Exercise to Reduce Cardiovascular Risk — How Much Is Enough?

Increasing levels of physical activity are associated with a decrease in cardiovascular events. Controlled clinical trials suggest that exercise has benefits in persons with coronary artery disease and in those with glucose intolerance. Exercise produces improvements in mood, blood pressure, insulin sensitivity, and plasma lipoprotein profiles, but the amount and intensity of exercise required in order to attain these benefits and the underlying mechanisms are poorly understood. In this issue of the Journal, Kraus et al. report on changes in plasma lipoprotein levels and particle sizes in an eight-month, randomized trial involving different amounts and intensities of exercise among overweight men and women with dyslipidemia. They found that low amounts of exercise at moderate or high intensity (the equivalent of walking or jogging 12 mi per week, respectively) are associated with potentially beneficial changes in the plasma lipoprotein profile. However, higher levels of high-intensity exercise (equivalent to jogging 20 mi per week) resulted in more pronounced changes in lipoproteins and were required to produce increases in the high-density lipoprotein (HDL) cholesterol level. The graded response of the plasma lipoprotein levels to increasing amounts of exercise may help to explain the progressive decrease in cardiovascular risk associated with increasing levels of exercise.

As compared with nonexercising controls, all exercise groups had potentially beneficial changes in plasma lipoproteins: decreases in total and very-low-density lipoprotein (VLDL) triglycerides, an increase in the size of low-density lipoprotein (LDL) particles, and a trend toward decreased numbers of LDL particles. In the groups with a low amount of exercise, these effects were independent of the intensity of exercise and were unrelated to improvements in physical fitness. However, an increase in HDL cholesterol levels and particle size and the largest effects on LDL were seen only in the high-amount–high-intensity group. These changes included a significant decrease in the number of LDL particles, implying a decrease in the LDL apolipoprotein B concentration, since there is one apolipoprotein B molecule per LDL particle. In view of the prominent elevation of HDL levels in long-distance runners, the findings regarding HDL may appear surprising, but they are concordant with other studies showing that the mean HDL response in exercise studies is small (1.2 mg per deciliter of HDL cholesterol) and that HDL levels are only increased at higher exercise levels (the equivalent of running 10 to 15 mi per week).

The exercise-induced changes in lipoprotein levels and particle sizes were very similar to those previously shown in subjects who exercised and lost weight or who lost weight by dieting. In some studies, lipoprotein changes have been correlated with loss of body weight and decreases in subcutaneous abdominal fat, suggesting that lipoprotein changes may in part reflect decreases in adiposity. In the study by Kraus et al., subjects were encouraged to maintain their base-line body weight, which led to the novel observation that potentially beneficial lipoprotein changes occurred with only small decreases in body weight (a mean decrease of 1.5 kg in the high-amount–high-intensity group).

Despite the plethora of observations of exercise-induced changes in the lipoprotein profile, there is limited understanding of the underlying mechanisms. Exercise conditioning is associated with an increase in lipoprotein lipase activity in adipose tissue and muscle. Increased lipoprotein lipase activity lowers VLDL and chylomicron triglyceride levels and enhances clearance of cholesterol-rich VLDL and chylomicron remnants (Fig. 1). VLDL triglycerides are exchanged for cholesteryl esters in LDL and HDL, a process mediated by cholesteryl ester transfer protein, and the triglyceride in HDL and LDL is then hydrolyzed by lipases, causing a decrease in the size of particles. The decrease in VLDL triglycerides results in the availability of less triglyceride for exchange and is probably a major mechanism underlying the increases in the size of LDL particles and in HDL cholesterol levels and particle size. Exercise and weight loss also reduce the level of cholesteryl ester transfer protein, perhaps because a fraction of this protein is made in adipose tissue. Another important factor underlying the changes in HDL is likely to be a decrease in hepatic lipase activity. Hepatic lipase degrades HDL phospholipids and triglycerides, producing smaller HDL particles that are rapidly catabolized.

The effects of exercise on HDL cholesterol levels are most clearly seen in overweight persons with high triglyceride levels and low HDL cholesterol levels at base line. In contrast, lean subjects with isolated low HDL cholesterol levels had no significant increase in HDL cholesterol with exercise, even though their lipoprotein lipase activity was increased. This suggests that the changes in HDL and LDL cholesterol may be secondary to improvements in hypertriglyceridemia, insulin resistance, and adiposity. Many of the improvements in lipoprotein variables and insulin sensitivity that are associated with habitual exercise are also seen after a single session of exercise. This finding could
indicate that short-term effects of exercise on insulin signaling in muscle are a fundamental mechanism underlying many of the observed changes in the lipoprotein profile.

Studies by Shulman and colleagues\(^{10}\) have demonstrated that the acute delivery of fatty acids to muscle results in insulin resistance. This effect is mediated by a decrease in insulin signaling through insulin receptor substrate 1 (IRS1) and phosphoinositide 3 kinase (PI3K) and a decrease in muscle glucose uptake by the glucose transporter GLUT-4. The resistance to insulin action in muscle leads to more generalized insulin resistance and increased release of fatty acids from adipose tissue. The liver synthesizes and secretes increased amounts of triglycerides and apolipoprotein B (apoB), in the form of very-low-density lipoprotein (VLDL). Increased levels of triglycerides in VLDL are exchanged for cholesteryl esters (CE) in low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Subsequent lipolysis of HDL and LDL triglycerides results in decreased size of particles. Exercise may reverse these abnormalities in part by diverting fatty acids in muscle toward mitochondrial oxidation. Other mechanisms for changes in LDL and HDL include increases in lipoprotein lipase activity and decreases in hepatic lipase and cholesteryl ester transfer protein (CETP).

What is the evidence that exercise-induced lipopro-
protein changes are beneficial? There is substantial evidence that VLDL and smaller remnant lipoproteins (which are present in the VLDL or intermediate-density fractions) are atherogenic, and reductions in the levels of these particles are likely to reduce atherosclerosis. Small, dense LDL particles are somewhat more susceptible to oxidation than larger LDL particles, but it is questionable whether lipoprotein oxidation in vitro will predict the atherogenic responses in humans. The size of LDL particles is inversely correlated with endothelial reactivity, as measured in studies of blood flow in the forearm, and endothelial reactivity appears to have predictive value for clinical events. In population studies, the size of LDL particles has been inversely correlated with the risk of myocardial infarction according to univariate analysis, but this effect was not significant after adjustment for triglyceride and HDL cholesterol levels.

Thus, it is possible but unproved that there is a benefit of changes in the size of LDL particles, and such changes are likely to be less important than changes in VLDL and LDL cholesterol and apolipoprotein B levels. The changes in HDL cholesterol levels produced by exercise are small but are similar to those that were associated with benefit in the Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial. However, it is uncertain whether the primary mediator of benefit is the change in HDL cholesterol. Although exercise results in the accumulation of larger LDL particles, HDL cholesterol measurements may provide much information about cardiovascular risk as do measurements of HDL-subfraction responses.

In summary, exercise is associated with a graded response in a number of different lipoprotein variables. The ensemble of changes is likely to be beneficial, even though the role of each individual component is debatable. The study by Kraus et al. documents an effect of exercise on lipoproteins with only minimal changes in body weight and provides a ray of hope for those who find it easier to exercise than to lose weight.

REFERENCES


Copyright © 2002 Massachusetts Medical Society.

Leukotriene Receptors and Aspirin Sensitivity

About 15 million people in the United States have asthma. In a small percentage of them, prevalently estimated at between 3 percent and 10 percent, acute, severe asthma accompanied by rhinorrhea and sometimes associated with hives, flushing, or abdominal pain develops after the ingestion of aspirin or nonsteroidal antiinflammatory drugs (NSAIDs). Patients with this syndrome, known as aspirin-sensitive asthma, often have severe rhinosinusitis and nasal polyposis. It is important to recognize aspirin-sensitive asthma clinically because severe episodes are life-threatening. The common feature of drugs that provoke asthma attacks in aspirin-intolerant persons is that they inhibit cyclooxygenase-1 (COX-1); selective inhibition of cyclooxygenase-2 (COX-2) appears not to provoke such a response. Cautious, incremental administration of oral doses of aspirin can lead to a state in which persons with aspirin-sensitive asthma can ingest aspirin without untoward reactions, but daily administration must be continued to maintain this state.

Persons with aspirin-sensitive asthma have increased basal biosynthesis of the cysteinyl leukotrienes, as evidenced by increased urinary excretion of leukotriene E4 (LTE4). Leukotrienes are the enzymatic prod-