

The Role of High-Density Lipoprotein in Cardiovascular Disease: Benefits, Functions, and Treatments

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Abstract. There is evidence that high-density lipoprotein (HDL) can prevent the development of cardiovascular disease, particularly atherosclerotic. The beneficial effects of HDL on the arterial wall are largely due to its rich function. For example, one of the essential components of HDL's atherosclerotic protective characteristics is reverse cholesterol transport (RCT). The low-density lipoprotein (LDL) oxidation risk may be decreased attributable to the anti-oxidation function of HDL, which would also decrease the possibility of atherosclerosis. In recent years, the anti-inflammatory function of HDL has been demonstrated to modulate and participate in several inflammatory phenomena of atherosclerotic plaque formation. Since various functional features of HDL have gradually shown to have positive effects on the treatment and prevention of atherosclerotic plaque development, a growing number of researchers are working to develop effective strategies to boost HDL. Fortunately, several treatment options have developed to increase HDL levels, including drugs and dietary patterns. This article will focus on the functional properties of HDL levels and several therapeutic approaches to raise HDL levels.

Keywords: CVD, HDL, Atherosclerotic, Dietary Pattern, Medication

1. Introduction

In many wealthy countries, atherosclerotic cardiovascular disease continues to be a major source of morbidity and mortality although low-density lipoprotein (LDL)-lowering therapies have been widely used. Cardiovascular disease (CVD) causes approximately 50,000 deaths per year in Canada [1]. Although some drugs have had substantial beneficial effects, many patients still suffer from CVD. Therefore, high-density lipoprotein (HDL) cholesterol has become a vital component in the search for new therapeutic strategies. The phenomenon has piqued the interest of researchers looking to switch from LDL to HDL in search of new therapeutic strategies. After a series of studies, HDL level has been shown to be negatively correlated with CVD, meaning that the risk of CVD decreases with increasing HDL levels. In detail, the key function of HDL in this atheroprotective potential may include its crucial role in RCT, which aids in reusing or excreting cholesterol from the body by assisting in its collection from the blood by the liver. Moreover, anti-inflammatory and antioxidant properties also belong to HDL, which may have the ability to contribute to the treatment of cardiovascular diseases. As a result, strategies to increase HDL levels have emerged, including several pharmacological and nutritional interventions. This article focuses on the differences between HDL and LDL, elaboration on the basic properties of HDL, and explore treatments for elevating HDL level, including medications, dietary patterns, regular exercise, and specific foods. Also, the article expounds on several available pieces of evidence on dietary interventions to raise HDL.

2. Cardiovascular Disease Due to Cholesterol

Coronary heart disease (CHD) is one of prevailing category of cardiovascular diseases (CVD), which frequently brought on by atherosclerosis of the coronary arteries that support blood to the heart muscle [1]. Additionally, the accumulation of lipids and other materials in the arteries causes atherosclerosis. In detail, atherosclerosis usually begins with an aggregation of streaks of soft fat in the inner walls of arteries, especially at branch points [1]. As these fatty streaks continue to be filled with cholesterol, calcium, and other lipids, they will gently enlarge and harden [1]. Finally, they are

wrapped by fibrous connective tissue and form plaques [1]. Plaques may cause a heart attack or stroke when they rupture by solidifying the arteries and restricting the flow of blood through them [1].

According to research, HDL cholesterol (HDL-C) concentration and the risk of cardiovascular disease with atherosclerosis have been found to be negatively correlated in case-control and prospective cohort studies throughout seven decades [2]. Moreover, the blood cholesterol level is frequently purposed to anticipate a person's propensity for suffering a stroke or heart attack and in large extended, the higher cholesterol predicted greater risk [3]. The reason for this phenomenon is that if the cholesterol accrues in the arteries, it may impede blood flow and then raising blood pressure, which might have catastrophic repercussions [3]. Therefore, lowering blood cholesterol become one of major effort to prevent or treat heart disease [3].

3. The Characteristics of HDL and LDL

Cholesterol is found in a variety of lipoproteins, mainly LDL and HDL [4]. The result of the population analysis is that contrary to HDL, the level of LDL cholesterol (LDL-C) demonstrates a positive relationship with CVD, indicating that the higher the LDL-C, the greater the chance of developing CVD [5]. One of explanation for this result is that high level of LDL-C, particularly for oxidized LDL, generally may promote a battery of events that induce plaque development and making it instability [4]. Then, atherosclerosis signaling molecules will be stimulated by oxidized LDL-C and those signalling will influence some immune cells transformation and replication to macrophages in arterial wall, which may increase the risk of plaque rupture and inflammation [4]. However, although HDL also contain cholesterol, increased HDL means that the cholesterol is returning from the cells to the liver for recycling or disposal, such as producing bile acids and excreting in the gastrointestinal tract [4]. Additionally, HDL have several outstanding capabilities, for example, anti-inflammatory which can prevent atherosclerotic plaque from breaking apart and reducing the risk of heart attacks [5]. That is why LDL generally refers as “bad” cholesterol, while HDL called a “good” cholesterol [5]. However, the differences between HDL and LDL are the properties of lipids and proteins, not cholesterol [5].

4. The Positive Properties of HDL

4.1. Reverse Cholesterol Transport

Although HDL has many beneficial functional properties, such as anti-thrombotic and anti-apoptotic, the most notable characteristic is its critical function in stimulating reverse cholesterol transfer (RCT), the procedure by which cholesterol is mobilized to liver from peripheral tissue [6] (Fig. 1).

The outflow of cholesterol from peripheral cells, particularly macrophage foam cells within atherosclerotic plaques, is the initial stage in RCT [7]. In addition, the predominant receptor for cholesterol effusions is HDL, which is delivered by a number of different methods, for example, active transport of the transmembrane family of protein channels binding to ATP and passive diffusion across cellular membranes [6]. One of the most well-known members of this family, ABCA1, which tends to drain cholesterol from lipid-rich tissues and deplete it or liberated forms of aPoA-I [6]. In addition, ABCG1 may also take part in the process of efflux of cholesterol.

When cholesterol experienced effluence to become the HDL particles, lecithin, cholesterol acyltransferase (LCAT), will briskly esterify it [6]. Afterwards, those cholesterol would decide to be stored in the core of the HDL-C particles [6, 7]. The gradient driving efflux usually preserve the direction from cell to the HDL particle for reason that the cholesterol content on the surface of this particle is comparatively diminish [6]. After that, with the help of the stimulation of cholesterol ester transporter protein (CETP), esterified cholesterol is transferred to lipoproteins that contain apoB, including such LDL or very low-density lipoprotein (VLDL). Another approach is for the liver to absorb cholesterol through the scavenger receptor class B type I (SR-BI) [6, 7]. Furthermore, after

becoming apoB-containing lipoproteins, the LDL receptors will help liver to collect cholesterol or those cholesterol will be transported to peripheral cell [6]. The two primary routes for cholesterol removal from the liver are lipoprotein synthesis or excretion with bile salts [6]. The bile acids are eventually eliminated through the feces [7].

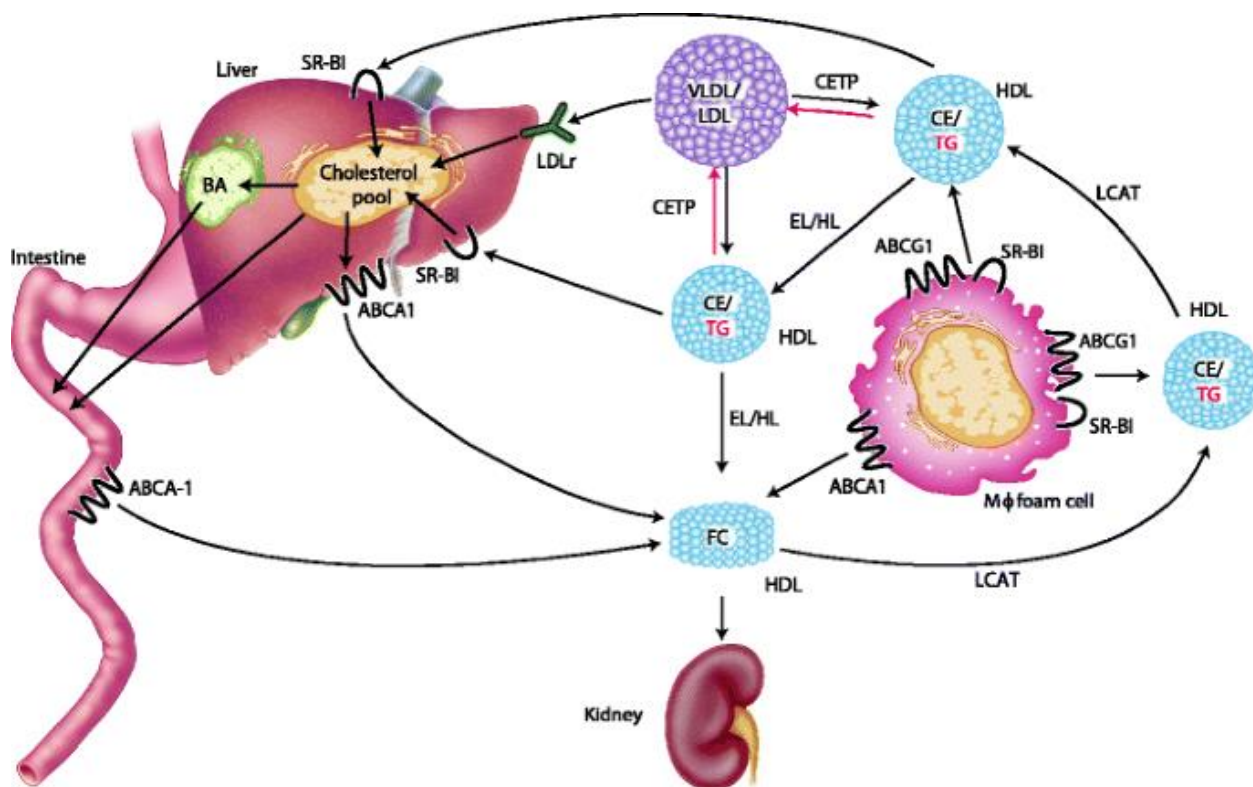


Fig. 1 The RCT route process [7]

4.2. Antioxidant Function

In addition to RCT, antioxidants are also a vital feature of HDL that contributes to the reduction the risk of CVD. HDL debilitate the bioavailability of various pro-oxidants associated with the development of atherosclerosis [6]. Since LDL that has not undergone oxidative alteration cannot become proatherogenic, the function of anti-oxidation of HDL prevents this from happening [6]. The principal reservoir of hydroperoxides in lipids in vivo is HDL, which consists of a variety of antioxidant agents, including paraoxonase and platelet-activating factor-acetylhydrolase [6]. This discovery provides multiple potential mechanisms for LDL oxidative modification damage. According to studies, if control HDL levels in the cellular and animal environment, the production of reactive oxygen species, such as superoxide, can be limited and help in restoring the physiological equilibrium of nitric oxide (NO) [6].

4.3. Anti-inflammatory Function

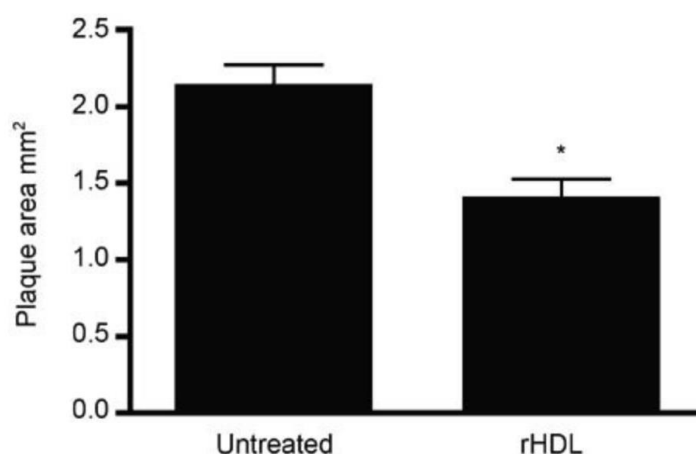
HDLs have been discovered to have anti-inflammatory characteristics, and a variety of inflammatory issues related to the formation of atherosclerotic plaque control by them. Additionally, monocyte chemotaxis, a crucial early stage in the development of atherosclerosis, is inhibited by HDL regulation of the production of pro-inflammatory adhesion molecules and chemokines in endothelial cells [6].

The benefits of HDL have been expanded to in vivo environments. For instance, lowering adhesion molecule expression in blood vessels and assisting chemokines and inflammatory cells penetrated into the arterial wall are connected to a rise in HDL-C [6].

Under the normal cholesterolemic condition, through a model of acute vasculitis inflammation, HDL was recently discovered to exhibit anti-inflammatory effects. One experiment substantiated the

HDL plays a crucial anti-inflammatory role in vivo. In this experiment, the researchers injecting rHDL into feeding rabbits and they observed a significant decrease in the expression of neutrophils and endothelial cell adhesion molecules [6].

According to the recent report, they contend that Instead of the total amount of HDL-C in the body, the quality of HDL determines the potential remodeling of existing atherosclerotic plaque [6]. They demonstrated that infusion of minute amounts of native or reconstituted HDL but do not increase in systemic HDL-C levels can significantly lowers lesion size (Fig. 2) and enhances the ratio of cells from smooth muscle to macrophages in an atherosclerotic plaque model [6].



Atherosclerotic lesion size in the abdominal aorta in rabbits that received no treatment or infusions of reconstituted HDL. * $p < 0.05$ for comparison with untreated animals (adapted from *Arterioscler Thromb Vasc Biol* 2005; **25**:2416-2421).

Fig. 2 Plaque size after increasing HDL levels [6]

5. Therapeutic Strategies to Raise HDL

5.1. Medication Ways

Based on the large number of clinical trials that unequivocally demonstrate that statins are effective in reducing LDL-C, the primary goal of lipid management remains to reduce LDL-C levels [6]. Fortunately, some medications that are currently authorized to treat individuals with high triglycerides and LDL-C may also be capable of elevating plasma HDL cholesterol levels [8]. For example, concentrations of plasma HDL cholesterol can be increased by 10 to 15% with statins, and fibrates and niacin may achieve the same result with a 25 to 30% increase [8]. Recently, many clinical interventions are emerging to enhance HDL levels, such as CETP inhibitors and peroxisome proliferator-activated receptor (PPAR) agonists.

5.1.1 CETP inhibitors

The emergence of a novel drug, CETP inhibitors, which can dramatically increase HDL-C and decrease LDL-C, has aroused great interest and concern among many professionals [8]. The schematic model in Fig. 3 provides an illustration of the specific of CETP in the metabolism of lipoproteins. Generally, liver has two routes to accumulate HDL-C. The first mode of transport is that CETP transfers cholesterol esters (CE) to VLDL-IDL-LDL lipoproteins, which reached to liver through the LDL receptor (LDLr) [8]. Additionally, The second mechanism including CE is selectively absorbed by hepatic SR-BI receptors [8]. Moreover, the HDL-SR-BI route is mainly employed to carry the majority of free cholesterol (FC) returned to the liver, while after transfer by CETP, the IDL-LDL-LDLr pathway is the primary path regulating CE transportation [8].

The explore of medications that inhibit the activity of CETP as a CVD therapeutic intervention has been controversial since CETP promotes both pro-atherogenic and anti-atherogenic results, which

are entirely separate effects. While levels of CE in VLDL-IDL-LDL will increase, HDL levels may decrease as a consequence of CETP-mediated transfer of CE [8]. As HDL levels decrease, the protective role that HDL plays in atheroprotective functions would be diminished, and this process might be recognized as pro-atherogenic [8]. On the other hand, CETP would encourage RCT, which has a preventive impact against atherosclerosis, when CE transport back to the liver through LDLr will be enhanced by increasing CE transfer to VLDL-IDL-LDL [8]. Therefore, it is hard to evaluate and predict the result of CETP activities. Further analysis of the possible protective impact of CETP inhibition in cholesterol-fed rabbits revealed that CETP inhibition enhanced HDL and prevented aortic atherosclerosis [6, 8]. In this experiment, JTT-705, a pharmacologic CETP inhibitor, was administered by researchers to rabbits with cholesterol, and results showed that non-HDL cholesterol and atherosclerosis were both reduced by roughly 50% and 70%, respectively, and that HDL-C levels were about two times higher [8]. To ascertain the therapeutic impact of CETP inhibitors on CVD, further research is still required.

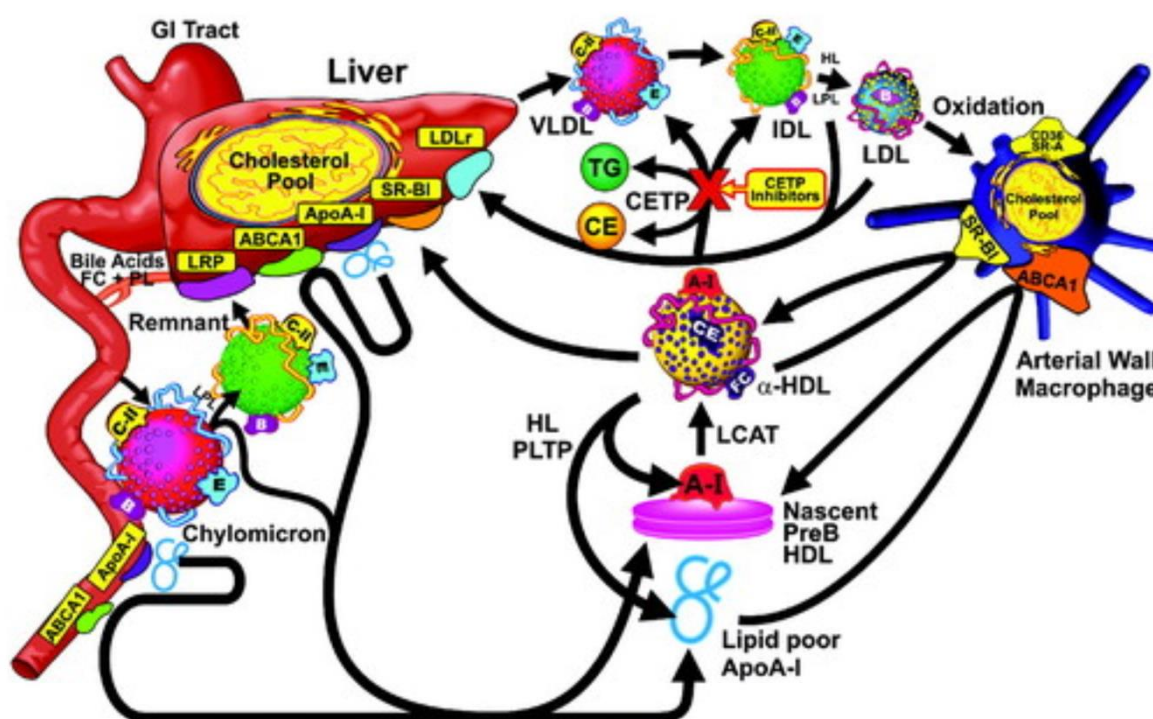


Fig. 3 The process of CETP in lipoprotein metabolism [8]

5.1.2 PPAR agonists

A family of nuclear transcription factors identified as PPARs has been shown to be essential in the control of a number of activities that affect metabolic homeostasis [6]. The biomarkers of PPAR family activation are characterized by increased HDL expression and function, and decreased plasma triglycerides, which can promote an anti-atherosclerotic lipid environment [6]. Furthermore, PPAR- α and PPAR- γ are play a role in reducing several crucial inflammatory cascade events, which will benefit in vascular protection [6]. Currently, fibrate and thiazolidinedione have been recognized as therapeutic drugs and they demonstrated to function as agonists of PPAR- α and PPAR- γ , respectively [6]. However, Both drugs are classified as modest agonists [6].

5.2. Diet Recommendation

Exercise is associated with higher HDL levels and better HDL performance such as the concentrations and functionality, however diets have a two-sided effect, meaning that different dietary patterns may have distinct beneficial or detrimental effects on HDL effectiveness [9]. According to some studies on the relationship between food and HDL, it suggested that a nutritious

diet, which mostly consisted of fruits, vegetables, legumes, fish, nuts, and olive oil, could boost the amount of HDL cholesterol particles in the blood [9]. Based on ACC/AHA 2019 guidelines for a healthy dietary pattern to prevent CVD, they recommend that decreasing the daily intake of saturated fatty acids (SFA), processed meats and sodium; and limit the consumption of high-sugar beverages and trans fats [9]. Additionally, the plant-based dietary pattern, such as the Mediterranean diet (MD), has been considered one of the healthy diet ways to prevent CVD because traditional MD has consisted of low saturated fat, and trans-fat and is rich in complex carbohydrates and fibre [10]. Eventually, this type of diet may improve lipid profiles, lower inflammation diminishes, and reduce the risk of CVD [10].

According to research, essentially removing a considerable number of trapped macrophages from the arterial wall can prevent or treat atherosclerosis. As it breaks adhesion, releases macrophages from artery walls, and promotes healing, resveratrol, an important antioxidant present in red grapes and red wine, can assist in goal which remove the macrophages from arterial walls [10]. Moreover, the majority of the MD is made up of extra virgin olive oil, which further contains abundant nutrients such polyphenols, oleic acid, and monounsaturated fatty acids [9]. Following the observation taken by Farras et al. (2017), the HDL-antioxidant level in a group of adults with hypercholesterolemia increased and the cholesterol efflux was raised by 1.3% by consumption of phenol-rich olive oils [9]. Moreover, the essential characteristics of fish oil are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). According to an experiment evaluating the effects of fish oil consumption on the atherosclerotic and antiatherosclerotic function of LDL and HDL particles, the HDL-C levels increased significantly [9].

Additionally, to increase HDL, smoking cessation, exercise, and weight loss are also essential. In detail, more than three times a week of moderate-intensity exercise was associated with an average 4% increase in HDL-C. For overweight adults, HDL-C may increase by an average of 1 percent for every 1 kilogram lose [11]. Quitting smoking can help increase HDL-C levels by 3% to 5.6% [11].

All in all, virgin quercetin, resveratrol, and olive oil are effective methods for raising the expression of ABCG1 and ABCA1 transporters, which facilitating cholesterol leave from macrophages [9]. As a result of the mechanistic preponderance of these presence in specific functional foods, which are effective in avoiding the storage of cholesterol in macrophages in the arterial wall, the chance of atherosclerosis progression caused by cholesterol is significantly decreased [9]. Additionally, Curcumin, ginger, legumes, nuts, and fish have also been demonstrated to reduce plasma CETP levels [9]. Regular exercise is equally important to help raise HDL levels. Consequently, a balanced lifestyle and functional foods may help to control and prevent atherosclerosis.

6. Conclusion

HDLs possess various beneficial biological activities, such as anti-oxidation and RCT, which give them great potential to modulate pathological events leading to all stages of atherosclerosis, and they create new therapeutic strategies for the treatment of cardiovascular programs. One of the most noticeable of the numerous advantageous functional characteristics of HDL is its ability to facilitate reverse RCT, the process by which, cholesterol is transported to the liver from peripheral tissues. In the liver, lipoproteins are synthesized or excreted as bile salts. moreover, the anti-oxidation function of HDL can inhibit the oxidative modification of LDL, thus greatly reducing the risk of atherosclerosis caused by LDL.

Regarding the prevention and treatment of cardiovascular diseases caused by atherosclerosis, these novel therapeutic approaches have the potential to make a substantial difference. The drugs used to increase HDL levels have been widely used in clinical studies, however, further research is needed on the effectiveness and feasibility of emerging drugs. In addition to the use of drugs to increase HDL levels, diet and lifestyle habits also contribute greatly to this. The MD diet which is based on vegetables, fish, and nuts is highly recommended. Moreover, reducing intake of SFA, high-sugar beverages and regular exercise may also help to improve HDL levels. The methods to enhance HDL

levels are constantly emerging and improved, and HDL's significance in the management of CVD is predictable.

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