Does Exercise Increase HDL Cholesterol in Those Who Need It the Most?

Paul D. Thompson, Daniel J. Rader

The Health, Risk Factors, Exercise, Training, and Genetics (HERITAGE) Family Study is a landmark multicenter trial designed to examine the physiological changes produced by exercise training and how genetics contributes to the variation in the response to exercise. Families underwent physiological and biochemical assessment before and after 5 months of supervised aerobic exercise training. This study is the largest intervention trial of the effects of exercise training on serum lipids, and the results for the entire cohort have been previously reported. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Couillard and colleagues present a detailed subgroup analysis of the lipid results for 200 white males that focuses on the effects of exercise on HDL cholesterol (HDL-C) levels. The results have important messages for both researchers and clinicians interested in the effects of exercise on lipid metabolism.

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Couillard and colleagues divided their subjects into 4 subgroups by using the 50th percentiles of plasma triglycerides (TGs) and HDL-C as cutpoints, 0.92 mmol/L (36 mg/dL) for HDL-C and 1.34 mmol/L (119 mg/dL) for TGs, thereby forming 4 subgroups: low TG/high HDL-C, high TG/high HDL-C, high TG/low HDL-C, and low TG/low HDL-C. The lattermost group is referred to as “isolated low HDL-C,” a common condition that is often, but not always, a risk factor for premature coronary disease. Interestingly, as expected, while the high TG/low HDL-C group had evidence of visceral obesity and insulin resistance, the isolated low HDL-C group did not. Both high-TG groups experienced a 13% to 15% decrease in TGs with exercise, which is consistent with multiple reports that exercise does effectively reduce TGs. The major question asked in this analysis was whether the HDL-C response to exercise was related to the baseline TG levels. HDL-C levels increased by an average of 4.9% in the high TG/low HDL-C group but only by 0.4% in the isolated low HDL-C group, statistically a significantly smaller response.

The present observation that exercise training fails to increase HDL-C in men with isolated low HDL-C levels is consistent with prior reports. One small study selected men who had low (<1 mmol/L, or 40 mg/dL; n = 7) or normal (>1.1 mmol, or 44 mg/dL; n = 10) HDL-C levels. Mean TG levels in the low HDL-C group were 1.81 mmol/L, or 160 mg/dL, and only 1.19 mmol/L, or 105 mg/dL, in the normal HDL-C group. Subjects exercised under supervision 4 hours weekly, consumed defined diets for 4 weeks before and during lipid measurement, and were required to maintain a stable body weight. Average HDL-C increased 12% (0.13 mmol/L, or 5.1 mg/dL) in the normal HDL-C subjects but by only 6% (0.05 mmol/L, or 1.9 mg/dL) in the low HDL-C subjects. Furthermore, TG levels decreased and intravenous fat clearance and postheparin lipoprotein lipase (LPL) activity increased only in the normal HDL-C group, suggesting that individuals with low baseline HDL-C values have an impaired ability to alter TG metabolism by exercise training. Williams et al., in a year-long exercise training program, noted the largest increase in HDL-C and reduction in TGs among subjects who exercised the most. Interestingly, those who exercised the most during the study had the highest HDL-C and lowest TGs at baseline, suggesting that high HDL-C and low TGs may somehow select for individuals more likely to sustain aerobic activity. In a subsequent study, Williams et al. confirmed that baseline HDL-C was related to the subjects’ running mileage (r = 0.34, P = 0.02), even after adjustment for baseline body weight (r = 0.32, P = 0.03). The idea that HDL-C level may select for exercise adherence has theoretical support, since fatty acids are a major energy source during endurance exercise and high HDL-C levels are associated with increased postprandial TG clearance. Therefore, increased generation of fatty acids could facilitate energy delivery to muscle and thereby increase adherence to exercise training. However, in the current study, adherence to the exercise protocol was carefully controlled, suggesting that factors other than the extent of exercise are responsible for the reduced effect of exercise in persons with baseline low HDL-C.

The mechanism by which exercise increases HDL-C is not fully understood but is believed to be related, at least in part, to increased expression of LPL. LPL activity is well known to be positively associated with HDL-C levels, and exercise is known to increase LPL activity. In the current study, however, LPL activity increased in all groups to a similar extent, and therefore, this mechanism cannot explain the failure of exercise to increase HDL-C levels in the isolated low HDL-C group. Increases in HDL-C with exercise have been shown to be associated with reduced HDL apolipoprotein catabolism in a normal, but not in a low, HDL-C group. Although the mechanism for reduced HDL catabolism with exercise was also thought to be related to LPL activity, it is possible that exercise has other physiological effects that influence HDL turnover and that these effects may differ depending on metabolic factors, such as visceral adiposity, insulin resistance, and TG levels. The effect of genetic variation in candidate genes on the variation in HDL-C response to exercise will be one of the fascinating additional
pieces of data to emerge from the HERITAGE Study in the future.

The HERITAGE study is a model for the investigation of the effect of exercise on serum lipids. The exercise training regimen was carefully standardized to heart rate by using cycle ergometers with built-in heart rate monitors. Caloric restriction and weight loss were not encouraged, so as to isolate the effects of exercise training. The results were adjusted for the expansion in plasma volume that occurs with exercise training and that can literally dilute the increases in HDL-C. Nevertheless, the present report has certain limitations. Subjects in both high-TG groups differed in multiple ways from the lower-TG subjects. The high-TG individuals were more obese, less fit, and older, making it difficult to separate the effect of baseline TGs from other factors that could affect the exercise response. Furthermore, as shown in Figure 1, the division of subjects into 4 subgroups was arbitrary, with most of the subjects clustering around the 50th percentile values. Only the distribution of the low HDL/high TG subjects was visibly different from the other groups. Consequently, it is not surprising that this group displayed the most distinctive changes with exercise training. Also, some of the decrease in TGs reported in the present study could be the result of an acute effect of recent exercise. In the current study, plasma lipids were assessed 24 hours after the last exercise session. The ability of an isolated exercise session to decrease TGs in hypertriglyceridemic subjects was first reported by Holloszy and others in 1964. Those investigators noted a remarkable decrease of 0.94 mmol/L, or 84 mg/dL, in TGs among 5 hypertriglyceridemic men (mean TG = 3.99 mmol/L, or 353 mg/dL) 20 hours after an isolated exercise session. This acute effect of exercise on TGs and HDL-C has been noted by others and seems related to the magnitude of energy expended during exertion. For the entire HERITAGE cohort, the TG values obtained 24 hours after the last exercise session were significantly lower than those obtained 72 hours after the last session, suggesting that some of the decreases in TGs are a transient effect of recent exercise. HDL-C results, however, were not subject to this acute exercise effect.

Overall, the magnitude of the effects of exercise training on absolute HDL-C levels is disappointing. In the complete HERITAGE cohort, 2 the average increase in HDL-C for men (n=299) and women (n=376) was only 0.03 and 0.04 mmol/L (1.1 and 1.4 mg/dL, P<0.001 for both), respectively. These small changes are surprising to many clinicians who often expect much greater increases in HDL-C, similar to the 0.54 mmol/L (20 mg/dL) difference between endurance athletes and sedentary subjects first noted by Dr Peter Wood and colleagues over a quarter century ago. Nevertheless, the much smaller changes in HDL-C in the HERITAGE subjects are consistent with the 0.03 mmol/L, or 1.2 mg/dL, increase reported in a meta-analysis of 66 exercise training studies. What are the implications of the HERITAGE Family Study results for researchers and clinicians interested in the effects of exercise on lipid metabolism? For researchers, the HERITAGE study provides a superb model for investigation of this area and indicates that the physiological changes induced by aerobic exercise and their effects on lipoprotein metabolism are complex. Studies of the impact of genetic polymorphisms on the response to exercise in this study are eagerly awaited. Future dynamic and kinetic studies of energy, fatty acid, and lipoprotein metabolism in both acute and chronic states of aerobic exercise will be required to address some of the remaining issues that cannot be answered through measurement of steady-state plasma levels alone. For clinicians, these results confirm that exercise training can reduce TGs and increase HDL-C in hypertriglyceridemic individuals but that exercise training has relatively little utility in increasing HDL-C in individuals with isolated low HDL-C levels. It remains to be determined whether more prolonged or intense training can increase HDL-C in isolated low HDL-C subjects. At the present time, however, the conventional wisdom that aerobic exercise training increases HDL-C must be tempered by the fact that the absolute increases in HDL-C are modest and may not occur at all in those with isolated low HDL-C. This should not, however, discourage clinicians from prescribing aerobic exercise, which is likely to have a variety of cardiovascular benefits beyond its effects on HDL-C.

References
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doi: 10.1161/hq0701.092147
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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