Editorial Comments

Exercise, Lipoproteins, and Coronary Artery Disease

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Although a sedentary lifestyle has been implicated as a risk factor for the development of coronary artery disease and although many studies have shown beneficial cardiovascular effects of exercise conditioning, there is no consensus on whether exercise has a direct influence on the mechanisms that cause coronary atherosclerosis. Based on the growing evidence for the role of lipoproteins in the development of coronary artery disease, the effects of exercise on lipoprotein metabolism have been receiving increased attention. Studies of lipoproteins in endurance athletes have generally shown them to have lower levels of triglyceride-rich lipoproteins and higher levels of high-density lipoproteins (HDL) than sedentary control subjects. Given the strong inverse relation between HDL cholesterol and risk of coronary artery disease, interest has focused on the mechanisms and the potential benefits of exercise-induced increases in HDL.

Attempts to produce increases in HDL cholesterol in sedentary men by endurance exercise have generally met with limited success.\textsuperscript{1,2} There may be a number of reasons for this. Wood et al\textsuperscript{1} showed that in 81 men undergoing a controlled 1-year exercise trial, a correlation existed between increased HDL and exercise level, expressed as average miles run per week. However, a significant increase in HDL cholesterol could be detected only in those men whose mileage during the last 7 months of the trial exceeded an average of 12 miles/wk, a level of exercise unlikely to be achieved by most individuals. Furthermore, a tendency occurred for those men with higher HDL cholesterol levels at baseline to achieve greater increases in both exercise level and HDL cholesterol,\textsuperscript{3} suggesting a selection effect related to interindividual metabolic differences, possibly in part genetic,\textsuperscript{4} that may influence the capacity for exercise conditioning. Finally, subsequent analyses in the same cohort of men indicated that exercise-induced weight loss was an essential element of the HDL response.\textsuperscript{5} This is consistent with a large body of evidence showing an inverse relation between HDL levels, particularly the relatively larger HDL\textsubscript{2} subspecies, and adiposity.\textsuperscript{6} Furthermore, similar increases in levels HDL\textsubscript{2} and HDL cholesterol were recently reported to occur with weight loss induced by exercise and by caloric restriction.\textsuperscript{7}

Although these studies suggest that weight loss is a critical factor mediating the effects of exercise on HDL, small increases in HDL concentrations also have been found to result from short-term exercise\textsuperscript{8} and prolonged exercise training\textsuperscript{2} in the absence of weight loss. Furthermore, HDL\textsubscript{2} levels in trained individuals may decrease substantially within several weeks after cessation of exercise.\textsuperscript{9} Possibly, the magnitude of short-term effects of exercise on HDL is modulated by relative lean mass as well as other metabolic adaptations associated with endurance training.

Exercise-induced changes in triglyceride metabolism may contribute to the HDL response. Although too extensive to summarize here, there is a large body of data attesting to the importance of triglyceride as an energy source for skeletal and cardiac muscle, and the depletion of cellular energy stores in muscle as well as adipose tissue with prolonged exercise can clearly serve as a major stimulus for increasing triglyceride fatty acid uptake by these tissues. Increased clearance of an intravenous fat bolus has been found to occur within 24 hours after a single prolonged exercise session.\textsuperscript{10} This may be mediated in part by increased activity of lipoprotein lipase, the rate-limiting enzyme for plasma triglyceride clearance that has been reported to increase in skeletal muscle and adipose tissue after short-term exercise,\textsuperscript{11} and after prolonged training.\textsuperscript{12-14} Recently, unilateral quadriceps muscle training has been found to result in interrelated increases in muscle lipoprotein lipase activity, triglyceride uptake, and HDL\textsubscript{2} production in the exercising limb,\textsuperscript{12} which is consistent with previous evidence that catabolism of...
triglyceride-rich lipoproteins may contribute directly to increases in HDL mass. Increased rate of clearance of an oral fat load\(^6\) and increased activity of lipoprotein lipase in adipose tissue\(^4\) also have been linked to increases in HDL\(_2\). Because adipose tissue lipoprotein lipase activity increases with weight reduction,\(^5\) the relation of adipose tissue lipoprotein lipase to HDL\(_2\) levels may contribute to the major influence of adiposity on HDL levels. However, not all studies have found a significant correlation of adipose tissue lipoprotein lipase activity with HDL\(_2\) cholesterol,\(^15,16\) and stronger evidence exists that activity of hepatic triglyceride lipase may mediate the relation between adiposity and plasma levels of HDL\(_2\).\(^16,17\)

Increased clearance of exogenous fat could also result from reduced hepatic triglyceride production because endogenous and exogenous triglyceride share a common saturable mechanism for removal\(^18\) and exogenous fat clearance is closely correlated with fasting plasma triglyceride levels.\(^19\) While such an effect has not been clearly documented in humans, some studies have found reductions in fasting triglyceride levels after exercise at times when increased fat clearance can no longer be shown.\(^10\)

Recently, Thompson et al\(^2\) reported that postheparin plasma lipoprotein lipase activity and intravenous fat clearance remained significantly elevated during prolonged exercise training (up to 48 weeks) in the absence of change in weight or estimated adiposity.\(^2\) These effects were also associated with reductions in fasting plasma triglyceride levels, although the reductions were no longer statistically significant after adjusting for an 8% increase in plasma volume. In the present issue of Circulation, Weintraub et al\(^20\) extend these findings by reporting that after a 7-week jogging program and in the absence of weight loss or diet change, increased maximum oxygen consumption was significantly correlated with decreased levels of fasting triglycerides and postprandial chylomicrons in conjunction with increased postheparin plasma lipoprotein lipase activity. Although these changes would have been more convincing if adjusted for changes in plasma volume,\(^2\) they are entirely compatible with the earlier reports of exercised-induced improvement in exogenous fat clearance. Furthermore, although the statistical power in this study of six subjects was relatively small, the lack of a significant increase in HDL cholesterol is consistent with the evidence previously reviewed that reduced body weight appears to be a critical determinant of the HDL response. This does not necessarily imply, as suggested by the investigators, that the effects on triglyceride and triglyceride clearance are the earliest effects of exercise training on lipoprotein metabolism because, as noted above, there may be small, short-term increases in HDL cholesterol with exercise, and these would be amplified if weight loss were allowed to occur. Also, exercise-related effects on HDL might have been detected in the study of Weintraub et al\(^20\) had the HDL\(_2\) and HDL\(_3\) subfractions been measured because increases in HDL\(_2\) and net increases in HDL cholesterol may have been offset to some extent by decreases in HDL\(_3\).\(^1,21\)

With this information in hand, are we in any better position to evaluate a link between exercise and protection from atherosclerosis? If we deal with the effects of exercise that occur independently of weight loss, we move from an emphasis on HDL to an emphasis on triglyceride-rich lipoproteins. This may be an appropriate change in focus because there is abundant evidence to suggest that triglyceride-rich lipoproteins, particularly intermediate-density lipoproteins and lipolytic remnants, can play a major role in atherosclerosis.\(^22,24\) However, Weintraub et al\(^20\) found that levels of larger chylomicrons, and not smaller chylomicron remnants, were reduced by exercise training, and there is no convincing evidence for the atherogeneity of these larger particles.

Another reason to focus on triglyceride-rich lipoproteins in the atherosclerotic process is their potential role in contributing to the epidemiologic relation of HDL cholesterol levels to risk of coronary artery disease.\(^6,23\) Although HDL is commonly believed to be involved in the early stages of “reverse transport” of cholesterol from the periphery to the liver for excretion, it is not clear to what extent increased levels of HDL reflect this process or even to what extent such reverse cholesterol transport contributes to reduced atherosclerosis risk. Based in part on the metabolic relations described above, increased HDL appears to be indicative of processes that result in reduced plasma residence of triglyceride-rich lipoproteins. Perhaps of equal importance, increased HDL cholesterol may reflect reduced partitioning of cholesterol to potentially atherogenic lipoproteins in the very low to low-density range. Of particular note in this regard is the finding that changes in levels of HDL\(_2\) are inversely related to changes in levels of smaller, denser subspecies of low-density lipoproteins (LDL)\(^25\) that may be preferentially associated with increased coronary disease risk.\(^24\) Thus, from a mechanistic standpoint, HDL levels may be a relatively stable marker for dynamic events that contribute to the exposure of the artery wall to atherogenic lipoproteins. Although one may question whether changes in triglyceride-rich lipoprotein metabolism without associated changes in HDL carry similar implications for atherosclerosis risk, this question assumes lesser importance when one considers that weight loss, and the potential for increasing HDL levels, characteristically accompanies long-term exercise training programs.\(^1\)

In considering the relation of exercise-induced lipoprotein changes to coronary disease risk, a final caution must be raised. To date, the only lipoprotein intervention that has been significantly correlated with the degree of coronary artery disease risk reduction is lowering of LDL cholesterol by pharmacologic means.\(^26\) Most studies of the effects of exercise training have shown small and generally insig-
significant reductions of LDL, particularly in the absence of weight loss.\textsuperscript{1,2} Although pharmacologic reductions in triglyceride and increases in HDL cholesterol have been achieved in the course of coronary risk reduction in other studies,\textsuperscript{27,28} the relation of these changes to lowered risk and the potential benefits of endurance exercise in this regard remain to be proved.

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