Journal of Clinical Lipidology (2007) 1, 175–181

Journal of Clinical Lipidology

Review Articles

Impact of exercise on blood lipids and lipoproteins

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KEYWORDS:
Aerobic;
Exercise;
Intensity;
Lipids;
Resistance;
Training

Abstract. Abnormal blood lipids are a significant cardiovascular health risk. Drug therapy and diet continue to be standard management strategies. However, considerable evidence supports physical activity and exercise as having a positive impact on abnormal lipids and such are often recommended as adjunctive interventions. The purpose of this review is to clarify the mechanisms by which exercise facilitates favorable changes in levels of blood lipids and lipoproteins. Studies relative to the effects of exercise on blood lipid levels are notable: The impact of exercise on high-density lipoproteins (HDL-C) is best studied and specify effects of intensity and amount of exercise as well as a genetic influence. Exercise also exerts an effect on HDL-C maturation and composition, cholesterol efflux, and cholesterol delivery to receptors (reverse cholesterol transport). Positive effects of exercise are also seen with blood triglycerides (TG), but little specific effect is seen on low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC). Abundant evidence supports the benefits of exercise on levels of certain blood lipids (namely HDL-C and TG). Although standard management of abnormal blood lipids is drug therapy and diet, it seems prudent to incorporate aerobic exercise as an important component of a healthy lifestyle. In certain individuals, drug therapy may be decreased in dosage or perhaps discontinued in the patient who is "exercise trained," especially if there is associated weight loss.

Pioneer epidemiological studies in the 1950s showed that individuals with certain occupations that demanded greater expenditure of energy in their daily living had lower rates of myocardial infarction and sudden death when compared to their more sedentary peers,[1,2] This observation was expanded when the degree of fitness, defined as greater functional capacity in standardized testing, had an inverse relationship with total and cardiovascular mortality.[3,4] As a therapeutic tool, exercise-based cardiac rehabilitation has demonstrated a 20% to 25% reduction in total mortality and 30% to 35% decrease in cardiovascular mortality in coronary disease patients.[5,6] In view of the well-established causal role of dyslipidemia in the pathogenesis of coronary heart disease, there has been a substantial interest to elucidate the lipid and lipoprotein mechanisms responsible for the beneficial consequences of greater energy expenditure and exercise on cardiovascular health. Exercise has the largest impact on so-called atherogenic dyslipidemia, characterized by low high-density lipoprotein cholesterol (HDL-C), high triglycerides (TG), and small-dense low-density lipoprotein cholesterol (LDL-C) particles.[7,8] This dyslipidemia is one of the characteristics of the metabolic syndrome, the newly recognized clinical entity that results from excessive visceral adiposity, associates with development of type 2 diabetes, and increases likelihood of cardiovascular complications.[9]

Proper management of abnormal blood lipids and lipoproteins is vastly important in the care of patients with (or at risk for) cardiovascular disease, stroke, and other types of atherosclerotic vascular disease. There are a number of effective drug therapies in use—including the more effective statins, which are marketed through a number of brand names. However, issues such as cost, adherence to therapy, and physician visits

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Submitted May 8, 2007; Accepted for publication May 31, 2007.

1933-2874/$ -see front matter
doi:10.1016/j.jacl.2007.05.006

to monitor therapy are all barriers to effectiveness of drug therapy.

The role of lifestyle change with regard to diet, weight control, and physical exercise is becoming more important in today's health care of chronic disease. These can be vastly important in management of abnormal blood lipids and lipoproteins. The discussion here will address the role and importance of physical activity and exercise as an important adjunct to standard drug therapy in management of abnormal blood lipids. Indeed, with appropriate dietary discretion, weight control, and physical activity/exercise, standard drug therapies may be used at lesser dose levels and, in some instances, totally discontinued.

Exercise and high-density lipoproteins

One of the striking cross-sectional lipid differences between individuals with high levels of aerobic capacity (ie, runners) and sedentary persons is the level of HDL-C, with an average 15.33 mg/dL higher concentration in runners, who were 2.48 kg/m^2 leaner.[10] This observation contrasts with intervention studies of regular aerobic physical training with diet held constant, that have shown a more modest elevation of HDL-C, average 4.3% (range, −5.8% to +25%).[11] The Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study, designed to evaluate the effect of 20-week endurance training on lipoproteins according to the influence of genetics and race, found that there is significant heterogeneity in the lipid response to exercise. The highest HDL-C response (+4.9%) was found in those individuals that had low HDL-C and high TG at baseline.[12] These individuals had higher visceral adipose tissue than those with isolated low HDL-C or normolipidemia. In fact, this study showed that changes in HDL-C and a lipid composite index had significant correlation with changes in body fat mass (−3.3%), while there was no correlation with change in maximal oxygen consumption as a measure of the training effect.[13] This observation raises the question of whether the exercise-induced HDL-C changes are dependent on weight loss, particularly from body fat. Other clinical studies that have assessed the impact of exercise on HDL-C using sedentary controls[14] or diet without exercise,[15] have shown significant correlations between running distances, changes in body mass and HDL-C change. When subjected to statistical adjustment, the correlation between HDL-C and running distance became nonsignificant, while that of HDL-C and change in body mass persisted. This observation was confirmed in a study that trained 17 overweight sedentary men 4 hours per week while keeping their body weight constant by overfeeding. The HDL-C increased 3.8 mg/dL, mostly a 33% (2.3 mg/dL) increase in HDL_2.[16] After 1 year of the weight-stable phase, the 17 men were randomly assigned to either a weight-stable group (same as initial) or a weight-loss group. The HDL-C decreased 2.0 mg/dL in the weight-stable group at 18 months (HDL_2-C decreased 1.3 mg/dL), while the weight-loss group (−9.4 kg) had an additional increase in HDL-C (3.3 mg/dL) and HDL_2-C (4.3 mg/dL).[17] At the end of the 18-month trial, weight loss accounted for 75% of the HDL-C and 85% of the HDL_2-C change. Overall, this evidence supports the significant influence of body fat loss in the exercise-induced increase in HDL-C. In contrast, a recent study that evaluated 24 weeks of endurance training on lipids and lipoprotein size change, found the modest beneficial changes in HDL-C (+3.3 ± 0.5 mg/dL, P = 0.09), HDL_2-C (+1.2 ± 0.3 mg/dL, P = 0.02), and HDL_3-C (+1.9 ± 0.5 mg/dL, P = 0.01), as well as the increase in the large HDL-C particle concentration and decrease in small HDL-C particle concentration were independent of baseline or change in body fat.[18]

Influence of amount and intensity of exercise

The contribution of the amount and intensity of exercise to lipoprotein changes without intended weight change was investigated in a randomized controlled trial.[19] The group assigned to high-amount, high-intensity exercise (equivalent of jogging 20 miles per week at 65% to 80% of maximal oxygen consumption during 8 months) had the only significant increase in HDL-C (+3.8 mg/dL) compared to the control group. The low-amount, high-intensity group, equivalent of jogging 12 miles per week (+0.8 mg/dL), the low-amount, moderate-intensity group equivalent of walking 12 miles per week at 40% to 55% of maximal oxygen consumption (+1.1 mg/dL) or the control group (−0.6 mg/dL) did not change significantly. Likewise, the high-amount, high-intensity group increased significantly the concentration of cholesterol in large high-density lipoproteins and the size of HDL-C particles as measured by nuclear magnetic spectroscopy. Although the participants were not advised to lose weight, the high-amount, high-intensity group lost 1.52 kg, raising the possibility that a change in body weight composition (ie, fat mass) could have influenced the result. Another study analyzed the effect of intensity and frequency of exercise, while the type (walking) and duration (30 minutes) were held constant.[20] At 6 months, only the hard-intensity, high-frequency group (walking at 65% to 75% of heart rate reserve, 5 to 7 days/week) had a significant increase in HDL-C (1.83 mg/dL) compared to the physician advice group. At 24 months, no significant change was observed. The group with moderate–intensity low-frequency (walking at 45–55% of heart rate reserve, 3–4 days/week, +1.44 mg/dL), moderate-intensity, high-frequency (+0.54 mg/dL) and hard-intensity low-frequency (−0.09 mg/dL) had no significant change at 6 or 24 months. These two trials differ in the baseline HDL-C and body mass index: Range was between 40.3 to 46.6 mg/dL and 29.0 to 29.6 in the initial trial,[19] and between 44.2 to 48.3 mg/dL and 27.6 to 28.9, respectively, in the other study.[20] The higher HDL-C response in the first

study is probably related to the lower concentration at baseline, which is also associated with higher weight and probably fat mass. This relationship was also observed in the HERITAGE Family Study.[12,21] In summary, these randomized studies indicate that both high-volume and high-intensity of exercise are required to induce a significant but modest change in HDL-C.

Influence of genetics

The HERITAGE Family Study evaluated major gene effects on baseline HDL-C, LDL-C, and TG and their response to a 20-week endurance training in 527 individuals from 99 white families and 326 individuals from 113 black families.[22] In white families, there was no evidence for a major gene effect in the baseline values of HDL-C, but such an effect was observed in the response to exercise, accounting for 19% of the variance. The major gene appeared to have a recessive mode of inheritance. Sixteen percent and 65% of variance in the response to exercise was accounted by a multifactorial effect and environment, respectively. By contrast, in black families, there was a major gene effect in the baseline HDL-C (45% of the variance), with a dominant pattern of inheritance, but no evidence of such effect in the response to exercise.

Apolipoprotein E3/3 genotype was found to have the highest HDL-C response (6%) to 6 months of supervised exercise training, compared to the 2% average increase of the common apolipoprotein E genotypes, E3/3, E2/3, and E3/4.[23] TG were lowered 12% in the apolipoprotein E3/3 group, while the average decrease was 11%. Interestingly, this genotype had the lowest gain in maximal oxygen consumption (5%), contrasting with the 10% average increase in the entire apolipoprotein E genotypes. Of note, E3/3 homozygotes have the highest frequency among apolipoprotein E allele variants in population prevalence studies. TG are usually higher in apolipoprotein E2 heterozygotes, while their TC and LDL-C are lower than in the E3/3 and E3/4 heterozygotes.[24] LDL-C levels are usually higher in E3/4 subjects than in E3 homozygotes. Reduced binding of apolipoprotein E4 to the HDL-C particle with more rapid transfer of apolipoprotein E to TG-rich lipoproteins increases hepatic delivery of these particles and cholesterol content of the hepatocyte, with subsequent suppression of LDL-C receptor activity and increase in serum LDL-C.[25] The increased LDL-C in apolipoprotein E4 heterozygotes contributes to their higher incidence of coronary heart disease. The mechanisms underlying the different HDL-C and maximal oxygen consumption response to exercise training between different apolipoprotein E genotypes are not well-understood. It could involve different activity of lipoprotein lipase–induced transfer of cholesterol ester from very low–density lipoprotein to HDL-C among apolipoprotein E genotypes, because apolipoprotein E facilitates interaction between very low–density lipoprotein and lipoprotein lipase.[25]

Apolipoprotein A1 is the major apolipoprotein associated with HDL-C. The −75 G/A single nucleotide polymorphism in the apolipoprotein A1 gene promoter influences the change in HDL-C subfraction induced by exercise training.[26] The amount of large HDL-C subfraction increased in the G homozygotes and decreased in the A carriers (1.8 ± 6.6 mg/dL vs -6.1 ± 2.3 mg/dL, $P < 0.005$). In contrast, the small HDL-C subfraction decreased in G homozygotes and increased in A carriers (-1.3 ± 6.6 mg/dL vs 4.7 ± 1.2 mg/dL, $P < 0.005$). Overall, total HDL-C change after exercise was 0.8 ± 7.2 mg/dL, not significantly different. Coronary heart disease patients have lower levels of large HDL-C particles than healthy controls.[27] At the same time, high levels of small HDL-C particles associate with greater coronary heart disease severity[28] and correlate with other risk factors for coronary heart disease.[29] From these observations, it appears that individuals with apolipoprotein A1 G homozygote status for the −75 G/A SNP have a favorable response in their HDL-C subfractions to exercise training. The mechanisms underlying the different response between G homozygotes and A carriers are not well-understood. Exercise training prolongs the HDL-C half-life.[30] It also alters the concentration of lecithin cholesteryl acyl transferase, acyl-coenzyme A cholesterol acyl-transferase, cholesteryl ester transfer protein, or plasma phospholipid transfer protein, enzymes that participate in the remodeling process of HDL-C (see, reverse cholesterol transport discussion). These effects could potentially amplify subtle changes in apolipoprotein A1 concentration induced by exercise training and lead to variation in HDL-C subfraction among the different carriers of −75 G/A SNP.[26] Other genotypes that have been suggested to participate in the variability of exercise-induced effect in HDL-C include that of cholesteryl ester transfer protein[31] and lipoprotein lipase.[32]

Influence on reverse cholesterol transport

HDL is the key lipoprotein in the process of delivering cholesterol from the surface of peripheral cells to the liver, known as reverse cholesterol transport. The initial step is the efflux of cholesterol from the cell toward nascent HDL, limited by the activity of the adenosine triphosphate (ATP)-binding cassette (ABC) transporter 1.[33] The next step involves the maturation of the nascent HDL particle through the acquisition of cholesterol esterified by lecithin cholesterol acyl transferase. Initially, it is transformed into the small and dense HDL3, and later to the larger, more buoyant HDL_2 particles, as HDL exchanges cholesteryl esters with triglycerides from VLDL-LDL series through the action of cholesterol ester transfer protein. The final step is the delivery of cholesterol to cellular receptors. One pathway involves the uptake of cholesterol from VLDL-LDL particles by the hepatic LDL receptor. Other direct HDL-mediated receptor pathways include a specific HDL receptor that captures and degrades the whole HDL particle. Another pathway involves the scavenger receptor type B class I (SR-BI) that binds HDL particles and removes HDL-C

esters selectively without degradation of the HDL particle. Once this particle is depleted of cholesterol esters, it recirculates to repeat the HDL cycle. Hepatic lipase hydrolyzes triglycerides and phospholipids in the HDL particle, facilitating its availability for receptor clearance.[34] Adipose and skeletal muscle lipoprotein lipases remove triglycerides from VLDL and other TG-rich lipoproteins, and have an indirect effect on the HDL metabolism and composition, potentially altering the uptake and delivery of cholesterol from the cell surfaces.[35] Modulation in the metabolic remodeling of HDL particles can alter their morphology and function.

HDL-C particle size is changed favorably by exercise training, resulting in higher levels of HDL_2-C and lower presence of HDL_3-C, such that the total HDL-C does not reflect accurately the HDL-C composition changes.[36] Randomized trials have revealed a consistent increase in HDL-C particle size with exercise training that appeared dose-dependent on amount of exercise.[18,19] Apolipoprotein A1 levels are higher in trained athletes than in sedentary controls,[39] although there is conflicting data regarding the effect of a prolonged exercise program on the plasma apolipoprotein A1 level.[12,38]

Effect of exercise on cholesterol efflux

An acute bout of exercise training elevates levels of nascent (pre-β) HDL-C, without increasing HDL-C or apolipoprotein A1 levels.[39] Because pre-β HDL-C particles are generated from α-HDL-C during the transfer of cholesterol esters to either receptor lipoproteins (very low–density lipoprotein cholesterol) or SR-BI, these findings seem to indicate that acute exercise increases the rate of formation of plasma pre-β HDL-C through enhanced α HDL-C particle utilization rather than from de novo apolipoprotein A1 synthesis.[40] In contrast, pre-exercise levels of pre-β HDL-C do not differ between athletes and sedentary controls, suggesting that pre-β HDL-C is rapidly redistributed to the α HDL-C series after exercise.[39] Similar to the effect of niacin, which selectively inhibits uptake of lipoproteins with predominant apolipoprotein A1 (LP-A1) by the hepatocyte receptor[41] and increase their availability and recirculation, exercise may promote reverse cholesterol transport by increasing pre-β HDL-C recycling from α HDL-C substrates that have been induced by exercise itself. This mechanism can explain the greater cholesterol efflux from cultured human fibroblasts when exposed to serum of athletes vs sedentary controls.[42]

Effect of exercise on HDL-C maturation

Cholesteryl acyl transferase participates in the conversion of pre-β HDL-C to α HDL-C and its activity is increased immediately after acute exercise.[43] Decreased cholesterol ester transfer protein activity increases level of α HDL-C because it increases its concentration of cholesterol ester. Cholesterol ester transfer protein activity has been observed to be greater among athletes than sedentary individuals,[37] although it has also been shown to be unchanged[44] or to decrease after exercise training.[45] Augmentation of cholesterol ester transfer protein activity could promote α HDL-C turnover and facilitate pre-β HDL-C formation, a potential cardioprotective effect through increased cholesterol efflux. Although increased activity of phospholipid transfer protein also potentially increases formation of pre-β HDL-C particles by promoting the exchange of cholesterol esters and phospholipids from α HDL-C species, there is no documented effect of exercise on phospholipid transfer protein. Hepatic lipase induces formation of smaller, denser HDL-C and LDL-C particles by hydrolysis of TG and phospholipids.[46] Its activity is decreased with prolonged exercise training.[47]

Lipoprotein lipases are a family of tissue-specific hydrolytic enzymes that have a key role in increased levels of HDL-C associated with exercise. The lipolysis of surface components in TG-rich lipoproteins and their fusion with HDL_3 increase the level of this particle, with subsequent elevation of HDL_2.[48] The increased activity of this enzyme seems particularly important in muscles because exercise depletes their TG content[49] and induces synthesis of lipoprotein lipase, with subsequent hydrolysis of TG from very low–density LDL-C series and transfer of cholesterol to HDL-C. In addition, aerobic exercise training increases the percentage of skeletal slow-twitch fibers, which have a higher capacity to metabolize fatty acids liberated by lipoprotein lipase from TG-rich lipoproteins.[50] Because exercise directly increases lipoprotein lipase activity in both trained and untrained individuals,[51] the overall effect of exercise on removal of circulating TG-rich lipoproteins seems to have a significant effect in atherogenesis.[35]

Effect of exercise on cholesterol delivery to receptors

Exercise training increases the biological half-life of apolipoprotein A1 by decreasing its fractional catabolic rate, without any change in its synthesis.[38] Pre-β HDL-C is elevated without increased level of apolipoprotein A1, suggesting that exercise blocks the hepatocyte clearance of α HDL-C, providing a faster turnover of apolipoprotein A1 particles to replenish levels of pre-β HDL-C.[39] Thus, exercise increases cholesterol efflux and also potentially augments the cholesterol ester uptake by the hepatocyte, an effect analogous to that of niacin.[41]

Exercise and low (non–HDL-C)-density lipoproteins

LDL-C cholesterol remains the most important clinical lipid target for the clinician in the prevention of coronary

Table 1 Lipid, lipoprotein, lipoprotein enzymes and transfer protein changes associated with exercise

	Regular exercise participation
Triglyceride	Decreases of 4–37%; approximate mean change of 24%
Cholesterol	No change
LDL-C	No change
Lp(a)	No change
HDL-C	Increases of 4–18%; approximate mean change of 8%
LPL	
Activity	Increased
Mass	Increased
HL	
Activity	No change or reduced (may be reduced with weight loss)
Mass	No information
LCAT	
Activity	Increased/no change
Mass	No information
CETP	
Activity	No change/increased
Mass	Increased

CETP, cholesteryl ester transfer protein; HDL-C, high-density lipoprotein cholesterol; HL, hepatic lipase; LCAT, lecithin: cholesterol acyltransferase; LDL-C, low-density lipoprotein cholesterol; LPL, lipoprotein lipase. From Fletcher B, Berra K, Ades, P, et al. Managing abnormal blood lipids: a collaborative approach. Circulation. 2005;112: 3184–3209, adapted with permission.

heart disease.[52] At the same time, it has been recognized that smaller and denser LDL-C particles are more susceptible to oxidation and initiation of the atherothrombosis cascade.[53] These LDL-C particles are usually found in combination with high TG and low HDL-C, the dyslipidemia associated with the metabolic syndrome.[9] Acute exercise and prolonged exercise training are associated with significant, interrelated changes on the different components of this dyslipidemia, including modification of LDL-C particle size and composition. Although the level of LDL-C is not consistently changed, exercise decreases the presence of small, dense LDL-C and increases that of larger, more buoyant LDL-C particles, in a relationship that appears dose-dependent with amount and intensity of exercise.[19] The observed changes in LDL-C particle size have been confirmed by another trial that has used nuclear magnetic resonance spectroscopy.[18] Apolipoprotein E3/3 homozygous genotype was the most responsive to exercise-induced beneficial changes in LDL-C particle size.[54]

Postprandial elevation of TG-rich lipoproteins and their remnants has been postulated as an important mechanism in atherogenesis.[55] Postprandial lipemia is reduced after an exercise session with a degree concordant to the amount of energy expenditure.[56] The chief mechanism for this effect is the lipoprotein lipase–induced clearance of TG-rich lipoproteins, along with a possible reduced hepatic synthesis associated with exercise training.[57] (Table 1 summarizes changes associated with exercise.)

Resistance exercise effects on lipids and lipoproteins

Compared to endurance training, less information exists supporting resistance training as a modifier of plasma lipids. Present studies are often contradictory, with some showing positive benefits of resistance exercise on the lipid profile,[58,59] while others find no benefits[60–62] Inter-study variation in methodologies most likely contribute to outcomes differences. Although it is unlikely that differences between studies can be attributed to any single factor, several possibilities exist, the most likely reason being variation in exercise amount (caloric expenditure) completed during resistance exercise. It may be that the caloric threshold for inducing lipid and lipoprotein-lipid changes is not reached with resistance training. Generally, TG concentrations are not altered by resistance exercise training[60–64] even when initial TG levels are elevated.[61] In contrast, decreased TG concentrations after resistance training are reported in elderly women[59] and after moderate-intensity, high-amount training.[65] TC,[61,66] LDL-C,[66] and apolipoprotein B[67] are

Table 2 Exercise terminology

Physical activity
Body movement by skeletal muscles resulting in energy expenditure beyond that at rest
Exercise
Subset of physical activity that is planned, structured, repetitive and purposeful
Fitness
Includes cardiorespiratory conditioning, muscle strength, body composition, and flexibility
Intensity
Reflects rate of energy expenditure
Vigorous: >60% $VO_{2\ max}$
Moderate: 40–60% $VO_{2\ max}$
Low: <40% $VO_{2\ max}$
Amount
Refers to total energy expenditure in physical activity
Frequency
Refers to how often exercise is performed; ie, six times weekly
Duration
Refers to length in time of an exercise session; ie, 30 minutes
Aerobic
Refers to dynamic exercise activity, ie, walking briskly or jogging
Resistance
Refers to exercise using force to resist motion; ie, lifting arm weights

$VO_{2\ max}$, maximal oxygen consumption.

usually not altered following resistance training when total body mass, lean body mass, and percentage body fat are not changed.[61,62,66] However, a decrease in body fat percentage and an increase in lean body mass after resistance training[63] are associated with decreased TC and LDL-C. Both TC and LDL-C may be reduced after circuit resistance training.[65] In most studies, HDL-C concentrations are unresponsive to resistance training.[61,66] When resistance exercise is combined with aerobic exercise, results are conflicting; HDL-C is increased[68] or unchanged.[62]

Conclusions

Present information supports a favorable exercise training impact on lipid and lipoprotein profiles. Although the quantitative effect is often small, it should not discourage the clinician from recommending an active lifestyle and structured exercise program to his or her patients. (Table 2 cites specific "exercise" terminology.) Regarding blood lipid disorders, the primary intervention is pharmacological while diet modification, weight loss, and exercise, although important, are considered adjunctive therapies. Because much is known about the exercise training–induced plasma lipid and lipoprotein modifications as well as the mechanisms responsible for these changes, one can now develop a comprehensive medical management plan that optimizes pharmacological and lifestyle modifications. Present scientific investigations are focusing on the molecular basis for lipid and lipoprotein changes as a result of various interventions (eg, knowing a person's apolipoprotein E genotype). Findings from these studies can provide better understanding as to why some individuals respond to exercise while others do not. Information regarding the interactive effects between regular exercise participation and pharmacological therapy is lacking. New knowledge from these areas, coupled with available lipid intervention information (diet modification and weight loss) can aid in optimizing individualized medical management for lipid disorders.

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