What Do Muscles Have to Do With Lipoproteins?

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Well-trained endurance athletes have average high density lipoprotein cholesterol (HDL-C) concentrations 20 mg/dl or 40–50% higher than those of sedentary men. Triglyceride levels characteristically are 20% lower in these athletes, and low density lipoprotein cholesterol (LDL-C) may be 5–10% less. Since skeletal muscles neither secrete nor directly catabolize lipoproteins, what links muscular exercise to lipoprotein metabolism? In this issue of Circulation and a related report, Williams and colleagues conclude that weight loss is critical to an exercise effect on HDL. In contrast, other exercise training studies suggest that HDL changes can occur without weight loss and that the exercise and weight loss effects are qualitatively different yet complementary. Does exercise itself alter lipid levels, or are the changes in lipoprotein concentrations dependent on changes in body composition that may accompany physical activity?

Recent interest in the lipoprotein effects of exercise has focused on HDL-C for obvious reasons. HDL-C is powerfully and inversely related to coronary heart disease (CHD), and a 1–2 mg/dl increment in HDL-C is associated with a 2–4% reduction in CHD risk. Although HDL’s importance as a CHD risk factor is widely accepted, its critical role in triglyceride metabolism is not generally appreciated, yet this function provides the likely link between exercise and lipoproteins.

The initial step in the plasma clearance of chylomicrons and very low density lipoproteins (VLDL) requires triglyceride hydrolysis at the endothelial surface by lipoprotein lipase (LPL), the rate-limiting enzyme for this reaction. HDL, a small, dense HDL species, serves as the receptor for the excess surface material, including phospholipids and cholesterol, that is generated during lipolysis. Free cholesterol is esterified on the HDL particle by lecithin:cholesterol acyl transferase, permitting cholesteryl ester to enter the HDL core. The HDL particle is the major site of intraplasmic cholesterol esterification, and this process helps to transform HDL into the larger and cholesterol-enriched HDL-C particle. Differences in HDL-C levels among subject groups are usually due to variations in the HDL subfraction. Consequently, greater LPL activity (LPLA) increases triglyceride clearance and HDL-C concentrations.

Results of acute exercise studies suggest that the energy demands of endurance exercise increase LPLA, which is directly responsible for many of the lipid and lipoprotein changes that occur with exercise. Fatty acids are the primary energy source for endurance activity, and much of this fat is derived from intramuscular triglyceride stores. Depletion of intramuscular triglycerides may stimulate secretion or synthesis of LPL in muscle capillaries. Indeed, an isolated session of stationary cycling increases postheparin LPLA in trained and untrained men, and running a marathon increases both LPLA and the clearance rate of artificial triglyceride emulsions. Alterations in postheparin LPLA do not occur immediately but are evident 18 hours after exercise. This augmented LPLA is associated with acute increases in HDL-C and decreases in plasma triglycerides, and the reduction in triglycerides further increases with the energy expended. Studies examining the arterial-venous difference in lipoproteins across isolated muscle beds demonstrate an acute exercise effect during exercise. Single-leg exercise increases HDL-C levels in the exercised limb, and the increase in HDL-C correlates with the estimated degradation of VLDL-triglyceride. LPLA is higher 4 hours after exertion in muscle samples obtained from the exercised leg. Similarly, forearm isometrics increase the venous content of HDL-C, and this effect is magnified when exercise is performed after a high-fat meal. Even the extreme exertion of a marathon run, however, does not increase the concentration of the major HDL apoproteins—apo A-I and A-II. Consequently, increased lipid delivery to HDL proteins during and after exertion mediates the acute increase in HDL-C concentrations with exercise.

These acute exercise effects are magnified by exercise training. In addition, chronic exercise prolongs the survival of HDL apoproteins. The synthetic rate of HDL proteins is similar in competitive distance runners and sedentary subjects, and endurance
training does not appreciably affect HDL protein synthesis. However, HDL proteins survive 27% longer in the circulation of physically active men, and exercise training increases the intraplasmonic half-life of apo A-I and A-II in previously sedentary men. These changes in HDL survival are accompanied by increases in postheparin LPLA and fat clearance. Increases in fat clearance exceed the change on postheparin LPLA, possibly reflecting qualitative as well as quantitative changes in LPL. Training enhances the muscle’s ability to oxidize fatty acids, which would limit their end-product inhibition of LPL. The factor directly prolonging HDL survival with training is not clear, but lipid enrichment of HDL particles during and after exercise may increase the core-to-surface ratio and retard HDL degradation.

Why, then, is there controversy over the contribution of weight loss to an exercise training effect? We suspect that much of this controversy is due to differences in experimental design, including the timing of phlebotomy, changes in dietary intake, the amount of exercise training provided, and whether differences in plasma volume are considered. Weight loss generally increases HDL levels. Acute caloric restriction, however, reduces HDL-C in obese women but increases HDL-C in lean distance runners. These apparently conflicting results may relate to the tissue-specific regulation of LPL. Fasting increases or does not change muscle LPLA but decreases adipose tissue LPLA, and the ultimate effect on serum HDL levels may depend on the relative contribution of these two tissues. Nevertheless, such results show the potential variability of the HDL-C response to weight loss depending on the subjects studied and the time from caloric restriction to lipid determination. Similarly, the interval from the last exercise to phlebotomy can influence the estimation of an exercise training effect. For example, one training study that reported no change in triglyceride levels measured lipids 48 hours after exercise to avoid the acute exercise effect. Diet also can influence conclusions concerning the effect of exercise on HDL. Increased carbohydrate intake reduces HDL-C and increases triglyceride concentrations, but physical activity appears to blunt this carbohydrate response. Seven-day diet records were used by Williams et al to measure dietary intake, but discrepancies between the amount of weight actually lost and reported reductions in calories consumed raise questions about the validity of such techniques for physiological studies. Insufficient cardiovascular training also may obscure the relation between exercise and HDL. In the present study, the increment in the trainers’ maximal oxygen uptake unadjusted for reduced body weight was approximately 7%, a low value for many training studies. Finally, changes in plasma volume can affect HDL concentrations. Plasma volume expands with training, so blood samples uncorrected for plasma volume may underestimate an exercise effect on total plasma HDL content and overestimate the effect on other lipoproteins. In fact, exercise cessation studies suggest that much of the lower LDL-C values noted in well-trained endurance athletes is due solely to their larger plasma volume. In contrast, weight loss reduces plasma volume, so serum samples may overestimate its HDL effect.

These considerations do not exclude a contribution of weight loss to the effect of exercise in HDL concentrations. They do, however, suggest that the issue is complex and that conclusions are strongly influenced by experimental design. Moreover, it remains likely that increased muscle LPLA attending repetitive exertion contributes directly to the increase in HDL-C with exercise training.

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References


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