Physical Activity, Blood Lipids, and Lipoproteins

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AMERICAN JOURNAL OF LIFESTYLE MEDICINE 2009; 3; 279 originally published online Apr 21, 2009;
DOI: 10.1177/1559827609334885

Physical ACTIVITY

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Abstract: *Dyslipidemia is a major modifiable cardiovascular disease (CVD) risk factor. While pharmacological treatment has been a focal point of dyslipidemia management for several years, increasing physical activity is a safe, cost-effective treatment option that should also be recommended by health care practitioners. Moderate aerobic exercise consistently increases high-density lipoprotein cholesterol (HDL-C) and reduces triglycerides (TG), independent of changes in body weight. However, reductions in total and low-density lipoprotein cholesterol are reported less often following aerobic exercise. Therefore, clinicians should understand that aerobic exercise is not likely to be an effective treatment option for their management. Recent empirical evidence also indicates that aerobic exercise may be of benefit for treating emerging lipid and lipoprotein risk factors such as lipoprotein particle size and number and triglyceride-rich lipoproteins. Further work is needed to clarify the impact of aerobic exercise on apolipoproteins. Based on current evidence, prescribing aerobic exercise as a means of increasing HDL-C and lowering TG is usually an efficacious strategy for treating these aspects of dyslipidemia. These effects are likely to be accompanied by changes in emerging lipid and lipoprotein risk factors.*

Keywords: dyslipidemia; exercise; prevention; cardiovascular; apolipoproteins

Dyslipidemia is a major modifiable cardiovascular disease (CVD) risk factor encompassing elevations in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and low levels of high-density lipoprotein cholesterol (HDL-C).[1] In addition, novel lipid and lipoprotein markers such as lipoprotein particle size and number, apolipoproteins, and triglyceride-rich lipoproteins are emerging risk factors that contribute to CVD risk.[2] The National Cholesterol Education Program Adult Treatment Panel III has put forth widely recognized guidelines establishing lipid and lipoprotein modification goals for both primary and secondary prevention.[1] Yet data from the National Health and Nutrition Examination Survey indicate that many adults have not achieved target levels for all lipids and lipoproteins.[3] Therefore, critical evaluation of the current strategies for dyslipidemia management is needed to strengthen treatment of this CVD risk factor.

Health care practitioners employ a broad range of therapeutic options to treat dyslipidemia, including pharmacological treatment (eg, statins) and lifestyle modification. While pharmacological agents have become the cornerstone in dyslipidemia treatment, concerns remain as to their safety and cost-effectiveness.[4] Furthermore, they are usually not prescribed until the atherosclerotic burden is relatively high, limiting their value in primary prevention.[5] This underscores the need to promote nonpharmacological treatment options for lipid and lipoprotein disorders. One such approach

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is increasing physical activity, which is a cost-effective preventive measure for CVD risk reduction.[6] Moreover, the cardioprotective benefit of exercise is due, at least in part, to its impact on blood lipids and lipoproteins.[7] Therefore, the purpose of this review is to examine the effects of physical activity and inactivity on traditional and emerging blood lipid and lipoprotein risk factors.

Total and LDL Cholesterol

Epidemiological data demonstrate a direct relation between TC concentrations and CVD mortality rate.[8] Typically, physically active individuals have lower TC than those who are less active.[9] However, reduced TC in habitually active persons may not relate to aerobic exercise training per se. Indeed, there is compelling evidence that aerobic exercise does not induce consistent reductions in TC.[10] Furthermore, instances in which aerobic exercise training resulted in reductions in TC may have been attributable to changes in body mass or composition.[11] Thus, lower TC in physically active individuals is likely a result of other factors such as favorable body composition or macronutrient intake.

In addition to TC, LDL-C has a central role in the development and progression of atherosclerosis and has been a principal lipid management target for several decades.[12] As in the case of TC, the vast majority of evidence indicates that aerobic exercise, acute or chronic, does not lower LDL-C.[9] For example, a recent meta-analysis of 49 randomized controlled trials demonstrated a nonstatistically significant trend for a 2% reduction in LDL-C in men aged 18 to 65 years following aerobic exercise training.[13] When statistically significant attenuations in LDL-C are reported following aerobic exercise training, they are often very modest in nature (ie, 4%-7%).[9] Such reductions, when attained, may be of physiological significance because every 1% reduction in LDL-C reduces coronary heart disease risk by 2% to 3%.[14] Yet from a clinical perspective, the significance of such reductions needs to be evaluated in light of current recommendations for LDL-C management. It is widely believed that LDL-C should be lowered as much as possible, and concentrations ≤100 mg/dL are now considered optimal.[15] Thus, individuals with even borderline high LDL-C values (130-160 mg/dL) may not be able to reduce LDL-C to optimal concentrations via aerobic exercise alone.

HDL-C and Triglycerides

HDL-C is anti-atherogenic for several reasons, including its role in reverse cholesterol transport and its anti-inflammatory and antioxidant properties.[16] Inasmuch, there has been increasing interest in recent years in targeting increasing HDL-C as a means of cardioprotection. Increases in HDL-C concentrations ranging from 4% to 25% (2-8 mg/dL) are consistently observed following aerobic exercise training.[17,18] Although these increases are quantitatively modest, they are meaningful because a 1-mg/dL increase in HDL-C is associated with a 2% to 3% decrement in coronary heart disease risk.[19] This appears to be an independent benefit of aerobic exercise because increases in HDL-C have been reported in the absence of alterations in body mass or composition[20]; however, changes in these variables may augment the response.[21]

There appears to be a threshold of approximately 1200 kcal/wk of total energy expenditure (TEE) to acquire exercise-induced alterations in HDL-C in both men and women.[9] In addition, increases in HDL-C occur in a dose-dependent manner, with greater increases resulting from greater TEE. These findings may be applied broadly because data from the HERITAGE Family Study indicate no differences in the HDL-C response to aerobic exercise by race, sex, or age.[22,23] One prominent exception that must be carefully considered when prescribing exercise to increase HDL-C is that there is evidence that HDL-C may not increase in those with isolated low HDL-C at baseline.[23]

Low levels of HDL-C are often seen in conjunction with elevations in TG, leading to uncertainty as to whether the latter is an independent CVD risk factor.[24] Yet there is evidence to support the inclusion of TG as an independent CVD risk factor.[25] For example, participants in the 2 upper TG tertiles of the Copenhagen Male Study had an adjusted coronary heart disease risk ratio of 2.2 compared with individuals in the lower TG tertiles.[26] Thus, although still controversial, TG may be an independent lipid variable contributing to CVD risk.

In addition to raising HDL-C, lowering TG is among the most consistently observed effects of aerobic exercise on blood lipids and lipoproteins. Indeed, cross-sectional studies demonstrate that physically active individuals have lower TG concentrations compared with their physically inactive counterparts.[27] Reductions in TG ranging from 4% to 37% (5-38 mg/dL) have been reported following aerobic exercise training in the absence of weight loss.[17] As for HDL-C, the caloric expenditure threshold to achieve reductions in TG is approximately 1200 kcal/wk for men.[9] Reductions in TG also occur in a dose response manner, with further caloric expenditure frequently leading to additional reductions.[28]

Two key clinical considerations need to be noted when prescribing aerobic exercise as a modality for TG reduction. First, while attenuated TG concentrations have been reported for a broad range of baseline values, the extent of the exercise-induced reduction may be greatest in individuals with high TG at baseline.[10] In addition, although reductions in TG with aerobic exercise are frequently reported in women, they are less frequent than in men.[9]

Lipoprotein Particle Size

Lipoprotein particle size and number may provide additional prognostic information beyond that from the traditional lipid and lipoprotein panel.[29] Although these parameters are not yet assessed routinely in clinical practice, they may be incorporated in the near future and are already recommended for evaluation of borderline situations.[30] It is therefore of interest to investigate whether aerobic exercise favorably modifies lipoprotein particle size and number.

Small, dense LDL particles are more atherogenic than larger, more buoyant LDL particles.[31] Moreover, the size of LDL particles has also been shown to more accurately assess CVD risk than LDL-C.[32] Cross-sectional evidence suggests that habitually active individuals do not exhibit significant differences in LDL particle size,[33] yet longitudinal studies have provided discordant findings. For example, Krauss et al[34] performed a randomized controlled trial and reported incremental improvements in both LDL particle size and number with increasing total volume of exercise, independent of changes in body mass. It is particularly noteworthy that this change occurred in the absence of changes in LDL-C concentration. Therefore, aerobic exercise may alter LDL particle size and number and thus reduce LDL-associated CVD risk, despite not always reducing LDL-C concentration.

Reductions in HDL particle size and number are also associated with increased CVD risk, although this may be partly explained by associations with other cardiovascular and metabolic risk factors.[35] Aerobic exercise also appears to modify HDL particle number and size, complementing the often observed increases in HDL-C. For example, it has been demonstrated that increases in both HDL particle size and concentration accompany increases in HDL-C following 6 to 8 months of regular aerobic exercise training, independent of weight loss and dietary changes.[34,36] Intriguingly, these exercise training adaptations have been shown to be sustained for 15 days following exercise cessation.[37] Taken together, these studies provide compelling evidence that the antiatherogenic modifications to the blood lipid and lipoprotein profile stemming from aerobic exercise include favorable changes in LDL and HDL particle size and number.

Apolipoproteins

Apolipoproteins are structural elements of lipoprotein particles that play integral roles in their metabolism.[38] Apolipoprotein B (apoB) is found in very low-density lipoprotein, as well as intermediate-density lipoprotein, LDL, and lipoprotein(a). There is only 1 apoB per molecule, and thus apoB serves as a direct indicator of the total number of atherogenic particles.[39] Accordingly, apoB measurement may provide additional information beyond measurement of LDL-C or even LDL particle number.[40]

The influence of aerobic exercise on apoB is currently controversial, with some studies finding decreases and others finding no change. Ring-Dimitriou and colleagues[41] reported that 9 months of aerobic exercise training lowered apoB by 18% in previously sedentary men and women. Conversely, other studies have demonstrated that similar volumes of aerobic exercise did not result in significant changes in apoB.[42] Possible explanations for these discordant findings may be related to changes in body mass or composition and aerobic fitness.

Apolipoprotein A-I (apoA-I) is a major constituent lipoprotein associated with HDL and accounts for 70% of its protein content.[43] Apo A-I concentration is predictive of long-term mortality in coronary heart disease patients.[44] Evidence from an analysis of Women's Health Study participants indicates that self-reported physical activity is associated with modestly higher apoA-I concentrations.[45] In contrast, exercise interventions have yielded conflicting results, with some studies reporting increases[46] and others no change.[47]

Lipoprotein(a) is a subfraction of LDL that contains apolipoprotein(a) and apoB. Retrospective case-control analyses and prospective studies have found an association between lipoprotein(a) and CVD.[29] Current evidence suggests that lipoprotein(a) is highly heritable and largely uninfluenced by acute or chronic exercise interventions.[48]

Taken together, these studies demonstrate that aerobic exercise possibly has a beneficial impact on apolipoproteins, but that is far from definitive. Further studies are needed to clarify whether increasing regular physical activity is a viable approach to favorably modifying apolipoproteins.

Triglyceride-Rich Lipoproteins/ Postprandial Lipemia

Recent evidence indicates that elevated postprandial TG is associated with increased CVD risk.[49] Because most individuals consume subsequent meals prior to the complete resolution of the proceeding one, most of the day is spent in the postprandial state. This underscores the importance of assessing postprandial lipid and lipoprotein concentrations.

Single sessions of aerobic exercise have been shown to reduce postprandial lipemia (PPL; <30%, on average) following a high-fat meal.[50] As with other lipid and lipoprotein parameters, the key variable mediating this response is TEE, with higher TEE typically eliciting larger attenuations in PPL.[51] It should be noted that 60 minutes of moderate-intensity brisk walking has been shown to effectively reduce PPL.[52] Thus, this effect is attainable by performing single exercise sessions that are consistent with current public health recommendations.[53]

Interestingly, this phenomenon appears to be a direct result of acute aerobic exercise. In fact, detraining studies have conclusively demonstrated that exercise-induced attenuations of PPL are absent within 48 to 60 hours following the most recent exercise session, even in physically trained cohorts.[54] Therefore, it is critical that frequent sessions of aerobic exercise are undertaken to favorably influence postprandial triglyceride metabolism.

Conclusion

In summary, aerobic exercise is a highly efficacious, cost-effective preventative strategy for CVD risk reduction. Modifications in blood lipids and lipoproteins are partly responsible for this benefit. Accordingly, health care practitioners should be strongly encouraged to prescribe aerobic exercise. Increases in HDL-C and reductions in TG are among the most frequently observed lipid and lipoprotein changes that should be expected following aerobic exercise. In

addition to these changes in conventional variables, aerobic exercise also favorably alters emerging lipid and lipoprotein risk factors such as HDL and LDL particle size and number and postprandial triglyceride-rich lipoproteins. Additional work is needed to clarify whether aerobic exercise is effective in changing apolipoproteins. AJLM

References

1. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *J Am Coll Cardiol.* 2004;44:720-732.
2. Fruchart JC, Nierman MC, Stroes ES, Kastelein JJ, Duriez P. New risk factors for atherosclerosis and patient risk assessment. *Circulation.* 2004;109:III15-III19.
3. Ghandehari H, Kamal-Bahl S, Wong ND. Prevalence and extent of dyslipidemia and recommended lipid levels in US adults with and without cardiovascular comorbidities: the National Health and Nutrition Examination Survey 2003-2004. *Am Heart J.* 2008;156:112-119.
4. Pletcher MJ, Lazar L, Bibbins-Domingo K, et al. Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering. *Ann Intern Med.* 2009;150:243-254.
5. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care.* 2008;31:811-822.
6. Lowensteyn I, Coupal L, Zowall H, Grover SA. The cost-effectiveness of exercise training for the primary and secondary prevention of cardiovascular disease. *J Cardiopulm Rehabil.* 2000;20:147-155.
7. Tambalis KD, Panagiotakos DB, Kavouras SA, Sidossis LS. Responses of blood lipids to aerobic, resistance, and combined aerobic with resistance exercise training: a systematic review of current evidence. *Angiology.* Epub ahead of print. October 30, 2008.
8. Castelli WP. Lipids, risk factors and ischaemic heart disease. *Atherosclerosis.* 1996;124(suppl):S1-S9.
9. Durstine JL, Grandjean PW, Davis PG, Ferguson MA, Alderson NL, DuBose KD. Blood lipid and lipoprotein adaptations to exercise: a quantitative analysis. *Sports Med.* 2001;31:1033-1062.
10. Kokkinos PF, Holland JC, Narayan P, Colleran JA, Dotson CO, Papademetriou V. Miles run per week and high-density lipoprotein cholesterol levels in healthy, middle-aged men: a dose-response relationship. *Arch Intern Med.* 1995;155:415-420.
11. Kiens B, Lithell H, Mikines KJ, Richter EA. Effects of insulin and exercise on muscle lipoprotein lipase activity in man and its relation to insulin action. *J Clin Invest.* 1989;84:1124-1129.
12. Lowering blood cholesterol to prevent heart disease. NIH Consensus Development Conference Statement. *Arteriosclerosis.* 1985;5:404-412.
13. Kelley GA, Kelley KS. Aerobic exercise and lipids and lipoproteins in men: a meta-analysis of randomized controlled trials. *J Mens Health Gend.* 2006;3:61-70.
14. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA.* 1993;269:3015-3023.
15. Steinberg D, Glass CK, Witztum JL. Evidence mandating earlier and more aggressive treatment of hypercholesterolemia. *Circulation.* 2008;118:672-677.
16. Das DK. Cardioprotection with high-density lipoproteins: fact or fiction? *Circ Res.* 2003;92:258-260.
17. Durstine JL, Grandjean PW, Cox CA, Thompson PD. Lipids, lipoproteins, and exercise. *J Cardiopulm Rehabil.* 2002;22:385-398.
18. Leon AS, Sanchez OA. Response of blood lipids to exercise training alone or combined with dietary intervention. *Med Sci Sports Exerc.* 2001;33:S502-S515.
19. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. *Circulation.* 1989;79:8-15.
20. Thompson PD, Cullinane EM, Sady SP, et al. Modest changes in high-density lipoprotein concentration and metabolism with prolonged exercise training. *Circulation.* 1988;78:25-34.
21. Wood PD, Stefanick ML, Williams PT, Haskell WL. The effects on plasma lipoproteins of a prudent weight-reducing diet, with or without exercise, in overweight men and women. *N Engl J Med.* 1991;325:461-466.
22. Leon AS, Rice T, Mandel S, et al. Blood lipid response to 20 weeks of supervised exercise in a large biracial population: the HERITAGE Family Study. *Metabolism.* 2000;49:513-520.
23. Thompson PD, Rader DJ. Does exercise increase HDL cholesterol in those who need it the most? *Arterioscler Thromb Vasc Biol.* 2001;21:1097-1098.
24. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation.* 2007;115:450-458.
25. Cullen P. Evidence that triglycerides are an independent coronary heart disease risk factor. *Am J Cardiol.* 2000;86:943-949.
26. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. *Circulation.* 1998;97:1029-1036.
27. Williams PT. Relationships of heart disease risk factors to exercise quantity and intensity. *Arch Intern Med.* 1998;158:237-245.
28. Weintraub MS, Rosen Y, Otto R, Eisenberg S, Breslow JL. Physical exercise conditioning in the absence of weight loss reduces fasting and postprandial triglyceride-rich lipoprotein levels. *Circulation.* 1989;79:1007-1014.
29. Carmena R, Duriez P, Fruchart JC. Atherogenic lipoprotein particles in atherosclerosis. *Circulation.* 2004;109:III2-III7.
30. Sulkes D, Brown BG, Krauss RM, Segrest JP, Sniderman AD, Roberts WC. The editor's roundtable: expanded versus standard lipid panels in assessing and managing cardiovascular risk. *Am J Cardiol.* 2008;101:828-842.
31. Chapman MJ, Guerin M, Bruckert E. Atherogenic, dense low-density lipoproteins: Pathophysiology and new therapeutic approaches. *Eur Heart J.* 1998;19(suppl A):A24-A30.
32. Cromwell WC, Otvos JD. Low-density lipoprotein particle number and risk for cardiovascular disease. *Curr Atheroscler Rep.* 2004;6:381-387.
33. O'Donovan G, McEneny J, Kearney EM, et al. LDL particle size in habitual exercisers, lean sedentary men and abdominally obese sedentary men. *Int J Sports Med.* 2007;28:644-649.
34. Kraus WE, Houmard JA, Duscha BD, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med.* 2002;347:1483-1492.
35. El Harchaoui K, Arsenault BJ, Franssen R, et al. High-density lipoprotein particle size and concentration and coronary risk. *Ann Intern Med.* 2009;150:84-93.
36. Halverstadt A, Phares DA, Wilund KR, Goldberg AP, Hagberg JM. Endurance exercise training raises high-density lipoprotein cholesterol and lowers small low density lipoprotein and very low-density lipoprotein independent of body fat phenotypes in older men and women. *Metabolism.* 2007;56:444-450.

37. Slentz CA, Houmard JA, Johnson JL, et al. Inactivity, exercise training and detraining, and plasma lipoproteins. STRRIDE: a randomized, controlled study of exercise intensity and amount. *J Appl Physiol.* 2007;103:432-442.
38. Ginsberg HN. Lipoprotein physiology. *Endocrinol Metab Clin North Am.* 1998;27:503-519.
39. Barter PJ, Rye KA. The rationale for using apoA-I as a clinical marker of cardiovascular risk. *J Intern Med.* 2006;259:447-454.
40. Contois JH, McConnell JP, Sethi AA, et al. Apolipoprotein B and cardiovascular disease risk: position statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. *Clin Chem.* 2009;55:407-419.
41. Ring-Dimitriou S, von Duvillard SP, Paulweber B, et al. Nine months aerobic fitness induced changes on blood lipids and lipoproteins in untrained subjects versus controls. *Eur J Appl Physiol.* 2007;99:291-299.
42. Angelopoulos TJ, Sivo SA, Kyriazis GA, et al. Do age and baseline LDL cholesterol levels determine the effect of regular exercise on plasma lipoprotein cholesterol and apolipoprotein B levels? *Eur J Appl Physiol.* 2007;101:621-628.
43. Joy T, Hegele RA. Is raising HDL a futile strategy for atheroprotection? *Nat Rev Drug Discov.* 2008;7:143-155.
44. Benderly M, Boyko V, Goldbourt U. Apolipoproteins and long-term prognosis in coronary heart disease patients. *Am Heart J.* 2009;157:103-110.
45. Mora S, Cook N, Buring JE, Ridker PM, Lee IM. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. *Circulation.* 2007;116:2110-2118.
46. Thompson PD, Yurgalevitch SM, Flynn MM, et al. Effect of prolonged exercise training without weight loss on high-density lipoprotein metabolism in overweight men. *Metabolism.* 1997;46:217-223.
47. Seip RL, Moulin P, Cocke T, et al. Exercise training decreases plasma cholesteryl ester transfer protein. *Arterioscler Thromb.* 1993;13:1359-1367.
48. Israel RG, Sullivan MJ, Marks RH, Cayton RS, Chenier TC. Relationship between cardiorespiratory fitness and lipoprotein(a) in men and women. *Med Sci Sports Exerc.* 1994;26:425-431.
49. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA.* 2007;298:299-308.
50. Petitt DS, Cureton KJ. Effects of prior exercise on postprandial lipemia: a quantitative review. *Metabolism.* 2003;52:418-424.
51. Gill JM, Hardman AE. Exercise and postprandial lipid metabolism: an update on potential mechanisms and interactions with high-carbohydrate diets (review). *J Nutr Biochem.* 2003;14:122-132.
52. Gill JM, Herd SL, Hardman AE. Moderate exercise and post-prandial metabolism: issues of dose-response. *J Sports Sci.* 2002; 20:961-967.
53. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc.* 2007;39:1423-1434.
54. Herd SL, Lawrence JE, Malkova D, Murphy MH, Mastana S, Hardman AE. Postprandial lipemia in young men and women of contrasting training status. *J Appl Physiol.* 2000;89:2049-2056.