



## Review Article

# High-density lipoprotein cholesterol (HDL-C) in cardiovascular disease: effect of exercise training

Nayoung Ahn, Kijin Kim\*

Department of Physical Education, College of Physical Education, Keimyung University, Daegu, Korea

## ARTICLE INFO

## Article history:

Received 29 June 2016

Received in revised form 2 July 2016

Accepted 4 July 2016

Available online 28 July 2016

## Keywords:

coronary artery disease

dysfunctional HDL

exercise training

high-density lipoprotein cholesterol (HDL-C)

## ABSTRACT

Decreases in high-density lipoprotein cholesterol (HDL-C) levels are associated with an increased risk of coronary artery disease (CAD), whereas increased HDL-C levels are related to a decreased risk of CAD and myocardial infarction. Although HDL prevents the oxidation of low-density lipoprotein under normal conditions, it triggers a structural change, inhibiting antiarteriosclerotic and anti-inflammatory functions, under pathological conditions such as oxidative stress, inflammation, and diabetes. HDL can transform into various structures based on the quantitative reduction and deformation of apolipoprotein A1 and is the primary cause of increased levels of dysfunctional HDL, which can lead to an increased risk of CAD. Therefore, analyzing the structure and components of HDL rather than HDL-C after the application of an exercise training program may be useful for understanding the effects of HDL.

© 2016 Korea Institute of Oriental Medicine. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

When blood cholesterol increases by 1%, the frequency of ischemic heart disease or coronary heart disease (CHD) increases by 2%.<sup>1</sup> High-density lipoprotein (HDL), which is small in size and rich in proteins, is one of the lipoproteins which bind to high-density cholesterol, known as a mediator for preventing the risk of CHD. HDL is commonly regarded as an index of health status because it reduces blood clotting by stimulating the secretion of nitric oxide (NO) inside endothelial cells and prevents inflammation by inhibiting the expression of inflammatory factors of endothelial cells. Additionally, HDL prevents the oxidation of low-density lipoprotein

(LDL) to limit the interaction and adsorption of monocytes and endothelial cells, while releasing cholesterol from endothelial cells via the reverse transport of cholesterol. Moreover, LDL prevents the secretion of endothelin, which is a powerful vasoconstrictor.<sup>2</sup>

HDL was recently reported to exert antiatherogenic effects through numerous biological mechanisms and has anti-inflammatory, antiapoptotic, and antithrombotic effects in the endothelial cells of healthy individuals.<sup>3-7</sup> Although HDL prevents the oxidation of LDL under normal conditions, it causes structural alterations under pathological conditions such as oxidative stress, inflammation, and diabetes, which may reduce the antiarteriosclerotic and anti-inflammatory functions. Decreases in HDL-cholesterol (HDL-C) levels have

\* Corresponding author. Department of Physical Education, College of Physical Education, Keimyung University, 1095 Dalgubeuldaero, Dalseo-gu, Daegu 704-701, Korea.

E-mail address: [kjk744@kmu.ac.kr](mailto:kjk744@kmu.ac.kr) (K. Kim).

<http://dx.doi.org/10.1016/j.imr.2016.07.001>

2213-4220/© 2016 Korea Institute of Oriental Medicine. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

been shown to increase the risk of coronary artery disease (CAD),<sup>8,9</sup> whereas increased HDL-C reduces the risk of both CAD and myocardial infarction. However, in recent clinical studies of lipid-modifying drugs, the influence was shown to be minimal. Therefore, a new approach for examining the structure and components of HDL, rather than using an HDL-C-based approach, is required. Particularly, because HDL can transform into various forms via changes in its structure and components, its antiarteriosclerotic and anti-inflammatory effects can also decrease. Therefore, studies should focus on the structure and components of HDL rather than HDL-C for the prevention and treatment of cardiovascular diseases.

### 1.1. Function of HDL-C: reverse cholesterol transport

HDL-C plays an important role in the homeostasis of total cholesterol. This can be achieved through a mechanism known as reverse cholesterol transport (RCT), by which HDL-C can prevent the occurrence of arteriosclerosis.<sup>10</sup> RCT removes surplus cholesterol from macrophages on the artery walls and discharges it out of the body after transport to the liver, thereby suppressing atherosclerotic carotid stenosis.<sup>11</sup> As RCT is the only mechanism removing surplus cholesterol inside the body, the maintenance of an appropriate HDL-C-concentration as well as its function are essential for preventing cardiovascular diseases.

The basic unit of HDL particles is apolipoprotein A1 (ApoA-1), which is a lipoprotein containing nearly no lipid. ApoA-1 is synthesized in the liver and gastrointestinal tract and secreted into the plasma. Through the action of ATP-binding cassette transporter A1, which is a membrane protein present in peripheral tissue, intracellular cholesterol is transported to ApoA-1 to form HDL.<sup>12</sup> Free cholesterol on the surface of HDL is then esterified by lecithin cholesterol acyltransferase (LCAT),<sup>13</sup> and the cholesterol ester moves towards the heart to form HDL<sub>3</sub>, which eventually forms small spheres. HDL<sub>3</sub> then binds to large amounts of cholesterol via the action of LCAT and various other serum factors, which combine to form larger HDL<sub>2</sub>. HDL<sub>2</sub>, which binds cholesterol ester (CE), reacts with ApoB lipoproteins (very low-density lipoprotein, intermediate-density lipoprotein, LDL, chylomicrons, etc.) and transfers cholesterol ester via the action of cholesteryl ester transfer protein, obtaining neutral lipids in exchange. HDL<sub>2</sub>, which contains large amounts of neutral lipids, is then reconverted into HDL<sub>3</sub> after the removal of cholesterol through the action of scavenger receptor class B type I or is disintegrated by hepatic lipase.<sup>14</sup>

### 1.2. Dysfunctional HDL-C and cardiovascular disease

HDL prevents the oxidization of LDL under normal conditions. However, in some pathological conditions including oxidative stress, inflammation, and diabetes, HDL undergoes a structural change and loses its antiarteriosclerotic and anti-inflammatory functions, eventually becoming dysfunctional HDL.<sup>15</sup> In various diseases, the levels of dysfunctional HDL excessively increases. HDL can be classified into various subtypes depending on the lipids and proteins binding to the HDL, whereas ApoA-1 is the most important protein component of HDL. ApoA-1 performs its function with HDL by interacting

with various proteins. Thus, the decrease and deformation of ApoA-1 are major causes for HDL dysfunction. Deformation of ApoA-1 decreases the binding strength to lipids, which decreases HDL stability. The HDL level in a CAD patient and saccharification of ApoA-1 was examined to determine their association with diabetes.<sup>16</sup> The saccharification of ApoA-1 was confirmed based on the formation of multimers.<sup>17</sup>

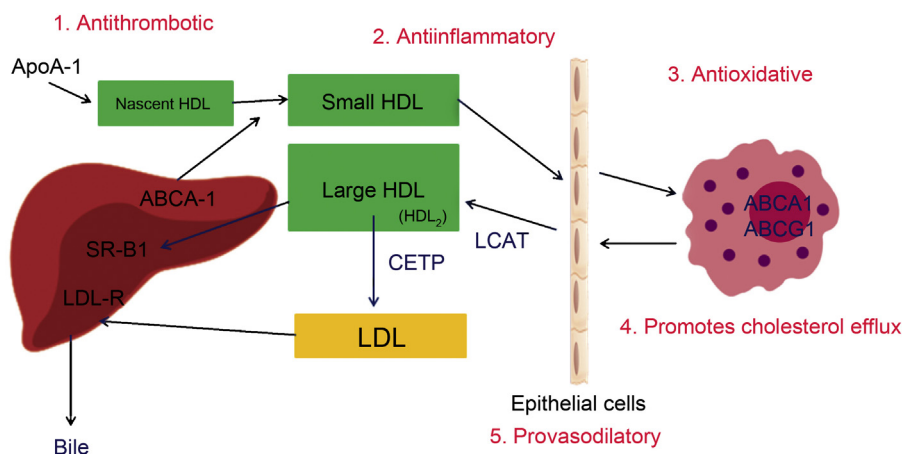
When HDL levels are decreased or when HDL function is altered, many changes indicating damage to the kidney are observed in the blood vessels. As the kidney function decreases, the HDL function or level decreases. Therefore, among patients with chronic kidney diseases, those with highly disrupted HDL distributions are prone to developing cardiac diseases. However, although RCT still occurs on the surfaces of tissues cells, additional studies are needed to determine the influence of increased HDL cholesterol level and HDL function on CAD (Figs. 1 and 2).

The quantitative decrease and saccharification of ApoA-1 are related to aging. Comparison of HDL between elderly and young participants showed that the composition of protein and lipid is significantly altered, particularly in terms of protein contents directly related to acute syndromes such as serum amyloid A (SAA). Therefore, dysfunctional HDL may increase along with various aging-related phenomena. Recent studies showed that chronic inflammation alters HDL structure. This dysfunctional HDL in turn increases SAA and decreases ApoA-1 concentration. By separating the subtype HDL<sub>3</sub>, which is small in size and high in density, ApoA-1 and SAA can be quantitatively analyzed to determine the fluctuations in dysfunctional HDL.<sup>18,19</sup> SAA and decreased anti-inflammatory function of HDL was found in the HDL of a chronic kidney disease patient. The HDL extracted from patients with acute coronary syndrome, psoriasis, and rheumatoid arthritis showed increased SAA.

### 1.3. Dysfunctional HDL-C and obesity

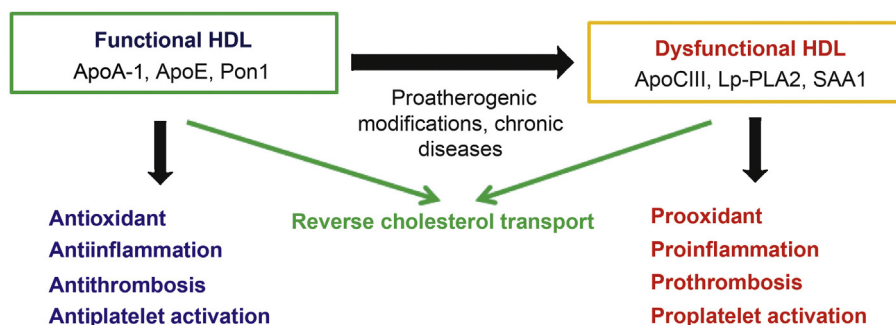
Obesity, along with decreased concentrations of HDL-C, also causes HDL-C dysfunction. Recent studies have demonstrated that HDL-C may accelerate atherosclerotic carotid stenosis, which differs from the results of previous studies.<sup>20</sup> Additionally, unlike HDL-C, which performs a normal function, the HDL-C extracted from the blood plasma of a patient with acute inflammation did not suppress monocyte chemotaxis.<sup>21</sup> Some reports have shown that the antioxidation effect of HDL-C does not properly occur in obese patients. For instance, Sorrentino et al<sup>22</sup> found that HDL-C separated from the blood plasma of type 2 diabetes patients showed significantly low endothelial protective activity.

In addition, decreased cellular cholesterol efflux capacity was predicted as another major factor inducing cardiovascular diseases in obese patients. The cellular cholesterol efflux capacity was significantly low in adults with CAD compared with healthy adults.<sup>23</sup> The mechanism of obesity involving HDL-C showed highly increased free fatty acid and very LDL. This in turn induces excessive activation of RCT, further accelerating HDL-C catabolism.<sup>24</sup> Moreover, in obese patients, activation of the cholesterol ester transfer protein LCAT, liver lipid proteinase, and protein phospholipid transfer protein is also altered.<sup>25</sup> A previous study suggested that



**Fig. 1 – Role of HDL-C and reverse cholesterol transport.**

**ABCA-1**, ATP-binding cassette transporter A-1; **ABCG1**, ATP-binding cassette subfamily G member 1; **ApoA-1**, apolipoprotein A-1; **CETP**, cholesteryl ester transfer protein; **HDL**, high density lipoprotein; **LCAT**, lecithin cholesterol acyltransferase; **LDL-R**, low density lipoprotein receptor; **SR-B1**, scavenger receptor class B type 1.



**Fig. 2 – The properties of functional HDL and dysfunctional HDL.**

**ApoA-1**, apolipoprotein A-1; **ApoCIII**, apolipoprotein CIII; **ApoE**, apolipoprotein E; **LP-PLA2**, lipoprotein-associated phospholipase A2; **Pon1**, serum paraoxonase/arylesterase 1; **SAA1**, serum amyloid A1.

obesity not only promotes the removal of ApoA-1, but also suppresses its expressed sequence at the cellular level,<sup>26</sup> although this mechanism remains to be confirmed.

#### 1.4. Effect of exercise training in HDL-C

HDL in athletes differed from that in ordinary individuals, showing a larger size and higher density. Thus, the quality of HDL is related to health. However, although HDL structure and function are related to cardiovascular diseases, few studies have examined postexercise training.<sup>27</sup> According to the Aerobic Center Longitudinal Study, death rates due to cardiovascular disease and differences in fitness level are unrelated.<sup>28</sup> However, strength fitness was found to be related to the risk of metabolic syndrome in males.<sup>29</sup> Roberts et al<sup>30</sup> showed increased HDL redox activity in an overweight training group compared with a nontraining group. Dysfunctional HDL was found to be low in the overweight training group, indicating that the risk of CHD from obesity stems from differences in strength fitness.

Overweight or obese people typically show high levels of oxidized LDL,<sup>31</sup> whereas those with high muscular strength show decreased levels of oxidized LDL.<sup>32</sup> Da Silva et al<sup>33</sup>

reported that resistance exercises enhance LDL-C clearance, whereas Volkmann et al<sup>34</sup> reported that dysfunctional HDL decreased after low-intensity exercise of patients with systemic lupus erythematosus. Therefore, metabolic syndrome and cardiovascular disease are highly attributed to dysfunctional HDL. The application of exercise programs is thought to be effective for reducing the risk of CHD by reinforcing the anti-inflammatory function of HDL.

## 2. Conclusion

Under normal conditions, HDL prevents the oxidation of LDL, whereas HDL undergoes structural alterations under pathological conditions such as oxidative stress, inflammation, and diabetes, which reduces the antiarteriosclerotic and anti-inflammatory functions. HDL can be transformed into various forms depending on the structure and components, and such dysfunctional HDL-C is closely related to CAD risk. The quantitative decrease or deformation of ApoA-1 is a major factor increasing dysfunctional HDL, demonstrating its antiarteriosclerotic and anti-inflammatory effects. Therefore, in order to utilize HDL to determine health information, analysis of the structure and components of HDL after the

application of an exercise program should be combined with the analysis of HDL-C.

### Conflicts of interest

The authors have no conflicts of interest to declare.

### REFERENCES

- Castelli WP. Cholesterol and lipids in the risk of coronary artery disease. The Framingham heart study. *Can J Cardiol* 1988;4(Suppl A):5A-10A.
- Chapman MJ, Goldstein S, Lagrange D, Laplaud PM. A density gradient ultracentrifugal procedure for the isolation of the major lipoprotein classes from human serum. *J Lipid Res* 1981;22:339-58.
- Barter PJ, Nichollas S, Rye KA, Anantharamaiah GM, Navab M, Fogelman AM. Antiinflammatory properties of HDL. *Circ Res* 2004;95:764-81.
- Mineo C, Deguchi H, Griffin JH, Shaul PW. Endothelial and antithrombotic actions of HDL. *Circ Res* 2006;98:1352-64.
- Nofer JR, van der Giet M, Tolle M, Wolinska I, von Wnuck Lipinski K, Baba HA, et al. HDL induces NO-dependent vasorelaxation via the lysophospholipid receptor S1P3. *J Clin Invest* 2004;113:569-81.
- Tall AR, Yvan-Charvet L, Terasaka N, Pagler T, Wang N. HDL, ABC transporters, and cholesterol efflux: implications for the treatment of atherosclerosis. *Cell Metab* 2008;7:365-75.
- Rye KA, Barter PJ. Antiinflammatory actions of HDL: a new insight. *Arterioscler Thromb Vasc Biol* 2008;28:1890-1.
- Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein (a), apolipoproteins A-I and B, and HDL density subfractions: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2001;104:1108-13.
- Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302:1993-2000.
- Shah PK, Kaul S, Nilsson J, Cercek B. Exploiting the vascular protective effects of high-density lipoprotein and its apolipoproteins: an idea whose time for testing is coming, part I. *Circulation* 2001;104:2376-83.
- Fielding CJ, Fielding PE. Molecular physiology of reverse cholesterol transport. *J Lipid Res* 1995;36:211-28.
- Attie AD, Kastelein JP, Hayden MR. Pivotal role of ABCA1 in reverse cholesterol transport influencing HDL levels and susceptibility to atherosclerosis. *J Lipid Res* 2001;42:1717-26.
- Dobiásová M, Frohlich J. Understanding the mechanism of LCAT reaction may help to explain the high predictive value of LDL/HDL cholesterol ratio. *Physiol Res* 1998;47:387-97.
- Masson D, Jiang XC, Lagrost L, Tall AR. The role of plasma lipid transfer proteins in lipoprotein metabolism and atherogenesis. *J Lipid Res* 2009;50:S201-6.
- Riwanto M, Landmesser U. High density lipoproteins and endothelial functions: mechanistic insights and alterations in cardiovascular disease. *J Lipid Res* 2013;54:3227-43.
- Van Linthout S, Spillmann F, Riad A, Trimpert C, Lievens J, Meloni M, et al. Human apolipoprotein A-I gene transfer reduces the development of experimental diabetic cardiomyopathy. *Circulation* 2008;117:1563-73.
- Patel S, Drew BG, Nakhla S, Duffy SJ, Murphy AJ, Barter PJ, et al. Reconstituted high-density lipoprotein increases plasma high-density lipoprotein anti-inflammatory properties and cholesterol efflux capacity in patients with type 2 diabetes. *J Am Coll Cardiol* 2009;53:962-71.
- Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, et al. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. *J Lipid Res* 2004;45:1169-96.
- Parks JS, Rudel LL. Alteration of high density lipoprotein subfraction distribution with induction of serum amyloid A protein (SAA) in the nonhuman primate. *J Lipid Res* 1985;26:82-91.
- Smith JD. Myeloperoxidase, inflammation, and dysfunctional high-density lipoprotein. *J Clin Lipidol* 2010;4:382-8.
- Van Lenten BJ, Hama SY, de Beer FC, Stafforini DM, McIntyre TM, Prescott SM, et al. Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. Loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures. *J Clin Invest* 1995;96:2758-67.
- Sorrentino SA, Besler C, Rohrer L, Meyer M, Heinrich K, Bahlmann FH, et al. Endothelial vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy. *Circulation* 2010;121:110-22.
- Khera AV, Cuchel M, de la Llera-Moya M, Rodrigues A, Burke MF, Jafri K, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med* 2011;364:127-35.
- Rashid S, Uffelman KD, Lewis GF. The mechanism of HDL lowering in hypertriglyceridemic, insulin-resistant states. *J Diabetes Complications* 2002;16:24-8.
- Rashid S, Genest J. Effect of obesity on high-density lipoprotein metabolism. *Obesity (Silver Spring)* 2007;15:2875-88.
- Mooradian AD, Haas MJ, Wehmeier KR, Wong NC. Obesity-related changes in high-density lipoprotein metabolism. *Obesity (Silver Spring)* 2008;16:1152-60.
- Lee H, Park JE, Choi I, Cho KH. Enhanced functional and structural properties of high-density lipoproteins from runners and wrestlers compared to throwers and lifters. *BMB reports* 2009;42:605-10.
- Katzmarzyk PT, Church TS, Blair SN. Cardiorespiratory fitness attenuates the effects of the metabolic syndrome on all-cause and cardiovascular disease mortality in men. *Arch Intern Med* 2004;164:1092-7.
- Jurca R, Lamonte MJ, Church TS, Earnest CP, Fitzgerald SJ, Barlow CE, et al. Associations of muscle strength and fitness with metabolic syndrome in men. *Med Sci Sports Exerc* 2004;36:1301-7.
- Roberts CK, Croymansa DM, Azizc N, Butchc AW, Leed CC. Resistance training increases SHBG in overweight/obese, young men. *Metabolism* 2013;62:725-33.
- Weinbrenner T, Schroder H, Escuriol V, Fito M, Elosua R, Vila J, et al. Circulating oxidized LDL is associated with increased waist circumference independent of body mass index in men and women. *Am J Clin Nutr* 2006;83:30-5.
- Kosola J, Ahotupa M, Kyrolainen H, Santtila M, Vasankari T. Good aerobic or muscular fitness protects overweight men from elevated oxidized LDL. *Med Sci Sports Exerc* 2012;44:563-8.
- da Silva JL, Vinagre CG, Morikawa AT, Alves MJ, Mesquita CH, Maranhao RC. Resistance training changes LDL metabolism in normolipidemic subjects: a study with a nanoemulsion mimetic of LDL. *Atherosclerosis* 2011;219:532-7.
- Volkman ER, Grossman JM, Sahakian LJ, Skaggs BJ, Fitzgerald J, Ragavendra N, et al. Low physical activity is associated with proinflammatory high-density lipoprotein and increased subclinical atherosclerosis in women with systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2010;62:258-65.