The Effect of Physical Exercise on Reverse Cholesterol Transport

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High-density lipoproteins (HDL) are recognized for their role in coronary artery disease (CAD) risk reduction. Plasma HDL plays a pivotal role in the reverse cholesterol transport (RCT) process. Physical exercise is well recognized as a modality that affects HDL metabolism. The purpose of this discussion is to describe the effects of physical exercise on RCT.

HIGH DENSITY lipoproteins (HDL) are acquiring emerging recognition for their role in coronary artery disease (CAD) risk reduction. Epidemiological studies recognize HDL-cholesterol as an independent CAD risk factor and indicate that a 1-mg/dL increase in plasma HDL-cholesterol levels is associated with a CAD risk reduction of 2% in men and 3% in women.[1] Randomized controlled trials using gemfibrozil for primary prevention of CAD in men have shown that raising plasma HDL-cholesterol levels reduces CAD-related mortality: A 3% to 5% CAD risk reduction is associated with a 1-mg/dL increase in plasma HDL-cholesterol levels.[2] A recent secondary prevention trial, the HDL Intervention Trial (HIT), showed that among men with CAD and low HDL-cholesterol levels, those randomized to receive gemfibrozil experienced a significant reduction in CAD events compared with patients receiving placebo, without affecting plasma low-density lipoprotein (LDL)-cholesterol levels,[3] and found that each 1-mg/dL increase in plasma HDL-cholesterol levels reduced CAD risk by approximately 2%.[4] These findings provide a strong rationale for treating patients with low HDL-cholesterol syndromes. Physical exercise is well recognized as a modality that increases plasma HDL-cholesterol levels. The purpose of this discussion is to describe the effects of physical exercise on HDL metabolism.

PHYSICAL EXERCISE AND CORONARY ARTERY DISEASE

Participation in regular physical exercise pursuits, associated with overall mortality reductions of 10% to 20%[5] and CAD risk-related mortality by approximately 40%,[6] is highly recommended for the prevention of CAD.[7] Higher levels of aerobic capacity are associated with increased longevity and reduced CAD mortality.[5,6]

Physical exercise can be grossly dichotomized as (1) aerobic or (2) strength-based (resistive), and can be administered as acute (a single exercise bout) or chronic (long-term exercise [physical exercise training {PET}]).[8] Isolated physical exercise sessions elicit acute metabolic responses that with frequent repetition produce more permanent adaptations, referred to as the training response.[9] Because aerobic-based physical exercise has been shown to affect plasma lipid and lipoprotein levels favorably (ie, lowering triglycerides and increasing plasma HDL-cholesterol levels) this discussion is focused on aerobic-based physical exercise. In some physical exercise studies, the effect of PET on plasma lipids and lipoproteins is assessed by comparing athletes (a surrogate for PET) with sedentary (a surrogate for non–exercise-trained) individuals.

A major mechanism by which regular physical activity and physical exercise training mitigate CAD risk appears to result from its impact on plasma HDL.[10-12] Acute exercise has generally been shown to increase plasma HDL-cholesterol levels by 4% to 43%.[11] A meta-analysis shows increased plasma HDL-cholesterol levels with regular aerobic physical activity and physical exercise training are more modest: 4.6% (range, −5.8% to +25%).[13] Coulliard et al[14] found physical exercise-induced increases in plasma HDL-cholesterol are more prominent among hypertriglyceridemics.[15] Recent findings from the HERITAGE Family Study confirm the heterogeneity in the responsiveness of HDL-cholesterol to exercise-induced changes.[16,17]. Participation in 12 weeks of aerobic-based PET resulted in a mean increase of plasma HDL-cholesterol levels of approximately 1.6 mg/dL (SD = 4.5 mg/dL). Indeed, half of the participants had no change or a decrease in plasma HDL-cholesterol levels with training.[18] Subjects characterized as having low baseline HDL-cholesterol levels (< 35 mg/dL) had greater exercise-induced HDL-cholesterol increases (2.0 ± 3.9 mg/dL) than those with HDL-cholesterol levels greater than 35 mg/dL (1.2 ± 5.2 mg/d). However, baseline HDL-cholesterol levels accounted for only 1.2% of HDL-cholesterol exercise-induced changes, while age and ethnicity were not significant predictors.

Although previously noted epidemiological and pharmaceutical studies show that each 1-mg/dL increase in HDL-cholesterol reduces CAD risk by 2% to 3% in men, based on studies indicating that PET raises plasma HDL-cholesterol by 1 to 2 mg/dL,[13,16] HDL-cholesterol–mediated CAD risk reduction should be 3% to 6%. Yet, the impact of physical exercise on CAD risk reduction isgreatly in excess of this expectation (ie, ~40%).[6,7] Increased plasma HDL-cholesterol levels are one of the multiple anti-atherogenic and antithrombotic mechanisms by which physical exercise reduces the risk of primary and secondary events.[19] Exercise-induced CAD risk reduction may also reflect other potentially anti-atherogenic aspects of HDL metabolism,[20-24] including (1) reverse cholesterol transport (RCT), (2) anti-oxidant effects,[25,26] and (3) antithrombotic properties,[27], in addition to (4) anti-inflammatory effects, (5) attenuation of endothelial dysfunction, and (6) reducing LDL retention.[23-28] Among these, RCT is the most widely charac-

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Table 1. Laboratory Methodologies Employed to Characterize HDL Particles

Laboratory Technique	Characterization of HDL
Precipitation	Cholesterol content
Ultracentrifugation	Particle density
Immunoaffinity assay	Apolipoprotein composition
Electrophoresis	Prebeta, alpha, and prealpha
Nuclear magnetic resonance spectroscopy	Particle size

terized[22,29] and is the focus of this discussion. Hence, determination of HDL-cholesterol alone may not adequately measure RCT and may underestimate important changes in this complex dynamic pathway. Physical exercise may increase the efficiency of RCT system rather that specific plasma constituents (ie, HDL-cholesterol) that may merely represent anti-atherogenic biomarkers that do not fully reflect the extent of increased RCT activity.

HDL-cholesterol represents a gross measurement of the HDL particle as it is a measurement of the total cholesterol content alone carried in plasma HDL. However, HDL particles are comprised of a collection of different molecular lipoprotein species containing cholesterol, triglycerides, apolipoproteins (apos), and phospholipids that vary in composition and function.[30] These particles are heterogeneous in size and density, as well as apo composition. A limitation presented in the interpretation of most physical exercise studies is that they measure plasma total HDL-cholesterol levels only and do not measure HDL subparticle composition. The manner plasma HDL is measured presents a difficulty for interpreting exercise-related HDL studies. Studies involving physical exercise have characterized plasma HDL according to (1) cholesterol content using precipitation techniques, (2) density distribution according to ultracentrifugation techniques, (3) apo composition using immunoaffinity techniques, (4) prebeta, alpha, and pre-alpha classifications using electrophoresis, and (5) particle size with nuclear magnetic resonance spectroscopy. Measured according to size and density using ultracentrifugation techniques, HDL is commonly separated as smaller, more dense HDL_3 and larger, more buoyant HDL_2 subspecies. Lipoproteins (LP)s measured according to apo composition using immunoaffinity techniques define HDL particles containing apo-AI without apo-AII (LP-AI) and HDL particles containing both apo-AI and apo-AII (LP-AI + AII). LP-AI is found in HDL_3 and LP-AI + AII is found in HDL_2 particles. Table 1 summarizes different methodologies for measuring the HDL particle. HDL subspecies composition has implications for CAD risk reduction. Studies using these analytical techniques indicate the HDL_2-cholesterol subfraction and LP AI are generally recognized as anti-atherogenic.[31-35]

HDL AND RCT

Plasma HDL plays a pivotal role in the RCT process.[20] RCT is comprised of a series of HDL-mediated steps whereby cholesterol is removed from peripheral tissues and brought to the liver where it is processed for excretion.[22,29] This process is shown in Fig 1 and serves as the basis for further discussion. This can be conceptualized as a 3-step process. Step 1 involves the formation of nascent HDL particles that accept free cholesterol from peripheral tissues. Step 2 involves the esterification of cholesterol by lecithin:cholesterol transferase (LCAT). This initiates the process of HDL maturation. The cholesterol ester enters the core of the HDL converting the discoidal-shaped particle to spherical HDL. During this process HDL is

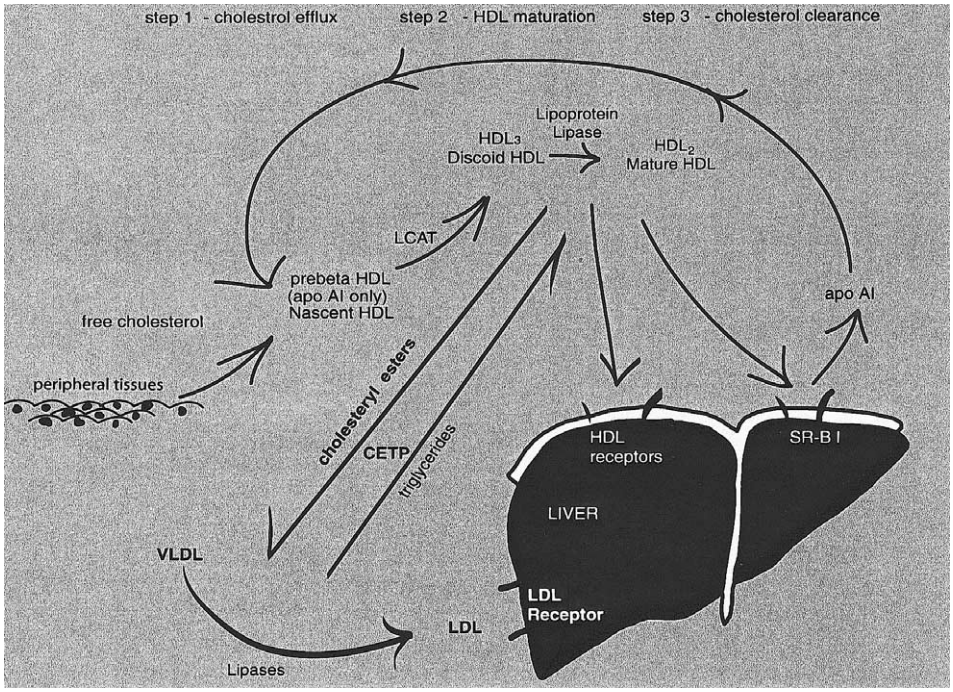

Fig 1. Schematic conceptualization of the RCT process.

remodeled by several enzyme systems, discussed below, transforming from small, dense HDL_3 particles to the larger, more buoyant HDL_2 particle as it acquires lipids and apos from delipidated triglyceride-rich particles as they are catabolized Step 3 encompasses the pathways of cholesterol clearance. This involves cholesterol delivery from HDL particles either directly or indirectly to tissues via cellular receptors. The liver is the main organ involved in cholesterol clearance and is the focus of this discussion.

Step 1: Cholesterol Efflux

This is the process by which cholesterol is removed from peripheral cells by nascent HDL particles. The efficiency of this process may be the rate-limiting step to the RCT process. The activity of the adenosine triphosphate (ATP)-binding cassette (ABC) transporter 1 considered to control the first step of RCT that is cellular cholesterol efflux towards nascent HDL.[36-38] Recent findings indicate that ABC transporter 1 mutations reduce cholesterol efflux, lower plasma HDL-cholesterol levels, and are associated with greater carotid artery intima-media thickness than subjects without ABC transporter 1 mutations.[39]

The cardioprotective effects of HDL have largely been attributed to the ability of apo AI-containing HDL particles to initiate cholesterol efflux and thereby facilitate the removal of excess cholesterol from peripheral tissues.[44] Specific subfractions of HDL, such as the prebeta HDL fraction, may be especially efficient at mediating cholesterol removal from peripheral cells by a membrane-microsolubilization process.[40-42] Prebeta HDL is a 67-kd species of plasma HDL that contains 2 copies of apo AI. Prebeta HDL is a molecular species of HDL that was not recognized until 1985.[43] Because of its high density, it was not included in HDL recovered from serum by ultracentrifugation in the traditional density interval 1.063 to 1.21 g/mL (ie, alpha HDL particles). In addition, its rapid conversion to HDL species of larger diameter, ex vivo, by LCAT, impeded its recognition by other techniques. The advent of the minimally perturbing chromatographic technique, selected affinity immunosorption,[44] which recovers apo AI-containing particles quantitatively from human plasma, has permitted the subsequent recognition of HDL, species of prebeta mobility, distinguishing them from the predominant mass of HDL that has alpha mobility (ie, alpha HDL).[43] Also described as "'nascent" HDL, prebeta HDL is secreted from the intestine and liver. Prebeta HDL is also formed during cholesterol clearance from alpha HDL during the transfer of cholesterol esters to acceptor lipoprotein[41] and the scavenger receptor, type BI (SR-BI) that also participates in the RCT pathway, endocytosing cholesterol esters into hepatocytes.[45,46] Both HDL particle species LP-AI and LP AI + AII contribute apo AI that is dissociated from these particles in the formation of prebeta HDL.[41]

Step 2: HDL Particle Maturation

This is the process by which nascent HDL particles, having acquired cholesterol from peripheral tissues, utilize the cholesterol so that is can be carried to hepatocyte receptors that remove HDL-borne cholesterol from the plasma. LCAT plays a pivotal role in esterifying cholesterol so that it may be more readily carried in the plasma by maturing HDL species.[47] Cholesteryl ester transfer protein (CETP) modulates equimolar exchanges of cholesterol esters and triglycerides between HDL particles and those of the very-low density lipoprotein (VLDL)-LDL series.[20,48] Discussed later, lipoprotein lipase activity also plays a role in HDL metabolism. Hepatic lipase[49] and phospholipid transfer protein exert direct effects on HDL metabolism. Hepatic lipase remodels LDL and HDL particles by hydrolysis of triglycerides and phospholipids, forming smaller, denser particles.[50] Adipose and skeletal lipoprotein lipases cause triglyceride removal from triglyceride-rich lipoprotein. Delipidation of these particles indirectly effects HDL metabolism as it alters HDL particle constituents.

Step 3: Cholesterol Clearance

HDL-mediated RCT delivers cholesterol to cellular receptors through indirect and direct pathways.[51] The independent pathway involves CETP-mediated exchange of cholesterol esters from HDL to the VLDL-LDL particle series, which then provides cholesterol removal by LDL receptors.[20,48] Direct HDL-mediated receptor pathways have been more recently identified on hepatocytes[52,53] and include (1) HDL receptor, and (2) scavenger receptor type B class I (SR-BI). HDL receptors are involved in holoparticle uptake of HDL and subsequent degradation. The SR-BI receptor binds HDL and mediates the selective uptake or removal of HDL-cholesterol esters without the uptake/degradation of HDL-apo AI.[45,46] Hence, the SR-BI receptor acts as a "docking" site so that cholesterol esters can be removed after which the HDL particle (depleted of cholesterol esters) "undocks" and recirculates to pick up more cholesterol esters from peripheral tissues. Another receptor, cubilin (the recently described endocytic receptor for intrinsic factor-vitamin B_{12}), has recently been identified[54,55] as a receptor that mediates HDL holoparticle endocytosis. However, cubulin has not been reported to be present in liver cells.

Hepatic lipase has been shown to play a major role in HDL catabolism by hydrolyzing both triglycerides and phospholipids within HDL particles, thus effecting its availability for receptor clearance.[49,50,56] It is conceivable that modulation of these HDL catabolic pathways may play an important role in regulating plasma levels of HDL particles. LP AI particles appear to be the most efficient in facilitating cholesterol ester uptake by SR-BI receptors. Hep G_2 cell uptake of [^{3}H] cholesterol ester is approximately 75% greater from LP-AI versus LP-AI + AII particles.[57] Niacin selectively inhibits hepatic LP-AI removal without effecting cholesterol ester uptake.[58] Reducing LP-AI removal increases plasma LP-AI levels and, as previously discussed, could increase prebeta HDL levels[20,21] and consequently facilitate RCT though SR-BI pathways by sustaining increased plasma levels of LP-AI that can promote both cholesterol tissue efflux and hepatocyte cholesterol uptake.

EFFECTS OF PHYSICAL EXERCISE ON HDL PARTICLES

Nye et al[59] noted the importance of evaluating HDL subfractions rather than total HDL-cholesterol to reflect HDL metabolism. They found that physical exercise training exerts a "masking effect" on total HDL-cholesterol by causing reciprocal changes in plasma HDL_2-cholesterol (increased) and

Table 2. Effects of Aerobic-Based Physical Exercise on the RCT System

	Acute Exercise	Exercise Training
Efflux		
Cholesterol efflux	?	+(ref = 69)
Prebeta HDL	+(ref = 67)	?
Apo AI	NC (ref = 63,64,70)	+(ref = 14,65,67,68),
Maturation		
LCAT	+(ref = 73,74)	+(ref = 71,72)
CETP	−(ref = 77), NC (ref = 78)	+(ref = 62), −(ref = 76)
Phospholipid transfer protein	?	?
Hepatic lipase	NC (ref = 77), +(ref = 76)	−(ref = 83,84,85)
Lipoprotein lipase	+(ref = 64,89,90)	+(ref = 964
Clearance		
HDL catabolism	?	−(ref = 93,99)

Abbreviations: +, increase; −, decrease; NC, no change; ?, unknown; LCAT, lecithin cholesterol acyl transferase; CETP, cholesteryl ester transfer protein.

HDL_3-cholesterol (decreased) subparticle levels. Indeed, Kantor et al[60] have shown variability in HDL-cholesterol subfraction response to acute physical exercise: exercise preferentially raises plasma HDL_2-cholesterol levels in exercise trained individuals and HDL_3-cholesterol levels in sedentary individuals. Nuclear magnetic resonance spectroscopy techniques employed in a recent study show that PET increases HDL size.[61] These findings indicate physical exercise increases the prevalence of larger, more buoyant HDL species (ie, HDL_2). Exercise also appears to effect apolipoprotein composition. Plasma apo AI and HDL_2-cholesterol levels are higher in trained athletes than in sedentary controls.[62] However, acute exercise appears to have no effect on plasma apo AI nor apo AII levels.[63,64] Some[14,65,66] but not other[67,68] studies indicate that PET raises plasma apo AI levels.

These findings indicate that physical exercise effects HDL composition and suggest that these changes in plasma levels of HDL constituents may be biomarkers for altered HDL metabolic pathways (ie, RCT). HDL-mediated RCT can be measured from a more physiological perspective as described below using studies that measure the dynamics of HDL-mediated processes in RCT.

EXERCISE AND RCT

Some physical exercise studies have employed measurements of the HDL metabolic processes pertaining to RCT. These are discussed in the context of the previously described model of HDL's participation in the RCT process and are summarized in Table 2.

Step 1: Exercise and Cholesterol Efflux

Gupta et al[69] have shown that the net mass of free cholesterol transport out of cultured human fibroblasts into athlete's (n = 11) serum is greater than that of sedentary controls (n = 13) (25.5 ± 8.0 *v* 7.1 ± 2.6 μg/mL/L, = .041). These findings are consistent with recent findings showing a single bout of aerobic exercise raises plasma prebeta HDL levels.[70] Following an acute bout of aerobic exercise a group 19 men and women (athletes, n = 9; sedentary, n = 10) experienced increased levels of plasma prebeta HDL (0.10 ± 0.06 to 0.130 ± 0.07 μg/mL, P = .012) without increased plasma HDL-C nor apo AI levels. These findings may be interpreted to indicate exercise-induced increases in plasma prebeta HDL levels are a product derived from enhanced alpha HDL particles utilization rather from de novo apo AI synthesis.[41] Prebeta HDL particles are generated from alpha HDL during the transfer of cholesterol esters to acceptor lipoproteins[41] and SR-BI, which also participates in the RCT pathway, endocytosing cholesterol esters into hepatocytes.[45,46] Both HDL particle species (LP-AI and LP-AI + AII) contribute apo AI that is dissociated from these particles acquired through the SR-BI receptor and can be "recycled" in the formation of prebeta HDL.[41] Despite the prebeta HDL raising effect of acute exercise, pre-exercise prebeta HDL levels did not differ between groups (athletes, 0.11 ± 0.04 μg/mL *v* sedentary, 0.11 ± 0.06 μg/mL).[70] This suggests that following exercise prebeta HDL particles are rapidly redistributed to the alpha HDL series. Hence, exercise-induced modulation of mechanisms that increase production of alpha HDL particles could contribute to increased recycling of prebeta HDL derived from alpha HDL substrates without raising prebeta HDL levels per se. This result appears to be similar to the reported effect of niacin that has been shown to selectively inhibit hepatocyte uptake of LP-AI.[58] By increasing particles that are highly efficient in cholesterol removal such as LP-AI and prebeta HDL, physical exercise may promote the RCT process by increasing HDL cycling of its apolipoprotein constituents. If prebeta HDL is a "rate-limiting" cholesterol acceptor in the early steps of cellular cholesterol efflux, then this offers an explanation for the finding of Gupta et al[69] that athletes have greater cholesterol efflux from fibroblasts than sedentary counterparts.

Step 2: Exercise and HDL Maturation

Increased LCAT activity increases alpha HDL formation from prebeta HDL and has been shown to be greater in athletes than sedentary counterparts[71,72] and is increased immediately after acute exercise.[73,74] Decreased CETP activity increases alpha HDL levels by increasing cholesterol ester content, and concomittently reduces HDL-triglyceride content by triglyceride transfer to non-HDL lipoprotein species, although some have questioned whether low CETP activity is cardioprotective.[75] On the other hand, increased CETP activity could facil-

itate alpha HDL turnover and promote prebeta HDL formation. In some studies CETP activity is greater among athletes than sedentary individuals,[62] while it has also been shown to decrease following physical exercise training.[76] Following acute exercise CETP activity is shown to be decreased[77] or unchanged.[78]

Increased phospholipid transfer protein activity participates in alpha HDL metabolism by exchanging esterified cholesterol and phospholipids from alpha HDL species enabling particle maturation from HDL_3 to HDL_2 series and enhancing alpha HDL recycling thus potentially increasing the formation of prebeta HDL particles.[79,80] The effect of physical exercise on phospholipid transfer protein activity has not been reported.

Hepatic lipase increases alpha HDL cholesterol levels by hydrolyzing alpha HDL triglycerides and phospholipids.[81,82] Hepatic lipase decreases with PET.[83-85] Although acute exercise appears not to alter hepatic lipase activity in untrained subjects,[86] in trained individuals it increases 12 to 16 hours following exercise.[76,86]

Lipoprotein lipase activity is increased. Lipoprotein lipases are a family of tissue-specific hydrolytic enzymes that are rate-limiting for the removal of circulating lipoprotein triglycerides and have been implicated in atherogenesis.[87,88] Acute exercise also increases lipoprotein lipase activity and oral fat tolerance.[64,89] This has been most widely shown in fit individuals performing at high levels of protracted physical exertion, but also has been shown to occur in sedentary individuals exercising for as little as 1 hour at 80% of maximal heart rate.[90] Adipose lipoprotein lipase activity, involved in triglyceride storage of acyl groups derived primarily from the hydrolysis of plasma lipoproteins, increases with PET.[91] Skeletal muscle lipoprotein lipase has become the recent focus of exercise-related effects on plasma triglyceride/HDL-related metabolism.[92] Although aerobic exercise does not increase muscle mass, it increases the percentage of skeletal slow twitch fibers. Exercise raises skeletal lipoprotein lipase activity in the capillary beds of skeletal muscles where fatty acids are hydrolyzed from circulation lipoproteins for energy utilization. Skeletal muscle fast twitch (type I) fibers have a greater lipolytic effect than do their slow twitch (type IIa and IIb) counterparts. Skeletal muscle fiber composition, which is modulated by physical exercise, has been proposed to explain exercise-related effects of plasma lipoproteins.[92,93] Tikkanane et al[94] have shown a higher percentage of slow twitch muscle fibers, which have a higher capacity to metabolize fatty acids liberated by lipoprotein lipase from triglyceride-rich lipoproteins, is associated with increased plasma HDL-cholesterol levels. Rat studies by Ong et al[95] show that although exercise does not affect skeletal muscle lipoprotein lipase transcription, the exercise-induced increase in skeletal muscle lipoprotein lipase activity is physiologically mediated at the post-transcription level. Patsch et al[96] have provided in vitro evidence that HDL is formed by the fusion of HDL_3 with surface components of triglyceride-rich lipoproteins liberated during lipolysis. Thus, the rise in HDL_3 and subsequently HDL_2 concentrations induced by physical exercise training may be a consequence of enhanced catabolism of triglyceride-rich lipoproteins. These observations have lead to the hypothesis that exercise acutely depletes intramuscular triglycerides, a finding that has recently been confirmed.[97] This stimulates the synthesis or translocation of lipoprotein lipase, which hydrolyzes triglycerides from lower-density lipoproteins with transfer of the excess surface cholesterol to the HDL particle.[89]

Step 3: Exercise, HDL, and Apo AI Clearance

Thompson et al[93] found that participation in 8 to 11 months of aerobic-based PET increased the biological half-life of apo AI by 10% ($P = .07$) by decreasing the fractional catabolic rate by a corresponding amount and not affecting apo AI synthetic rate. A similar finding was noted for apo AII. Herbert et al[98] found that the mean biological half-life of HDL proteins was longer in runners (6.2 days) than in sedentary controls (3.8 days). Tracer studies of radioiodinated autologous HDL demonstrated that runners did not produce more HDL protein but rather catabolized less.

These findings suggest that the effect of PET on HDL metabolism may be analogous to that of niacin.[58] Findings showing that aerobic exercise increases plasma prebeta HDL (comprised mainly of apo AI) levels without increasing apo AI levels[70] suggest that exercise efficiently replenishes prebeta HDL particles by blocking hepatocyte clearance of alpha HDL particles (ie, LP AI). The resulting effect would provide greater amounts of apo AI from the alpha HDL particles to generate prebeta HDL. This increases the efficiency of the RCT with respect both to improving cellular cholesterol efflux but also cholesterol ester delivery and uptake by hepatocytes. This concept suggests that aerobic-based PET may effect hepatocyte HDL-cholesterol and HDL-apo AI removal pathways differently as shown in previous studies involving niacin.[58] Hence, following aerobic-based PET, there may be a selective decline in LP-AI removal while hepatoctye cholesterol ester uptake is unchanged or potentially increases. This will potentiate the formation of prebeta HDL and increase cellular cholesterol efflux.

CONCLUSIONS

The findings from randomized clinical trials in primary[2] and secondary[3] prevention underscore the importance of increasing plasma HDL-cholesterol for reducing CAD risk. Although PET has been historically promoted for increasing plasma HDL-cholesterol levels, for most individuals the impact of physical exercise on plasma HDL-cholesterol levels is relatively small and dose not account for the effect of physical activity and CAD risk reduction noted in epidemiologic studies.[6,7]

The clinician who promotes physical exercise to reduce CAD risk should not be disheartened by this lower-than-expected effect of physical exercise on plasma HDL-cholesterol levels. Plasma HDL-cholesterol may be conceptualized as a biomarker of the anti-atherogenic reverse cholesterol transport process. This is a dynamic, physiological process upon which physical exercise modulates a number of pivotal components. Plasma HDL-cholesterol is, perhaps, analogous to the tip of the iceberg of the underlying RCT process. Research scientists should continue to chip away at the mass of this iceberg in order to continue to delineate the mechanism(s) by which physical exercise impacts the reverse cholesterol transport system.

REFERENCES

1. Gordon DJ, Probstfield JL, Garrison RL, et al: High density lipoprotein cholesterol and cardiovascular disease: Four prospective American studies. Circulation 79:8-20, 1989
2. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. N Engl J Med 317:1237-1246, 1987
3. Robbins HB, Robins SJ, Collins D, et al: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med 341:410-418, 1999
4. Robbins SJ, Collins D, Wittes T, et al: Relation of gemfibrozil treatment and lipid levels with major coronary events VA-HIT: A randomized controlled trial. JAMA 285:1585-1591, 2001
5. Lee I-M, Skerrett PJ: Physical activity and all-cause mortality: What is the dose-response relation? Med Sci Sports Exerc 33:S459-S471, 2001 (suppl)
6. Kohl HW: Physical activity and cardiovascular disease: Evidence for a dose response. Med Sci Sports Exerc 33:S472-S483, 2001 (suppl)
7. Pate RR, Pratt M, Blair SN, et al: Physical activity and public health: A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. JAMA 273:402-407, 1995
8. Thompson PD, Crouse SF, Goodpaster B, et al: The acute versus the chronic response to exercise. Med Sci Sports Exerc 33:S438-S445, 2001 (suppl 6)
9. Haskell WL: Health consequences of physical activity: Understanding and challenges regarding dose-response. Med Sci Sports Exerc 26:649-660, 1994
10. Thompson PD, Crouse SF, Goodpaster B, et al: The acute versus the chronic response to exercise. Med Sci Sports Exerc 33:S438-S445, 2001 (suppl)
11. Leaf DA, Parker DL, Schaad D: Changes in VO_{2max}, physical activity, and body fat with chronic exercise: Effects on plasma lipids. Med Sci Sports Exerc 29:1152-1159, 1997
12. Wood PD, Stephanick ML: Exercise, fitness, and atherosclerosis. in, Bouchard C, Shephard RJ, Stephens T, et al (eds): Exercise, Fitness, and Health: A Consensus of Current Knowledge. Champaign, IL, Human Kinetics, 1990, pp 407-424
13. Leon AS, Sanchez OA: Response of blood lipids to exercise training alone or combined with dietary interventions. Med Sci Sports Exerc 33:S502-S515, 2001 (suppl 6)
14. Couillard C, Despres J-P, Lamarche B, et al: Effects of endurance exercise training on plasma HDL cholesterol levels depend on levels of triglycerides. Arterioscler Thromb Vasc Biol 21:1226-1232, 2001
15. Thompson PD, Rader DJ: Does exercise increase HDL cholesterol in those who need it the most? Arterioscler Thromb Vasc Biol 21:1097-1098, 2001
16. 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 49:513-520, 2000
17. Bouchard C, Rankinen T: Individual differences in response to regular physical activity. Med Sci Sports Exerc 33:S446-S451, 2001 (suppl)
18. Leon AS, Gaskill SE, Bergerson J, et al: Variability in the response of HDL cholesterol to exercise training in the HERITAGE Study. Int J Sports Med 23:1-9, 2002
19. Leon AS: Exercise following myocardial infarction: Current recommendations. Sports Med 29:301-311, 2000
20. Tall AR, Jiang X, Luo Y, et al: 1999 George Lyman Duff Memorial Lecture: Lipid transfer proteins, HDL metabolism, and atherogenesis. Arterioscler Thromb Vasc Biol 20:1185-1188, 2000
21. von Eckardstein A, Nofer J-R, Assman G: High density lipoproteins and arteriosclerosis. Role of cholesterol efflux and reverse cholesterol transport. Arterioscler Thromb Vasc Biol 21:13-27, 2001
22. Fielding CJ, Fielding PE: Molecular physiology of reverse cholesterol transport. J Lipid Res 36:211-228, 1995
23. Shah PK, Kaul S, Nilsson J, et al: Exploiting the vascular protective effects of high-density lipoproteins and its apolipoproteins: An idea whose time is coming, part I. Circulation 104:2376-2383, 2001
24. Shah PK, Kaul S, Nilsson J, et al: Exploiting the vascular protective effects of high-density lipoprotein and its apolipoproteins: An idea whose time is coming, part II. Circulation 104:2498-2502, 2001
25. Durrington PN, Mackness B, Mackness MI: Paraoxonase and atherosclerosis. Arterioscler Thromb Vasc Biol 21:473-480, 2001
26. Navab M, Berliner J, Subbanagounder G, et al: HDL and the inflammatory response induced by LDL-derived oxidized phospholipids. Arterioscler Thromb Vasc Biol 21:481-488, 2001
27. Saku K, Ahmad M, Glas-Grenwalt P, et al: Activation of fibrinolysis by apolipoproteins of high density lipoprotein in man. Thromb Res 39:1-8, 1985
28. O'Connell BJ, Genest J: High-density lipoproteins and endothelial dysfunction. Circulation 104:1978-1983, 2001
29. Kashyap ML: Basic considerations in reversal of atherosclerosis: Significance of reverse cholesterol transport. Am J Cardiol 63:56H-59H, 1989
30. Fruchart J-C, Ailhaud G, Bard J-M: Heterogeneity of high density lipoprotein particles. Circulation 87(Suppl III):22-27, 1993
31. Walldius G, Jungner I, Holme I, et al: High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): A prospective study. Lancet 358:2026-2033, 2001
32. Bararas R, Puchois P, Fruchart J-C, et al: Cholesterol efflux from cultured adipose cells is mediated by LP A-I particles but not by LP A-I:A-II particles. Biochem Biophys Commun 142:63-69, 1987
33. Rinninger F, Kaiser T, Windler E, et al: Selective uptake of cholesteryl esters from high-density lipoprotein-derived LPA-I and LPA-I:A-II particles by hepatic cells in culture. Biochim Biophys Acta 1393:277-291, 1998
34. Puchios P, Kandoussi A, Fievert P, et al: Apolipoprotein A-I-containing lipoproteins in coronary artery disease. Atherosclerosis 68: 35-40, 1987
35. Amouyel P, Isorez D, Bard JM, et al: Paternal history of early myocardial infarction is associated with decreased levels of lipoparticle A-I in adolescents. Arterioscler Thromb 13:1640-1644, 1993
36. McNeish J, Finer AG, Morrison JR, et al: High density lipoprotein deficiency and foam cell accumulation in mice with targeted disruption of ATP-binding cassette transporter-1. Proc Natl Acad Sci USA 97:4245-4250, 2000
37. Orso E, Ghiselli GW, Francone OL, et al: Transport of lipids from golgi to plasma membrane is defective in tangier-disease patients with Abc-1-deficient mice. Nat Genet 24:192-196, 2000
38. Dean M, Hamon Y, Chimini G: The human ATP-binding cassette (ABC) transporter superfamily. J Lipid Res 42:1007-1017, 2001
39. van Dam MJ, de Groot E, Clee SM, et al: Association between increased arterial-wall thickness and impairment in ABCA1-driven cholesterol efflux: An observational study. Lancet 359:37-4, 2002
40. Phillips MC, Gillote KL, Haynes MP, et al: Mechanisms of high density lipoprotein-mediated efflux of cholesterol from cell plasma membranes. Atherosclerosis 137:S13-S17, 1998 (suppl)
41. Hennessy LK, Kunitake ST, Kane JP: Apolipoprotein A-I-containing lipoproteins, with or without apolipoprotein A-II, as progenitors of pre-B high-density lipoprotein particles. Biochemistry 32:5759-5765, 1993
42. Asztalos B, Zhang W, Roheim PS, et al: Role of free apoli-

poprotein A-I in cholesterol efflux: Formation of pre-alpha-migrating high-density lipoprotein particles. Arterioscler Thromb Vasc Biol 17: 1630-1636, 1997

43. Kunnitake S, La Sada K, Kane J: Apolipoprotein A-I-containing lipoproteins with pre-beta electrophoretic mobility. J Lipid Res 26:549-555, 1985

44. McVicar JP, Kunnitake ST, Hamilton RI, et al: Characteristics of human lipoproteins isolated by selected affinity immunosorption of apolipoproteins A-I. Proc Natl Acad Sci USA 81:1356-1360, 1984

45. Acton S, Rigotti A, Landschultz K, et al: Identification of scavenger receptor SR-B1 as a high density lipoprotein receptor. Science 271:518-520, 1996

46. Krieger M: Scavenger receptor class B type I is a multiligand HDL receptor that influences diverse physiologic systems. J Clin Invest 108:793-797, 2001

47. Glomset JA, Norum KR: The metabolic role of lecithin:cholesterol acyltransferase: perspectives from pathology. Adv Lipid Res 11:1-65, 1973

48. Tall AR: Metabolic and genetic control of HDL cholesterol levels. J Intern Med 231:661-668, 1992

49. Carr MC, Ayyobi AF, Murdoch SJ, et al: Contribution of hepatic lipase, lipoprotein lipase, and cholesteryl ester transfer protein to LDL and HDL heterogeneity in healthy women. Arterioscler Thromb Vasc Biol 22:667-673, 2002

50. Kuusi T, Saarinen P, Nikkila EA: Evidence for the role of hepatic endothelial lipase in the metabolism of plasma high density lipoprotein2 in man. Atherosclerosis 36:589-593, 1980

51. Willnow TE, Nykjaer A, Herz J: Lipoprotein receptors: New role of ancient proteins. Nat Cell Biol 1:E157-E162, 1999

52. Fidge NH: High density lipoprotein receptors, binding proteins and ligands. J Lipid Res 40:187-201, 1999

53. Rigotti A, Kreiger M: Getting a handle on "good" cholesterol with the high-density lipoprotein receptor. N Engl J Med 341:2001-2012, 1999

54. Hammad SM, Steingrimur S, Twal WO, et al: Cubulin, the endocytic receptor for factor-vitamin B12 complex, mediates high-density holoparticle endocytosis. Proc Natl Acad Sci USA 96:10158-10163, 1999

55. Kozyraki F, Fyfe J, Kristiansen M, et al: The intrinsic factor-vitamin B12, cubilin, is a high-affinity apolipoprotein A-I receptor facilitating endocytosis of high-density lipoporotein. Nat Med 5:656-661, 1999

56. Santamarina-Fojo S, Haudenschild CC, Shamburek RD, et al: The role of hepatic lipase in lipoprotein metabolism and atherosclerosis. Curr Opin Lipidol 9:211-219, 1998

57. Sakai T, Kamanna VS, Kashyap M: Niacin, but not gemfibrozil, selectively increases LP-AI, a cardioprotective subfraction of HDL, in patients with low HDL-cholesterol. Arterioscler Thromb Vasc Biol 21:1783-1789, 2001

58. Fy-You J, Kamanna VS, Kashyap ML: Niacin decreases removal of high-density lipoprotein apolipoprotein A-I but not cholesterol ester by Hep G2 cells: Implication for reverse cholesterol transport. Arterioscler Thromb Vasc Biol 17:2020-202, 1997

59. Nye ER, Carlson K, Kirstein P, et al: Changes in high density lipoprotein subfractions and other lipoproteins induced by exercise. Clin Chim Acta 113:51-57, 1981

60. Kantor MA, Cullinane EM, Sady SP, et al: Exercise acutely increases HDL-cholesterol and lipoprotein lipase activity in trained and untrained men. Metabolism 36:188-192, 1987

61. Kraus WE, Houmard JA, Duscha BD, et al: Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med 347:1483-1492, 2002

62. Sasaki J, Tanabe Y, Tanaka H, et al: Elevated levels of HDL_2-cholesterol and apo A-I in national class Japanese male marathon runners. Atherosclerosis 70:175-177, 1988

63. Kantor MA, Cullinane EM, Herbert PN, et al: Acute increase in lipoprotein lipase following prolonged exercise. Metabolism 33:454-457, 1984

64. Sady SP, Thompson PD, Cullinane EM, et al: Prolonged exercise augments plasma triglyceride clearance. JAMA 256:2552-2555, 1986

65. Kiens B, Jorgensen I, Lewis S, et al: Increased plasma HDL-cholesterol and apo A-I in sedentary middle-aged men after physical conditioning. Eur J Clin Invest 10:203-209, 1980

66. Thompson PD, Yurgalevitch SM, Flynn MM, et al: Effect of prolonged training without weight loss on high-density lipoprotein metabolism in overweight men. Metabolism 46:217-223, 1997

67. Thompson PD, Cullinane EM, Sady EP, et al: Modest changes in high-density lipoprotein concentration and metabolism with prolonged exercise training. Circulation 78:24-34, 1988

68. Wood PD, Stefanick WM, Dreon DM, et al: Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. N Engl J Med 319:1173-1179, 1988

69. Gupta AK, Ross EA, Myers JN, et al: Increased reverse cholesterol transport in athletes. Metabolism 42:684-690, 1993

70. Jafari, M, Leaf DA, MacRae HS, et al: The effects of physical exercise on plasma prebeta-1 high density lipoprotein. Metabolism (in press)

71. Tsopanakis C, Kotsarellis D, Tsopanakis A: Plasma lecithin: cholesterol acyltransferase activity in elite athletes from selected sports. Eur J Appl Physiol 58:262-265, 1988

72. Lopez-S A, Vial R, Balart L, et al: Effect of exercise and physical fitness on serum lipids and lipoproteins. Atherosclerosis 20: 1-9, 1974

73. Frey I, Baumstark MW, Berg A, et al: Influence of acute maximal exercise on lecithin:cholesterol acyltransferase activity in healthy adults of differing aerobic performance. Eur J Appl Physiol 62:31-35, 1991

74. Urata H, Sasaki J, Tanabe Y, et al: Effect of mild aerobic exercise on serum lipids and apolipoprotiens in patients with coronary artery disease. Jpn Heart J 28:27-34, 1987

75. Inazu A, Brown ML, Hesler CB, et al: Increased high-density lipoprotein levels caused by a common cholesteryl-ester transfer protein gene mutation. N Engl J Med 323:1234-1238, 1990

76. Seip RL, Moulin P, Cocke T, et al: Exercise training decreases plasma cholesteryl ester transfer protein. Arterioscler Thromb 13:1359-1367, 1993

77. Foger B, Wohlfarter T, Ritsch A, et al: Kinetics of lipids, apolipoproteins, and cholesteryl ester transfer protein in plasma after a bicycle marathon. Metabolism 43:633-639, 1994

78. Grandjean PW, Crouse SF, Rohak JJ: Influence of cholesterol status on blood lipid and lipoprotein enzyme responses to aerobic exercise. J Appl Physiol 89:472-480, 2000

79. Day JR, Albers JJ, Loftonday CE, et al: Complete cDNA encoding human phospholipid transfer protein from human endothelial cells. J Biol Chem 269:9388-9391, 1994

80. Nishida HL, Nishida T: Phopspholipid transfer protein mediates transfer of not only phosphatidylcholine but also cholesterol from phosphotidylcholine-cholesterol vesicles to high density lipoproteins. J Biol Chem 272:6959-6964, 1997

81. Fan JA, Bensadoun A, Lauer SJ, et al: Overexpression of hepatic lipase and transgenic rabbits leads to a marked reduction of plasma high density lipoprotein and imtermediate density lipoproteins. Proc Natl Acad Sci USA 91:8724-8728, 1994

82. Barrans A, Collet R, Barbaras R, et al: Hepatic lipase induces the formation of prebeta-1 high density lipoprotein (HDL) from tri-

acylglycerol-rich HDL_2: A study comparing liver perfusion with in vitro incubation with lipases. J Biol Chem 269:11572-11577, 1997

83. Haskell WL: Exercise-induced changes in plasma lipids and lipoproteins. Prev Med 13:23-36, 1984

84. Williams PT, Krauss RM, Wood PD, et al: Lipoprotein subfractions of runners and sedentary men. Metabolism 35:45-52, 1986

85. Thompson PD, Cullinane EM, Sady SP, et al: High density lipoprotein metabolism in endurance athletes and sedentary men. Circulation 85:140-152, 1991

86. Durstine JL, Haskell WL: Effects of exercise training on plasma lipids and lipoproteins. Exercise Sports Sci Rev 22:477-521, 1994

87. Eckel RH: Lipoprotein lipase: A multifunctional enzyme relevant to common metabolic diseases. N Engl J Med 320:1060-1068, 1989

88. Goldber IJ: Lipoprotein lipase and lipolysis: Central roles in lipoprotein metabolism and atherosclerosis. J Lipid Res 37:693-707, 1996

89. Kantor MA, Cullinane EM, Herbert PN, et al: Acute increase in lipoprotein lipase following prolonged exercise. Metabolism 33:454-457, 1984

90. Kantor MA, Cullinane EM, Sady SP, et al: Exercise acutely increases HDL-cholesterol and lipoprotein lipase activity in trained and untrained men. Metabolism 36:188-192, 1987

91. Nikkila EA: Role of lipoprotein lipase in metabolic adaptation to exercise and training, in Borensztajn J (ed): Lipoprotein Lipase. Chicago, IL, Evener, 1987, pp 187-199

92. Thompson PD: What do muscles have to do with lipoproteins? Circulation 81:1428-1430, 1990

93. Thompson PD, Cullinane EM, Sady EP, et al: Modest changes in high-density lipoprotein concentration and metabolism with prolonged exercise training. Circulation 78:24-34, 1998

94. Tikkanen HO, Naveri H, Harkonen M: Skeletal muscle fiber distribution influences serum high-density lipoprotein cholesterol level. Atherosclerosis 120:1-5, 1996

95. Ong JM, Simsolo RB, Saghizadeh M, et al: Effects of exercise training and feeding on lipoprotein lipase gene expression in adipose tissue, heart and skeletal muscle of the rat. Metabolism 44:1596-1605, 1995

96. Patsch JR, Prasad D, Gotto AM, et al: Postprandial lipemia: A key for the conversion of high density lipoprotein 2 into high density lipoprotein 3 by hepatic lipase. J Clin Invest 74:2017-2023, 1984

97. Rico-Sanz J, Moosavi M, Thomas EL, et al: In vivo evaluation of the effects of continuous exercise on skeletal muscle triglycerides in trained humans. Lipids 35:1313-1318, 2000

98. Herbert PN, Bernier DN, Cullinane EM, et al: High-density lipoprotein metabolism in runners and sedentary men. JAMA 252: 1034-1037, 1984