Therapeutic Approaches to the Regulation of Metabolism of High-Density Lipoprotein

– Novel HDL-Directed Pharmacological Intervention and Exercise –

Bo Zhang, PhD; Emi Kawachi, PhD; Shin-ichiro Miura, MD, PhD;
Yoshinari Uehara, MD, PhD; Akira Matsunaga, MD, PhD;
Masahide Kuroki, MD, PhD; Keijiro Saku, MD, PhD

High-density lipoprotein (HDL) and low-density lipoprotein (LDL) particles transport cholesterol in plasma and play an important role in cellular cholesterol homeostasis, which influences cell function. The risk of coronary artery disease (CAD) associated with high levels of LDL-cholesterol (LDL-C) can be reduced by treatment with statins, which reduce LDL-C levels by inhibiting cellular cholesterol synthesis. However, patients who are treated with high doses of statins, especially secondary CAD prevention, regardless of their resulting LDL-C levels, are still at high risk of CAD. Therefore, there has been growing interest in HDL-directed therapies. Inhibitors of cholesteryl ester transfer protein (CETP) substantially increase HDL-C levels (by 31–138%). However, it is still unclear whether or not CETP inhibitors can reduce the risk of CAD associated with low HDL-C levels, while reconstituted HDL or apolipoprotein A-I mimetic peptides increase the functionality of HDL. Low levels of HDL-C are often complicated with metabolic disorders, including hypertriglyceridemia, metabolic syndrome, and type 2 diabetes mellitus, and lifestyle changes are effective for correcting these conditions. Physical activity and exercise training increase HDL-C levels, especially HDL₂-C levels, by multiple mechanisms. Therefore, although using HDL-directed therapies that increase HDL-C levels and/or improve the function of HDL is a reasonable approach for reducing the residual risk of CAD as a complement to LDL-C-lowering therapy, lifestyle modifications including exercise to improve metabolic disorders should be considered as the first option. (*Circ J* 2013; **77**: 2651–2663)

Key Words: Cholesteryl ester transfer protein; Coronary artery disease; Exercise training; High-density lipoprotein; Lifestyle change

Coronary artery disease (CAD) is a leading cause of death worldwide. Atherosclerosis results in angina and myocardial infarction (MI). Dyslipidemia is one of the many risk factors for CAD. High-density lipoprotein (HDL) and low-density lipoprotein (LDL) transport cholesterol in plasma and have direct effects on cellular cholesterol homeostasis, and an imbalance between HDL and LDL (ie, low HDL cholesterol [HDL-C] and high LDL-C levels) is associated with an increased risk of CAD.

A high plasma level of LDL-C is a major risk factor for CAD. Therapy with statins [inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase], which inhibit cholesterol biosynthesis, effectively reduces the levels of both LDL-C and modified forms of LDL in human plasma,^{1–4} and significantly reduces the risk of CAD,^{5,6} as evidenced by primary and secondary clinical intervention studies.^{7,8}

A low level of HDL-C is a risk factor for CAD, independent of LDL-C.^{7–9} Thus, the HDL-C level inversely correlates with the risk of CAD regardless of whether the LDL-C level is low or high. The causes of low HDL-C levels are multiple and complex. The HDL-C level is under strong genetic control, and multiple genes that influence the HDL-C level have been identified.^{10,11} However, single nucleotide polymorphisms (SNP) in the multiple genes that raise or lower HDL-C levels do not seem to predict the risk of MI,^{12,13} which suggests that low HDL-C levels per se do not cause CAD and that the influence of environmental factors (eg, lifestyle) on HDL-C levels should be emphasized. In fact, a low HDL-C level is often complicated with metabolic disorders, including hypertriglyceridemia (HTG), metabolic syndrome (MetS), and type 2 diabetes mellitus (T2DM).¹⁴ Also, physical activity has been shown to modify the effects of LPL gene polymorphism, which is asso-

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Department of Biochemistry (B.Z., M.K.), The AIG Collaborative Research Institute of Cardiovascular Medicine (B.Z., S.M., Y.U., A.M., K.S.), Department of Cardiology (E.K., S.M., Y.U., K.S.), Department of Molecular Cardiovascular Therapeutics (S.M., Y.U., K.S.), and Department of Laboratory Medicine (A.M.), Fukuoka University School of Medicine, Fukuoka, Japan

Mailing address: Bo Zhang, MS, PhD, Department of Biochemistry, Fukuoka University School of Medicine, 7-45-1, Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. E-mail: bozhang@fukuoka-u.ac.jp or Keijiro Saku, MD, PhD, FACP, FACC, Department of Cardiology, Fukuoka University School of Medicine, 7-45-1, Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. E-mail: saku-k@fukuoka-u.ac.jp

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Figure 1. Therapeutic approaches to the regulation of high-density lipoprotein (HDL) metabolism include pharmacological interventions and lifestyle modifications. Statins, fibrates, and nicotinic acid (niacin) are available in daily clinical practice and moderately increase the HDL cholesterol (HDL-C) level. The novel HDL-directed therapies include those that increase HDL quantity and HDL function. Cholesteryl ester transfer protein (CETP) inhibitors, torcetrapib, dalcetrapib, anacetrapib, and evacetrapib, have entered large-scale clinical trials and substantially increase the HDL-C level (31–138%), but 2 of the trials have been terminated in failure or because of insufficient outcomes. Reconstituted HDL and apoA-I mimetic peptides are also novel HDL-directed therapies that improve the function of HDL. Among lifestyle modifications, exercise, the moderate consumption of alcohol, dietary fat intake, and smoking cessation all increase the HDL-C level. However, alcohol consumption also increases the triglycerides (TG) level and dietary fat intake increases the low-density lipoprotein cholesterol (LDL-C) level. Regular exercise decreases TG levels and reduces both the risk factors associated with coronary artery disease (CAD), including obesity, hypertension (HT), type2 diabetes mellitus (DM), and metabolic syndrome (MetS), and the risk of CAD.

ciated with HDL-C levels, on the risk of MI in women of European ancestry.¹⁵

In addition to their LDL-C-lowering effects, statins raise HDL-C levels by 5–20%.¹⁶ However, patients who are treated with high doses of statins, regardless of their treated LDL-C level, are still at considerable risk for cardiovascular disease.^{17,18}

Therefore, HDL-directed therapies¹⁹ have gained attention with regard to their potential to reduce the residual risk of CAD. Inhibitors of cholesteryl ester (CE) transfer protein (CETP) substantially increase HDL-C levels (by 31–138%) (Figure 1),^{20,21} but it is not yet clear whether CETP inhibitors reduce the risk of CAD.

Because CAD has multiple risk factors, an overall reduction of CAD risk factors in addition to elevated HDL-C levels is necessary for the prevention of CAD.^{22,23} Lifestyle changes are effective for primary and secondary cardiovascular disease prevention. Physical activity and exercise training increase HDL-C levels²⁴ and have many atheroprotective effects (Figure 1).²⁵

This review provides a brief summary of the role of HDL in plasma cholesterol transport, HDL heterogeneity and function. Therapeutic approaches to the regulation of HDL me-

tabolism are categorized as pharmacological interventions and lifestyle modifications (Figure 1), and the relation between the HDL-C-raising effects of CETP inhibitors and CAD risk, new approaches to increasing HDL functionality, the HDL-C-raising effects of lifestyle modifications, especially exercise training, and the mechanisms by which exercise raises HDL-C levels are discussed.

Role of HDL in Cholesterol Homeostasis

Role of HDL in Reverse Cholesterol Transport (RCT)

Cholesterol is transported in plasma by lipoproteins. Free cholesterol (FC) is contained in the outer phospholipid (PL) monolayer of lipoproteins, together with apolipoproteins and other proteins, and CE is contained in the core of lipoproteins together with triglycerides (TG).

The liver is the major site of cholesterol synthesis. Dietary cholesterol, which is absorbed by the small intestine, is transported to the liver by chylomicrons (CM). These 2 sources of cholesterol are packaged in the liver into very low-density lipoprotein (VLDL), which is secreted into plasma. Plasma VLDL is catabolized into intermediate-density lipoprotein

(IDL) and then into LDL after the hydrolysis of TG by the action of lipoprotein lipase (LPL) and hepatic lipase (HL), respectively. LDL-containing cholesterol is used by peripheral cells through the endocytosis of LDL particles by LDL-R (Figure 2).²⁶

HDL particles are major acceptors of FC that has been effluxed from cells. FC (ie, non-esterified cholesterol) is pumped from cells to HDL through 2 transmembrane proteins: adenosine triphosphate (ATP)-binding cassette (ABC) transporters A1 and G1 (ABCA1 and ABCG1).²⁷ ABCG4, a transporter of unknown function, has very recently been shown to be highly expressed in bone marrow megakaryocyte progenitors and promote the efflux of cellular cholesterol to HDL in these cells.²⁸ ABCA1 and ABCG1 are transcriptionally regulated by liver X receptor (LXR) upon heterodimerization with retinoid X receptor (RXR).²⁹ LXR functions as a nuclear cholesterol sensor that is activated in response to elevated intracellular cholesterol.³⁰ Apolipoprotein (apo) A-I, the major protein of HDL, is synthesized by the liver and intestine, and secreted into plasma as lipid-poor apoA-I or discoidal nascent HDL. Lipid-poor apoA-I efficiently removes cholesterol from cells by interacting with

ABCA1, followed by esterification of cholesterol by the enzyme lecithin:cholesterol acyltransferase (LCAT).²⁷ The more lipidated HDL then accepts cholesterol that is transported to the cell surface by ABCG1 (Figure 2).²⁷

Nascent HDL removes cellular cholesterol and matures into spherical HDL by the action of LCAT. CE in mature HDL is transferred to plasma apo-B containing lipoproteins (eg, VLDL and IDL) by the action of CETP in exchange for TG (Figure 3), or removed from plasma by the liver via the selective uptake of HDL-CE by scavenger receptor class B type I (SR-BI) or HDL holoparticle uptake by receptors for HDL holoparticles (Figure 2).¹¹ Thus, HDL transports cholesterol from peripheral cells to the liver for excretion (known as reverse cholesterol transport, RCT).³¹

HDL Heterogeneity, Remodeling, and Function

HDL consists of heterogeneous particles that differ in shape, electric charge, and composition of lipids and proteins.^{32,33} HDL is separated into spherical alpha-migrating HDL and pre-beta-migrating HDL (pre-β HDL) on agarose gel according to electrophoretic mobility.³⁴ Ultracentrifugation separates HDL

into large HDL₂ (1.063–1.125 g/ml) and small HDL₃ (1.125–1.21 g/ml) subfractions on the basis of density.³³ Pre- β HDL, HDL₃, and HDL₂ are functionally distinct particles. Discoidal nascent HDL (lipid-poor apoA-I) and pre- β HDL are the most efficient acceptors of FC effluxed from cells via ABCA1¹¹ or TG-rich lipoproteins (TRL).^{35,36} Small HDL₃ particles are better acceptors of FC effluxed from cells via ABCG1 than large HDL₂ particles.¹¹

HDL particles are continuously remodeled by plasma factors.³² LCAT converts discoidal HDL into spherical HDL and increases the size of HDL by converting HDL₃ into HDL₂. HDL₂ is converted back into HDL₃ with the shedding of lipid-poor apoA-I from HDL by the action of CETP and HL (Figure 2). Lipid-poor apoA-I can be glomerularly filtered and catabolized by the kidney.^{37,38} Phospholipid transfer protein (PLTP) transfers PLs between HDL and TRL, as well as between different HDL particles. PLTP remodels HDL into large and small particles and lipid-poor apoA-I.^{34,39} Endothelial lipase (EL), which has phospholipase activity and hydrolyzes HDL PL,⁴⁰ converts large HDL into small HDL.^{41,42} Cellular factors also remodel HDL. ABCA1 and ABCG1 are crucial for the formation of HDL, and the hepatic HDL receptor, SR-BI, which selectively uptakes HDL-CE, converts large HDL

into small HDL.^{43,44} CETP (exogenous and cell-associated) also mediates the selective acquisition of CE from HDL by the liver, resulting in CE depletion of HDL.^{45,46}

The protective effects of HDL against atherosclerosis are mainly related to its role in RCT, which unloads cholesterol from lipid-laden macrophages in atheroma.²⁷ Transcytosis of lipid-poor apoA-I and HDL from plasma through aortic endothelial cells has been shown to be modulated by cell-surface ABCA1, ABCG1, SR-BI, and FoF₁ ATPase.^{47–49} HDL also has many other atheroprotective properties: antioxidant, antiinflammatory, endothelium-protective, fibrinolytic, antithrombotic, antiapoptotic, immunosuppressive, and antidiabetic.^{16,50–55}

However, HDL can be altered to become functionally deficient (impaired function) or dysfunctional (complete loss of function) in patients with, or who are high risk of, CAD and under conditions of infection and inflammation (Figure 4).¹¹ The cholesterol efflux ability of apoB-depleted serum has been shown to be inversely associated with carotid atherosclerosis and the risk of CAD independent of the HDL-C level.⁵⁶ The ability of HDL (apoB-depleted serum) to prevent the oxidation of LDL, as measured by an HDL inflammatory index, was reduced in patients with acute coronary syndrome (ACS).⁵⁷ HDL from patients on chronic hemodialysis had reduced antichemotactic ability and an increased macrophage cytokine response.⁵⁸ HDL separated from patients with CAD and high HDL-C promoted, but did not inhibit, monocyte chemotaxis.⁵⁹ HDL during an acute-phase response in patients after cardiac surgery became pro-inflammatory, and increased LDL oxidation and the secretion of monocyte chemoattractant protein 1 (MCP-1) by cells in the artery wall.⁶⁰

Therefore, the plasma HDL-C level may not reflect the function of HDL, depending on the metabolic background. Changes in the composition of HDL (surface proteins, core neutral lipids, and surface amphiphilic lipids) in metabolic conditions associated with accelerated atherosclerosis and elevated cardiovascular risk can impair its biologic activities (Figure 4).¹¹ Recent proteomic analyses have identified more than 40 proteins in human HDL,^{61,62} which can be divided into several major subgroups: apolipoproteins (eg, apoA-I and apoA-II), enzymes [eg, LCAT and paraoxonase (PON1)], lipid transfer proteins (eg, CETP and PLTP), and minor proteins.¹¹ These latter HDL proteins include acute-response proteins [eg, serum amyloid A (SAA)], complement components (eg, C3), and proteinase inhibitors (eg, alpha-2-antiplasmin).¹¹ Lipidomic analyses have identified more than 100 individual molecular species of lipids.^{63,64} HDL lipids include PLs (eg, phosphatidylcholine and sphingomyelin), steroids (eg, cholesterol and oxysterols), CE, TG, and minor lipids [eg, diacylglycerides, monoacylglyceride, free fatty acids, and lysosphingolipids].¹¹ Posttranslational oxidative modification of apoA-I, particularly through a myeloperoxidase (MPO) pathway,^{65,66} can also lead to HDL dysfunction (Figure 4),^{67,68} which dramatically reduces the ability of apoA-I to promote cholesterol efflux through the ABCA1 pathway.⁶⁹

Pharmacological Interventions That Regulate HDL Metabolism

Because a low level of HDL-C is a major risk factor in patients who are treated aggressively for LDL-C,⁹ raising the HDL-C level is considered to be a promising approach to reducing the residual risk of cardiovascular disease as a complement to LDL-C-lowering therapy.⁷⁰ However, because of the complexity of HDL metabolism, it is not easy to raise the HDL-C level.

Pharmacologic Therapies That Raise the HDL-C Level

Currently available lipid-modulating drugs have modest effects on the HDL-C level (Figure 1).

Statins Statins raise the HDL-C level by 5–20%.¹⁶ Among the various statins, pitavastatin has the strongest HDL-C-raising effect (see review by Yamashita et al¹⁶). Statins increase the HDL-C level by increasing the production of HDL in the liver because of increased hepatic expressions of apoA-I and ABCA1.¹⁶

Fibrates Fibrates, agonists of peroxisome proliferator-activated receptor α (PPAR α),⁷¹ raise the level of HDL-C by 2–20% depending on the TG level.⁷² Fibrates increase the HDL-C level by increasing the hepatic synthesis of the major HDL apoproteins,⁷³ apoA-I and apoA-II, by activating PPAR α .⁷⁴

Nicotinic Acid (Niacin) Nicotinic acid (niacin) raises the HDL-C level by 20–30%,⁷⁵ which makes it the most effective HDL-C-raising drug currently available, but its use is limited because of its adverse effect of skin flushing.⁷⁶ In addition, a

recent meta-regression analysis did not support the claim that niacin-raised HDL-C levels are beneficial.⁷⁷ Niacin increases the HDL-C level by decreasing the catabolism of HDL-apoA-I without altering the production of apoA-I in the liver.⁷⁸

Novel HDL-Directed Drugs That Raise HDL-C Levels: Do CETP Inhibitors Reduce the Risk of CAD?

A deficiency of CETP, which results in markedly reduced rates of turnover of apoA-I,⁷⁹ is a monogenic cause of inherited high HDL (4–6-fold greater than normal) in humans.^{36,80} Therefore, CETP inhibition is the target of a pharmacological approach to raising HDL-C to decrease the risk of cardiovascular disease. Small-molecule CETP inhibitors that have entered clinical development, including torcetrapib,^{81–84} dalcetrapib,^{21,85,86} anacetrapib,^{20,87} and evacetrapib,^{88,89} significantly increase the HDL-C level in humans. They also decrease LDL-C levels, except dalcetrapib, which has minimal effect on the LDL-C level.⁸⁶

Torcetrapib Torcetrapib has not shown any protective

Figure 5. FAMP, a novel apoA-I mimetic peptide that is small with 24 amino acids, has been shown to enhance the function of high-density lipoprotein (HDL).¹⁰¹ FAMP may induce cellular cholesterol efflux by 2 mechanisms: (1) internalization and transcytosis in macrophages or aortic endothelial cells, and the removal of intracellular cholesterol (Upper middle panel), and (2) physical interactions between FAMP and ABCA1 to transport intracellular cholesterol to the circulation (Lower middle panel), and this latter mechanism may be predominant.

effects against coronary atherosclerosis in atorvastatin-treated patients with CAD, as demonstrated in the ILLUSTRATE trial,⁸¹ or against carotid atherosclerosis in atorvastatin-treated patients with familial hypercholesterolemia (FH) and mixed dyslipidemia, as demonstrated in the RADIANCE 1 and 2 studies.^{82,83} Unexpectedly, torcetrapib therapy resulted in an increased risk of mortality and morbidity in patients who were at high risk of coronary events, which led to early termination of the ILLUMINATE trial.⁸⁴ The adverse effects of torcetrapib were attributed to off-target effects of the drug, including an increase in blood pressure that resulted from the increased production of aldosterone^{84,90} and impairment of endothelial function.^{91,92}

Dalcetrapib Dalcetrapib is a CETP modulator that inhibits the heterotypic transfer of neutral lipids (CE and TG) between HDL and apoB-containing lipoproteins (eg, VLDL and LDL; Figure 3), but preserves the homotypic transfer of CE among HDL particles (eg, from HDL₃ to HDL₂).^{93,94} The safety of dalcetrapib was examined in patients with, or who were at high risk of, CAD in the dal-VESSEL and dal-PLAQUE trials.^{85,86} Dalcetrapib showed no adverse effects on endothelial function as assessed by brachial flow-mediated dilation,⁸⁶ blood pressure,^{85,86} vessel structure as assessed by carotid MRI,⁸⁵ and plaque size and arterial inflammation as assessed by PET/CT using ¹⁸F-fluorodeoxyglucose as a tracer.⁸⁵ The

dal-OUTCOMES trial tested the hypothesis that dalcetrapib reduces cardiovascular morbidity and mortality in patients with recent ACS.⁹⁵ However, dalcetrapib did not reduce the risk of recurrent cardiovascular events,²¹ which resulted in termination of the dal-OUTCOMES trial because of futility, as well as all the studies in the dal-HEART program, which originally involved 6 clinical trials: dal-OUTCOMES (terminated), dal-OUTCOMES 2, dal-PLAQUE, dal-ACUTE, dal-PLAQUE (completed), and dal-VESSEL (completed).

Anacetrapib The safety of anacetrapib was also examined in patients with, or who were at high risk of, CAD in the DEFINE trial.²⁰ Anacetrapib did not result in the adverse cardiovascular effects observed with torcetrapib.²⁰ Although dalcetrapib moderately increased the HDL-C (31–40%) and had minimal effects on the LDL-C levels,²¹ anacetrapib increased HDL-C by 138% and also decreased LDL-C by 40% compared with placebo.²⁰ The REVEAL trial, which aimed to determine whether anacetrapib reduces the risk of major coronary events in patients with circulatory problems (history of MI, cerebrovascular atherosclerotic disease, peripheral arterial disease, or T2DM with other evidence of symptomatic CAD) and who are treated with atorvastatin to lower their LDL-C levels, is ongoing and will be completed in 2017.⁹⁶

Evacetrapib Evacetrapib is another novel CETP inhibitor that is being tested in a clinical outcome trial (ACCELERATE⁷⁶).

Similar to anacetrapib, it has effects on both the HDL-C and LDL-C level; it increased the HDL-C level by 54–129% and reduced the LDL-C level by 36% in patients with dyslipidemia (high LDL-C or low HDL-C level),⁸⁹ and does not increase blood pressure or induce aldosterone.⁸⁸ The ACCELERATE trial aimed to test the effects of evacetrapib on cardiovascular outcomes (time to first occurrence of the composite endpoint of cardiovascular death, MI, stroke, coronary revascularization, or hospitalization for unstable angina) in patients who were at high risk for vascular disease.⁹⁷

It is still uncertain whether raising the HDL level by pharmacological therapy with CETP inhibitors can reduce the risk of CAD, suggesting that raising the HDL-C level alone may not be enough to prevent CAD.

Novel HDL-Directed Therapies That Improve the Function of HDL

ETC-216 Nissen et al reported that 5-weekly intravenous infusions of a recombinant apoA-_{Milano}/PL complex (ETC-216) caused significant regression of coronary atherosclerosis as measured by intravascular ultrasound (IVUS) in patients with ACS.⁹⁸ A single infusion of reconstituted HDL in patients with heterozygous FH promoted RCT as indicated by an increase in fecal sterol secretion.⁹⁹

CSL112 A new formulation of full-length, plasma-derived human apoA-I (apoA-I/phosphatidylcholine complex) caused a strong and immediate increase in the ABCA1-dependent efflux capacity of plasma after infusion into rabbits.¹⁰⁰

FAMP Recently, a peptide that mimics human apoA-I without complexing with PL, FAMP (Fukuoka University ApoA-I Mimetic Peptide), has been shown to enhance the function of HDL, and suppress aortic plaque formation in apoE-knockout mice fed a high-fat diet.¹⁰¹ FAMP markedly increases pre- β HDL, and also increases overall cholesterol efflux from peripheral tissues. FAMP may enhance cellular cholesterol efflux by 2 mechanisms (**Figure 5**): (1) internalization and transcytosis in macrophages or aortic endothelial cells, and the removal of intracellular cholesterol, and (2) physical interactions between FAMP and ABCA1 to transport intracellular cholesterol to the circulation, and this latter mechanism may be predominant. Another apoA-I mimetic peptide, 4F, removes plasma oxidized lipids (PLs and fatty acids) and improves the antiinflammatory properties of HDL.¹⁰²

Lifestyle Modifications That Raise the HDL-C Level

Low HDL-C levels are commonly associated with metabolic disorders and risk factors for CAD including HTG, insulin resistance, MetS, T2DM, and physical inactivity. Lifestyle changes are effective for primary and secondary cardiovascular disease prevention and are recommended in guidelines for clinical practice.^{22,23} Lifestyle modifications, including exercise, smoking cessation, weight loss, moderate alcohol consumption and dietary fat intake, may increase the HDL-C level (**Figure 1**), typically by 5–10%.^{11,103} However, alcohol consumption increases the TG level,¹⁰⁴ and dietary fats also increase the LDL-C level.^{105,106} Physical activity and regular exercise decrease the TG level and reduce many of the risk factors of CAD, including obesity, hypertension (HT), and T2DM, as well as the risk of CAD (**Figure 1**).²⁵ Regular physical activity and aerobic exercise training are related to a reduced risk of fatal and non-fatal coronary events in healthy individuals, subjects with coronary risk factors, and cardiac patients over a wide age range,²² and therefore this review focuses on the effects of exercise on HDL metabolism.

Figure 6. High-density lipoprotein (HDL) metabolism and the mechanism by which exercise affects the catabolism of HDL particles. (1) Exercise induces lipoprotein lipase (LPL) on the surface of endothelial cells of skeletal muscle, adipose tissue, and the liver. Increased activity of LPL increases the hydrolysis of triglycerides (TG) in TG-rich lipoproteins (TRL: ie, chylomicrons [CM] and very-low-density lipoprotein [VLDL]) into free fatty acids (FA) and glycerol, leading to the release of the surface components of TRL particles, which are mainly free cholesterol (FC) and phospholipids (PL). HDL₃ particles accept the surface components released from TRL particles, and FC is converted into cholesteryl esters (CE) by the action of lecithin:cholesterol acyltransferase (LCAT). CE is packaged into the core of HDL particles, leading to the conversion of small HDL₃ to large HDL₂ particles and increased plasma HDL-C levels. (2) Exercise-induced reduction of TG levels reduces the exchange of CE and TG between HDL and apoB-containing particles (eg, VLDL and IDL), that is catalyzed by the CE transfer protein (CETP), and the subsequent hydrolysis of HDL-TG by hepatic lipase (HL). These processes lead to the reduced transfer of CE from HDL to apoB-containing particles and the reduced conversion of HDL₂ to HDL₃ particles, which also leads to increased HDL-C levels.

HDL-C-Raising and Atheroprotective Effects of Exercise

Exercise training has consistently been shown to increase HDL-C levels, especially HDL₂-C levels, in normal, overweight, and hypercholesterolemic subjects, patients with T2DM, and patients with CAD.^{107–118}

Exercise training increases the HDL-C level by 2.53 mg/dl,¹¹⁰ which should be associated with a decrease in cardiovascular risk of approximately 7%, according to epidemiological data on the relationship between HDL-C and the risk of CAD.¹¹⁰ However, physical activity is associated with a much greater reduction in the risk for developing CAD (30–35%).²⁵ In fact, short-term exercise training has been shown to increase HDL function (antioxidant capacity) without significant changes in the HDL-C levels in patients with MetS.¹¹⁹ In addition to its HDL-C-raising effect, exercise training has also been shown to have many other atheroprotective effects, including the preservation of endothelial function, and antioxidative and anti-inflammatory effects.^{120–122} The mechanism of the antiinflammatory effects of exercise involves reduction of visceral fat mass, increased production and release of inflammatory cytokines from contracting muscle (**Figure 4**), and reduced expression of Toll-like receptors on monocytes and macrophages.¹²² Skeletal muscle has recently been identified as an endocrine organ that produces, expresses, and releases cytokines and other peptides, which are called myokines.^{123–125} Myokines appear to be in-

Figure 7. Mechanism by which exercise increases the production of high-density lipoprotein (HDL) particles. Exercise increases AMP-activated protein kinase (AMPK), SIRT1 (a mammalian sirtuin), and peroxisome proliferator-activated receptor (PPAR) γ coactivator 1 α (PCG-1 α) in skeletal muscle, adipose tissue, and the liver. AMPK activates SIRT1, and SIRT1 in turn activates AMPK. Both AMPK and SIRT1 activate PCG-1 α , leading to the coactivation of nuclear receptors including PPARs. Activation of PPAR α in the liver leading to the increased synthesis of apolipoprotein (apo) A-I. SIRT1 also activates liver X receptor (LXR) independent of PCG-1 α , leading to the increased expression of ABCA1 transporter, a target gene of LXR that is responsible for cholesterol efflux from cells to apoA-I/lipid-poor apoA-I. Therefore, both the activation of PPAR α and increased expression of ABCA1 (indicated by the numbers 1 and 2) result in the increased production of lipid-poor apoA-I, which, by acquiring free cholesterol (FC) and phospholipids (PL) from peripheral cells or from hydrolysis of triglyceride-rich lipoproteins, is rapidly converted to mature HDL particles by the action of LCAT. Skeletal muscles release a large quantity of interleukin-6 (IL-6), a myokine (cytokines secreted from muscle), into the blood during contraction. Exercise also increases the plasma concentration of adiponectin, an adipokine (cytokines secreted from adipocytes). IL-6 and adiponectin activate PPAR α by binding to their respective receptors, IL-6 receptor (IL-6R) and adiponectin receptor (AdipoR). Therefore, the systemic effects of IL-6 and adiponectin on the liver may also contribute to exercise-induced HDL neogenesis.

involved in the mediation of exercise-induced antiinflammatory, immunoregulatory, and metabolic effects.^{123–126}

Mechanisms of the HDL-Raising Effects of Exercise

The mechanisms by which exercise increases HDL-C levels involve exercise-induced changes in multiple tissues (adipose tissue, skeletal muscle, the liver, etc.) (Figures 6,7).

Exercise-induced adaptations in human skeletal muscle tissue (higher LPL activity and VLDL-TG uptake) are largely responsible for the increased HDL-C and HDL₂-C levels.²⁴ Increased hydrolysis of TRL by increased LPL activity^{118,127} leads to the release of FC, PL, and apoC-II on the surface of

TRL. HDL₃ particles accept these surface components of TRL.³⁵ FC is subsequently esterified into CE by LCAT and packaged into the core of HDL particles.³⁵ By this process, HDL₃ is converted into larger HDL₂ particles,³⁵ leading to an increased HDL₂-C level (Figure 6). In fact, the effects of endurance exercise training on HDL-C and HDL₂-C levels has been shown to depend on the TG levels in healthy sedentary men.¹²⁸ Also, exercise caused changes in the distribution of HDL subfractions (increased HDL₂-C and decreased HDL₃-C) in hypercholesterolemic men,¹¹⁴ and increased the size of HDL particles in overweight men and women with dyslipidemia.¹¹⁵ However, evidence regarding the predictive value of the HDL₂-

C and HDL₃-C levels against CAD is conflicting in humans, and controversy also exists in regard to the relative importance of the HDL subfractions.^{129,130}

An inverse relationship is known to exist between the TG and HDL-C levels. The action of CETP produces TG-rich HDL₂ particles. HDL-TG is a substrate of HL and the hydrolysis of HDL₂-TG and -PL by HL causes the conversion of HDL₂ to HDL₃ particles.³⁵ Therefore, the exercise-induced reduction in the plasma TG level^{113,115,116,118,128} and decreased HL activity¹¹⁸ also partly contribute to the increased HDL-C and HDL₂-C levels (Figure 6).

Exercise training reduces the amount of abdominal visceral and subcutaneous fat in obese women with MetS,¹³¹ and these changes in body fat negatively correlate with those in HDL-C and HDL₂-C.¹³² Although the mechanism by which exercise-induced changes in adipose tissue increases the HDL-C level is not fully understood, adiponectin, an antiinflammatory cytokine¹³³ synthesized by adipocytes and present in high levels in the blood,¹³⁴ mediates the effects of exercise on HDL-C. Plasma adiponectin concentrations have been shown to correlate positively with HDL-C levels in men and women.¹³⁵ In overweight/obese subjects with T2DM, lifestyle intervention (increased physical activity and reduced caloric intake) increased the adiponectin concentration by 11.9% and the HDL-C level by 9.7%, and the changes in adiponectin concentration were independently associated with those in the HDL-C level.¹³⁶ Short-term exercise training has been shown to drastically increase adiponectin levels in overweight males.¹³⁷ Because adiponectin is an important determinant of apoA-I catabolism,¹³⁸ and adiponectin increases apoA-I synthesis and ABCA1 expression in the liver,^{16,139,140} the exercise-induced increase in adiponectin reduces the catabolism of HDL and increases the production of HDL leading to an increase in the HDL-C level.

Exercise training without weight loss (by controlling the diet and adjusting energy intake) has been shown to not only reduce the fractional catabolic rate of HDL but also to increase the synthetic rate of apoA-I in overweight men.¹¹⁸ Consistent with this finding, a recent study showed that exercise increased both the HDL-C level and the HDL particle number in overweight/obese men.¹²⁷ Exercise-induced protein content of AMP-activated protein kinase (AMPK) in skeletal muscle in these subjects was closely and positively correlated with the HDL-C and HDL₂-C levels and HDL particle number.¹²⁷ It is possible that exercise-induced changes in the liver contribute to the increased HDL-C level by increasing HDL neogenesis (Figure 7).

AMPK and nicotinamide adenine dinucleotide (NAD⁺)-dependent protein deacetylases, sirtuins, are fuel-sensing enzymes that are present in all eukaryotic cells.¹⁴¹ Silent information regulator T1 (SIRT1) is the most studied of the 7 sirtuins that have been identified in mammalian cells.¹⁴¹ PPAR γ co-activator 1 α (PGC-1 α), which is activated via phosphorylation by AMPK¹⁴² and deacetylation by SIRT1 (Figure 7),¹⁴³ co-activates multiple transcription factors, including nuclear receptor PPAR α ,¹⁴⁴ to regulate the many genes involved in glucose and fatty acid metabolism.¹⁴⁵ AMPK activates SIRT1 by increasing cellular NAD⁺ levels,^{141,146} and SIRT1 in turn activates AMPK by deacetylation of the AMPK kinase serine-threonine liver kinase (LB1).¹⁴¹

Exercise increases the PPAR α protein content in skeletal muscle in humans,¹²⁷ the AMPK activity in the liver, adipose tissue, and skeletal muscle in rats and mice,^{147–149} and the protein expression of SIRT1 and PGC-1 α in rat skeletal muscle.¹⁵⁰ AMPK, SIRT1, and PGC-1 α all positively regulate the transcriptional activity of PPAR α ,^{151,152} which is highly expressed in the liver, heart, and skeletal muscle.¹⁵³ Activation of PPAR α

increases the HDL-C level by increasing the production of apoA-I and apoA-II, and decreases the TG level by increasing the hepatic expression of LPL in humans.¹⁵³

Furthermore, SIRT1 deacetylates and activates the nuclear receptor, LXR, which promotes transcription of the target genes involved in lipid metabolism, including the ABCA1 transporter.¹⁵⁴ Deletion of SIRT1 reduced HDL-C production in mice and reduced ABCA1-mediated cholesterol efflux and HDL formation in cultured cells.¹⁵⁴ Therefore, exercise-induced activation of enzymes (AMPK and SIRT1) and nuclear receptors (PPAR α and LXR) in the liver contributes to the production of HDL (Figure 7).

It is possible that the systemic effects of adiponectin and IL-6 on the liver play a role in the exercise-induced increase in HDL neogenesis. Adiponectin has been shown to activate AMPK, SIRT1, and PCG-1 α in the skeletal muscle of mice via adiponectin receptor (AdipoR) 1.¹⁵⁵ Adiponectin also promotes HDL production via increased apoA-I synthesis and ABCA1 expression in the liver.^{16,139,140} IL-6 is a cytokine (myokine) that is synthesized and released in large quantities from contracting skeletal muscle, which results in plasma concentrations that are 50- to 100-fold higher than those seen at rest.¹⁵⁶ In rodents, IL-6 induced AMPK activity in muscle and adipose tissue.^{149,157}

Conclusions

HDL consists of heterogeneous particles that differ with respect to their lipid and protein composition, size, and electric charge. Although there has been a growing interest in HDL-directed therapies as well as statin therapy to resolve the residual risk factors for CAD, it is still unclear whether or not CETP inhibitors can reduce the risk of CAD. Low HDL-C levels are often complicated with metabolic disorders, and lifestyle changes, especially exercise, are effective for the prevention of cardiovascular disease. Therefore, although HDL-directed therapies that increase the HDL-C level and/or improve the function of HDL is a reasonable approach to reducing the residual risk of CAD as a complement to LDL-C-lowering therapy, lifestyle modifications including exercise to improve metabolic disorders should be considered as the first option.

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