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High-density lipoprotein cholesterol — friend or enemy?

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Abstract

The article provides a review of the literature on the effect of excess and deficiency of high-density lipoprotein cholesterol on the prevention and treatment of cardiovascular pathology. Information about high-density lipoproteins structure, function, antiatherogenic role and the prospect of using various high-density lipoproteins subclasses in the pharmacotherapy of dyslipidemic conditions are also described. It is proven that a lowered level of such cholesterol is a predictor of cardiovascular disease. At the same time, many observations confirm the correlation between elevated high-density lipoprotein levels and mortality from myocardial infarction and other acute cardiovascular conditions. In large studies, the use of cholesterol ester transfer protein inhibitors and other drugs increased the level of high-density lipoprotein, but the unreduced risk of cardiovascular disease confirms the lack of positive results from the use as a therapeutic target. In addition, it was found that the composition of high-density lipoprotein cholesterol protein differs in healthy and diseased people: it becomes "dysfunctional", losing its antioxidant and anti-inflammatory properties in diseased individuals. The atheroprotective activity of properly functioning high-density lipoprotein cholesterol is often impaired in clinical situations associated with oxidative stress. In these cases, high-density lipoproteins can have some changes, and even if the quantity is within the normal range, the quality is no longer the same. Thus, it is necessary to identify a better therapeutic target than high-density lipoprotein cholesterol levels, as there is currently insufficient clinical trial data to recommend targeted high-density lipoprotein therapy.
Keywords: cholesterol, high density lipoproteins, low density lipoproteins, atherosclerosis, myocardial infarction.

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Introduction

Cholesterol (CS; ancient Greek χολή—bile + στερεός—solid) is an organic compound, a natural polycyclic lipophilic alcohol. It is carried in the blood by lipoproteins, complex protein-lipid complexes, including phospholipids, free fatty acids, cholesteride, and neutral fats.

Among lipoproteins, the blood plasma lipoproteins are the most studied. According to their physical properties, they are divided into fractions depending on molecular size, namely, high-density lipoproteins (HDL), low-density lipoproteins (LDL), intermediate-density lipoproteins, very low-density lipoproteins, and chylomicrons [1].

Clinical specialists mainly focus on LDL and HDL despite various lipid metabolism indicators, since LDLs are important risk factors for cardiovascular disease (CVD). At the same time, HDLs are well known in for their putative role in the reverse transport of CS and other atheroprotective functions [2].

Structure and functions of HDL

HDL forms a heterogeneous class of lipoproteins that differ in structure, shape, size, density, metabolism, and properties. They have a high level of protein relative to lipids. Therefore, they have the highest density among lipoproteins but at the same time the smallest size (8–11 nm in diameter). The HDL composition includes proteins (up to 55%), phospholipids (up to 30%), CS (about 10%), and triglycerides (5%).

The prototype HDL particle contains 2–5 molecules of apolipoprotein A-I (apoA-I) and approximately 100 molecules of phosphatidylcholine or sphingomyelin. In addition to apoA-I, one of the main HDL proteins is apolipoprotein A-II. It has been suggested that these apolipoproteins have different metabolic properties and, therefore, may have different protective potentials [3]. Quantitative changes in apoA-I and the main lipid components of HDL (phosphatidylcholine, sphingomyelin, CS, and CS esters) cause significant HDL heterogene-

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ity in shape, density, size, and charge, which can be analyzed using electron microscopy, ultracentrifugation, gel filtration, electrophoresis in polyacrylamide gel, or nuclear magnetic resonance spectroscopy and agarose gel electrophoresis.

HDL particle heterogeneity is determined by the set of proteins and lipids in a single particle. It is essential to identify and characterize specific HDL particles regarding proteins and lipids to reveal cardioprotective properties. Identification is performed using physical isolation, purification, immunoprecipitation, chemical cross-linking, co-partitioning, and bioinformative assays. Determining which proteins and lipids are localized in HDL particles will enable using them in therapy for further research [4].

It has been proposed to divide HDLs into five subclasses (very small, small, medium, large, and very large HDLs) to facilitate their use in clinical trials and report the results more clearly [5].

HDL CS versus LDL CS

It is believed that LDL CS is "harmful," and HDL CS is "beneficial," but is it so?

LDL CS has been identified as the major atherogenic lipoprotein, and its central role in the development of atherosclerosis has been confirmed in numerous studies [6–8]. In contrast, epidemiological, pathological, and experimental studies have demonstrated that HDL CS is involved in reducing atherosclerosis risk through a variety of pathophysiological mechanisms. However, such a hypothesis is complicated by the heterogeneity and HDL particle functionality under various pathophysiological conditions [9].

While the role of LDL CS as a risk factor for atherosclerosis and coronary heart disease development has been proven, studies results on triglycerides and HDL CS are contradictory [10].

Some genetic evidence supports that triglycerides affect coronary heart disease risk, and the causal relationship with HDL is still less understood [11].

Genome-wide studies have shown that multiple genetic loci are associated with serum HDL CS levels, but most of these loci are also associated with triglycerides and LDL CS levels. This significantly complicates how the association of HDL CS levels with these genes influences CVD risk [4].

Deficiency and HDL excess

Low plasma HDL CS levels are associated with increased coronary heart disease risk. HDL particles have many effects *in vitro* and *in vivo* that can protect arteries from various types of damage and accelerate the healing of injuries. Despite their positive functions, they are not applied successfully in therapy. One reason is HDL particle complexity, which comprises more than 80 different proteins, more than 200 types of lipids, several messenger ribonucleic acids (mRNAs), and other potentially bioactive molecules. This physiological heterogeneity is further enhanced by inflammatory conditions that increase the risk of CVD, diabetes mellitus, chronic kidney disease, and rheumatic diseases [5].

For more than four decades, it has been recognized that elevated serum HDL CS levels are associated with reduced CVD risk and its consequences. Many prospective observational studies conducted worldwide have confirmed the inverse relationship between HDL CS and cardiovascular risk in people regardless of gender, race, or ethnicity. Therefore, it was assumed that further increases in HDL CS levels through lifestyle changes and pharmacological intervention would reduce CVD risk. Animal studies support this assumption. Lipid management guidelines worldwide have promoted the recognition of HDL CS as a therapeutic target, especially for high-risk patients.

In response to many questions and inaccuracies, the National Lipid Association convened an expert panel to assess the current status of HDL CS as a therapeutic target, review the state of knowledge about the structure, composition, and function of HDL particles, and determine the role of HDL in preventing or promoting atherosclerotic disease. The panel concluded that although low HDL CS levels define patients at increased risk, and many studies suggest HDL may play various anti-atherogenic roles, HDL CS is not a therapeutic target. As described in the established guidelines, atherogenic lipoproteins (LDL CS and non-HDL CS) should remain the primary and secondary therapy targets in patients at risk [4].

The National Lipid Association emphasized that the clinical implications of low HDL CS levels need to be further explored. The development of new drugs designed to regulate serum levels and HDL particle functionality should also be increased. Based on a considerable number of fundamental scientific and clinical studies, the need to analyze the therapeutic effect of HDL has been confirmed [4].

The data obtained in further studies showed that the relationship between HDL CS and mortality is not linear at all concentrations of HDL CS. Thus, according to CANHEART, the correlation between HDL CS and mortality is U-shaped, with both high and low levels of HDL CS being associated with an increased risk of all-cause mortality [12].

Mendel's randomized trial examined the relationship between plasma HDL CS and the risk of myocardial infarction. It turned out that some

genetic mechanisms that increase the blood plasma HDL CS level do not reduce the risk of myocardial infarction. These data cast doubt on the concept of a decrease in the risk of myocardial infarction with an increase in plasma HDL CS levels [13]. Carriers of the LIPG 396Ser allele (frequency 2.6%) had higher levels of HDL CS (0.14 mmol/l and higher, $p = 8 \times 10^{-13}$) than similar levels of other lipid and non-lipid risk factors for myocardial infarction than non-carriers. This difference in HDL CS was expected to reduce the risk of myocardial infarction by 13% (odds ratio 0.87, 95% CI 0.84–0.91). However, because of genetic assessment, the researchers noted that the 396Ser allele was not associated with the risk of myocardial infarction [14].

A recent study by Boekholdt et al. demonstrated that an increase in HDL CS levels was not associated with a lower probability of serious CVDs, regardless of established risk factors. However, the authors reported an association between elevated apoA-I levels and reduced risk of major cardiovascular events [15]. This study did not provide evidence to support a significant benefit from an increase in HDL CS, regardless of the effect of lowering non-HDL CS. Thus, this cast doubt on the hypothesis that lipid-modifying therapy should be aimed at increasing HDL CS levels.

On the other hand, studies revealed an association of increased apoA-I levels with a reduction in cardiovascular risk of independently identified risk factors, supporting the justification for using apoA-I as a target for atherosclerosis treatment[3]. Based on those described above, we can conclude that it is more important to determine the level of apolipoproteins included in lipoproteins rather than the lipoprotein level.

Studies related to HDL CS

Despite significant advances in vascular medicine, CVDs remain the primary cause of death worldwide [16]. It was assumed that increasing the HDL level using therapeutic agents would be the leading solution to this problem. However, contrary to expectations, the pharmacological increase in HDL levels could not reduce CVD risk [4].

Currently, due to the general availability of statins and their widespread use, the goal of lowering LDL levels has been achieved. However, achieving the second goal, increasing HDL levels, seems to be more complicated. The three main agents used to increase HDL levels to reduce CVD and mortality are niacin, fibrates, and the recently developed inhibitors of cholesterol ester transfer protein (CETP). The HPS2-Thrive study showed that adding niacin to statin-based LDL CS lowering therapy significantly reduced the risk of major vascular disease but increased side effects, namely, gastrointestinal complications, bleeding, musculoskeletal disorders, and diabetes mellitus [17, 18].

Fibrates have been shown to reduce the incidence of some CVDs consistently, but only in patients with high serum triglyceride levels and low HDL CS levels [19]. In contrast to CETP inhibitors, fibrates increased HDL CS levels mainly due to stimulating apoA-I synthesis [19]. In the class of CETP inhibitors, three agents (anacetrapib, dalcetrapib, and torcetrapib) have been studied. Two studies with the promising torcetrapib were terminated prematurely due to adverse events in the treatment groups. One study involving dalcetrapib was also terminated due to the lack of effect [20]. Most attempts to reduce CVD or mortality by increasing HDL CS using these three drug classes other than statins have been unsuccessful [21].

In the USA, the Netherlands, Canada, and France, a randomized study was conducted to assess the effect of CER-001 on atheroma. Intravascular ultrasonography and quantitative coronary angiography evaluated coronary atherosclerosis before treatment and after the last infusion. The study involved 507 patients. Some of them received six weekly infusions of placebo 3 mg/kg, 6 mg/kg, and the rest received CER-001 at 12 mg/kg.

CER-001 represents engineered mimic pre-β-HDL lipoprotein particles and consists of recombinant human apoA-I and two phospholipids. This drug has previously been shown to mobilize rapidly large amounts of CS into the HDL fraction after intravenous administration.

The results of measuring the total volume of atheroma (mean values) were 22.71; 23.13; 21.50, and 23.05 mm^3 with placebo and CER-001 3; 6, and 12 mg/kg, respectively. There were no significant differences in the drug and placebo effects [22].

Gregory et al. conducted a study with dalcetrapib [23], a CS ester transfer protein inhibitor. Its use increases HDL CS levels and reduces the incidence of CVDs. Dalcetrapib 600 mg daily or placebo was randomly prescribed to 15,871 patients with acute coronary syndrome. At the time of randomization, the mean HDL CS was 42 mg/dL (1.1 mmol/L) and the mean LDL CS was 76 mg/dL (2.0 mmol/L). During the study, HDL CS increased from baseline by 4%–11% in the placebo group and by 31%–40% in the dalcetrapib group. Dalcetrapib had a minimal effect on LDL CS.

Patients were followed for an average of 31 months. Compared with placebo, dalcetrapib did not reduce recurrent CVD risk and did not significantly affect human health or overall mortality. Thus, dalcetrapib increased HDL CS levels in patients with a recent acute coronary syndrome,

but did not reduce recurrent cardiovascular event risk [23].

In the dal-OUTCOMES study, dalcetrapib therapy increased HDL CS, but this did not reduce major CVD risk [23]. According to intravascular ultrasound, in several randomized clinical trials, direct HDL mimetic administration increased plasma HDL CS but did not slow down the atherosclerosis progression. Thus, there is no evidence obtained in randomized trials confirming that an increased blood plasma HDL CS level helps reduce atherosclerotic CVD risk. It is unknown whether therapy that affects HDL particle function will reduce CVD risk [24].

A multicenter, randomized, double-blind, placebo-controlled study of evacetrapib, an inhibitor of the CS ester transport protein, included 12,092 patients. Study participants had at least one of the conditions of acute coronary syndrome within the previous 5–30 days, including atherosclerotic cerebrovascular disease, peripheral arterial disease, diabetes mellitus, and coronary heart disease. Patients were randomly distributed to receive evacetrapib 130 mg or a corresponding placebo administered daily, and standard medical therapy.

The primary efficacy endpoint was the occurrence of CVD, namely myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina. After three months, a decrease in the average LDL CS level by 31.1% was noted when taking evacetrapib versus a 6.0% increase with placebo, and a 133.2% increase in the average level of HDL CS was registered when taking evacetrapib compared with an increase of 1.6% when taking the placebo.

After 1363 of the 1670 planned CVD events, the Safety Monitoring Board recommended early trial termination due to the lack of efficacy. On average, after 26 months of evacetrapib or placebo, CVD occurred in 12.9% of patients in the evacetrapib group and 12.8% of patients in the placebo group (hazard ratio 1.01; 95% confidence interval 0.91–1.11; $p = 0.91$). Although the CS ester transfer protein inhibitor evacetrapib had beneficial effects on established lipid biomarkers, evacetrapib treatment did not lower CVD incidence in patients at high risk of CVD [25].

In addition to the current trials of anacetrapib and evacetrapib, studies are being conducted with new agents that will further investigate the effect of increasing HDL, namely HDL infusions, HDL mimetics, novel CETP inhibitors, liver X-receptor agonists, farnesoid X-receptor agonists, and RVX-208 [4].

The suitability of HDL as a therapeutic target is increasingly questioned. This is an essential prerequisite for searching for biomarkers that will better indicate the functionality of HDL than HDL CS or apoA-I plasma levels. Also, it can serve to guide the development of anti-atherogenic drugs and clinical management of patients with an increased risk of cardiovascular events [5].

Types of HDL CS

Both LDL and HDL are heterogeneous, including different subfractions depending on the isolation method (≥7 LDL subtypes and 10 HDL subtypes) [2].

The Lipoprint HDL system can distinguish between 10 HDL subfractions, HDL1–HDL10. However, according to the interpretation of the Lipoprint HDL system, these 10 HDL subfractions are divided into three subclasses of the HDL family, as follows:

1) a large subclass of HDL (1–3 subfractions);
2) an intermediate HDL subclass (4–7 subfractions);
3) a small HDL subclass (8–10 subfractions).

Subpopulations of HDL particles contain entirely different amounts of free CS and cholesteryl ester molecules per particle. Large particles comprise several times more CS molecules than small particles that are poor in CS [4].

Based on this interpretation, a large HDL class is considered to be the "protector" of the arteries and the "beneficial" HDL CS in the range of HDL lipoproteins [26]. The intermediate HDL class is also considered a good type, and already small HDL constitute the atherogenic part of this family. Quantification of small HDL can play an important role in identifying patients at risk for CVD [26].

Several studies have shown that large particles have a lower atheroprotective activity than small dense HDL. However, there are also studies that, on the contrary, demonstrated that small dense HDLs could even exhibit proatherogenic properties, increasing atherosclerosis risk [27]. It has been suggested that an important role in determining the atheroprotective action of HDL is played to a greater extent by their functional activity associated with the aspects of the HDL range [28, 29].

In their study, Garcia-Rios et al. emphasized that small HDLs under certain conditions can lose their cardioprotective properties and exhibit atherogenicity [2]. They demonstrate a strong atheroprotective effect in healthy donors, including antioxidant and anti-inflammatory activity, while these properties are absent under conditions of atherogenic dyslipidemia [30]. In the study by Pirillo et al., small HDLs showed a direct relationship with the presence and severity of atherosclerotic lesions. At the same time, large HDLs had an inverse relationship with the presence and severity of coro-

nary heart disease [31]. In this study, during treatment with nicotinic acid, a decrease in the level of small HDL subfractions was noted, and an increase in the concentration of large HDL subfractions. Conversely, in the case of combined therapy with statins and nicotinic acid, an increase in small HDL levels was registered, and a decrease in intermediate HDL, which have the maximum antiatherogenic potential [32].

Thus, among the subgroups of HDL, small HDLs in healthy people have a powerful atheroprotective effect, including an increased potential for CS efflux and a stronger antioxidant and anti-inflammatory effect [30]. However, under conditions such as atherogenic dyslipidemia, the properties of small HDL can be quite different. In a clinical study, small HDL was associated with the presence and severity of atherosclerotic lesions. In contrast, large HDL was negatively correlated with coronary heart disease and its severity and progression [31].

Despite the studies proving the atherogenic potential of small HDL and the anti-atherogenic potential of large HDL, their authors came to contradictory conclusions regarding the efficiency of HDL subclasses differentiated by size [33, 34]. The association of CV risk with HDL subclass size is sometimes controversial, as a significant association with CVD risk has been revealed for small HDL in some studies [34] and for intermediate HDL [33, 35] or large HDL [33, 34] in other studies.

Dysfunctional HDL

The expression "dysfunctional HDL" has been proposed in the literature to describe HDL that loses its antioxidant and anti-inflammatory properties, its main functions. Recent cases have confirmed that the atheroprotective activity of properly functioning HDL CS is often impaired in clinical situations associated with oxidative stress. The review presented lays the groundwork for a new approach to understanding how the functional properties of HDL help reduce CVD [3].

In some clinical situations, a high level of HDL CS is possible. In these cases, HDL CS may undergo some changes, and even if its level is within the normal range, its quality changes [3].

Despite the interest of many practitioners, it remains unclear whether the concept of dysfunctional HDL can improve clinical practice. Therefore, it is essential to determine whether indicators of dysfunctional HDL provide clinically useful information [4].

Dysfunctions include reduced HDL activity or ability to induce CS efflux from macrophages and other cells, inhibit lipid oxidation in LDL and cell membranes, and reduce the release and expression of cytokines, cell surface activation markers by macrophages or dendritic cells. Molecular changes are based on three main types of HDL dysfunction [5]:

1) changes in the protein part (proteome) composition;

2) post-translational protein modifications;

3) changes in the lipid part and other cargo molecules.

Although the molecular basis of dysfunctional HDL is poorly understood in both animal and human models, it is critical to developing standardized, high-performance tests that can evaluate HDL function and be used in human studies. When used in large and diverse populations, such analyses should determine whether new HDL values are associated with loss of function and whether dysfunction provides clinically useful information [4].

Conclusion

For more than 50 years, a low level of HDL CS has been known as an independent marker of increased cardiovascular risk, but despite great advances in knowledge about the structure, function, and metabolism of HDL, increasing it was ineffective for preventing and treating atherosclerosis. In light of the information presented, it can be concluded that there is a need to determine a better therapeutic target than the HDL CS level [5].

Currently, there are insufficient clinical trial data to recommend targeted HDL therapy. However, we can state with confidence that "too much" of anything never leads to positive results i.e., a critically low level of HDL CS, as well as a high one, will not cure a patient of a disease, in particular a cardiovascular pathology [12].

A consensus statement from the National Lipid Association does not recommend pharmacological intervention at low HDL CS levels, given the lack of positive results from randomized prospective studies [4]. Otherwise, the referring to these new guidelines, apparently national, is necessary.

It is required to define and fully characterize the large number of proteins, enzymes, apoproteins, bioactive lipids, phospholipids, fatty acids, and mRNAs within HDL and their influence on HDL functionality. Without this information, it will be difficult to understand how and why HDL "protects" or "causes harm" depending on the clinical circumstances. It is also required to establish the most informative clinical measurements of HDL particles/subfractions to improve CVD risk assessment, develop treatments that can affect the content of specific HDL components with atheroprotective properties, and establish more clearly the effect of

specific treatment methods on the increase or functionality of HDL, or both [4].

It will be possible with better understanding to identify and increase pharmacologically HDL subpopulations that have desirable atheroprotective properties; conduct clinical tests to assess HDL or its components, identifying people with increased atherosclerotic vascular disease risk [4].

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