control, insulin sensitivity, and plasma lipoprotein levels. Second, it is still controversial whether all patients with isolated low HDL cholesterol are at increased risk of CHD. It is not uncommon to find low HDL cholesterol levels among lean subjects on a low-fat intake who also have low plasma cholesterol and LDL cholesterol levels.[11] It is doubtful that this lipid profile is associated with a very high CHD risk. Further studies are needed to better characterize the isolated low HDL cholesterol phenotype from a metabolic and genetic standpoint.

In summary, results of the present study suggest that regular endurance exercise is particularly helpful to improve the lipid lipoprotein profile of men with low HDL cholesterol levels along with abdominal obesity and elevated TG concentrations. However, it appears that subjects with low HDL cholesterol levels as an isolated trait are much less responsive to endurance exercise training, at least as far as their plasma lipoprotein profile is concerned. This finding is concordant with the common observation that it is very difficult in clinical practice to increase the cholesterol content of HDL among subjects with low HDL cholesterol concentrations, when the latter is an isolated lipoprotein characteristic.

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