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REVIEW ARTICLE

Role of HDL in Atherogenesis: Cholesterol and Atheroprotection

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Abstract: Atherosclerosis is a major global health burden, responsible for a significant proportion of cardiovascular morbidity and mortality worldwide. Its high prevalence and severe clinical consequences have made it a subject of extensive research. Despite considerable advances, the complexity of its pathogenesis continues to hinder the development of effective preventive strategies and therapeutic interventions. Current evidence implicates chronic inflammation, dysregulated lipid metabolism, cholesterol accumulation, and multiple atherogenic modifications of LDL particles as key drivers of atherogenesis. In contrast, lipids of the HDL class are widely recognized for their atheroprotective properties. In this review, we consolidate current data on the role of HDL in atherosclerosis, with particular focus on HDL-associated cholesterol (HDL-C) as a clinically and biologically relevant parameter.

Keywords: Atherosclerosis, HDL Cholesterol, HDL-C, Atherogenesis, Atheroprotection, Lipid Metabolism, LDL Oxidation, Cardiovascular Disease, Reverse Cholesterol Transport, Dyslipidemia, Inflammation, Plaque Formation, Lipoprotein, Cholesterol Efflux

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Introduction

HDL Structure

HDL- high-density lipoprotein-is a type of blood macromolecular constituent. Its size is from 8-10 nm and density is on average from 1.063-1.21 g/mL and it contains different proteins and lipids. HDL generally comprises apolipoproteins and a number of other proteins, among them are acute phase proteins and enzymes, as well as polar lipids and sometimes nonpolar lipids in small quantities. HDL may be isomers with various constituents of macromolecules with diverse composition, and biological and chemical properties. In the physiological state, HDL has a strong ability to modify antioxidants [1]. In a pathological state, HDL has different variations e.g., oxidation. Most of the HDL lipids are the internal cholesterol esters triglycerides and surface phospholipids. Phospholipids are generally represented by phosphatidylcholine, which makes up 32-35 mole percent of the total amount of lipids in HDL. Lysophosphatidylcholine is also an essential HDL phospholipid, that makes up 1.4-8.1 mole percent of all lipids. Another structural lipid that can stiffen surface lipids is sphingomyelin, which is also a substantial sphingolipid in the bloodstream, making up 5.6-6.6 mole percent of all lipids. It is formed mainly from lipoproteins rich in triglyceride, less often from novel HDL [2]. Transesterification of phospholipids with cholesterol catalyzed by Lecithin Cholesterol Acyl Transferase (LCAT) leads to the formation of the Cholesterol Ester (CE) on HDL, which is a lipid with high hydrophobicity. These lipids make up 36-mole percent of all HDL lipids and form the HDL lipid core. In the lipid monolayer on the HDL, particle surface can be found a small quantity of free sterol, which affects the fluidity of the lipid/monolayer/surface [3].

HDL consists of multiple proteins, such as apolipoproteins, lipid transfer proteins, enzymes, acute phase response proteins, protease inhibitors, complement components, and others.

Apolipoproteins and lipases are regarded as substantial HDL constituents. Other protein components typically take part in infection prevention, complement regulation, and acute phase response. 70% of HDL protein is apoAI, the essential functional and structural HDL constituent. It is considered that pretty much all HDL particles comprise apoAI. The main apoAI action is the LCAT activation, cell receptor interaction, and numerous Antiatherosclerosis (AS) HDL activities. The second biggest HDL apolipoprotein is apoAII, which makes up 15-20% of all HDL proteins. ApoAII may be found in approximately 50% of the HDL particles [4].

HDL Functions in Norm

The main HDL-C function is to transport the cholesterol from the peripheral tissues to the liver. The most part of the peripheral tissue cells cannot catabolize cholesterol, so they accumulate it. Consequently, a reverse transfer mechanism is required to bring cholesterol back to the liver. The transporters ABCA1 and ABCG1 help HDL-C to high-density Lp. [5]. After that, the free cholesterol is incorporated into the HDL-C particle by LCAT, which finally results in the absorption of cholesterol in the liver via three different pathways: SR-B1, CETP, and LDL receptor pathways. Participation in such biodistribution of lipids, which ensures that cholesterol accumulated in the atherosclerotic plaque foam cells is absorbed and returned to the bile and liver (reverse cholesterol transport), emphasizes the anti-inflammatory and antiatherogenic characteristics of HDL-C [6]. This HDL-C characteristic is the main reason for the cardioprotective action, as oxidation of LDL is considered to be a key inducer of pro-inflammatory reactions in subendothelium as well as atherosclerotic plaque formation. Another part of the HDL-C antiatherogenic effect is the protection of endothelium [7]. A large amount of data indicates that these salutary effects can be induced by bioactive lipids comprising HDL-C and HDL-bound Sphingosine 1-Phosphate (S1P) specifically. It is an altered phospholipid that was proven to promote the production of nitric oxide in endothelium through nitric oxide synthase activation. Furthermore, S1P is known to be an important chemoattractant for endothelial cells. It is also able to facilitate the assembly of VE adhesive compounds in ECs that contain cadherin thus limiting pathological vascular permeability [8]. As demonstrated by Sattler and colleagues, S1P injections led to a restoration of the impaired functionality and vasodilatory action of HDL-C in individuals with coronary artery disease [9]. In addition, an increase of 1-SD in S1P in plasma depleted of apoB reduced the risk of acute coronary syndrome by 30%. Apolipoprotein M is mainly found in the HDL fraction of plasma. ApoM is a physiological carrier protein for sphingosine 1-phosphate in HDL. Studies demonstrate that the atheroprotective action is in part due to this particle. The reason is possibly its association with apoM, which is able to promote preβ-HDL development and antioxidative characteristics and to increase the outflow of cholesterol from the foam cells of macrophages [10].

Moreover, the amount of apolipoprotein AI in HDL-cholesterol shows the level of cardioprotection. Florido and colleagues observed that ACS risk was reduced by about 50% as a result of increasing the apoA-I level by 1 SD in plasma depleted of apoB. ApoA-I is able to promote the inactivation and subsequent transfer of lipid peroxides thereby averting the oxidation of LDL and also mediating efflux of cholesterol [11]. The availability of cholesterol in lipid rafts in immune cells along with the following toll-like receptors, B-and T-cell receptors, and MHC-II complex adjustment depend on HDL-C, which may thus be a part of the immune system modulation. Furthermore, immune cell transfer is promoted by some molecules carried by HDL-C, including S1P. Those characteristics of HDL-C are believed to be associated with their anti-inflammatory and proinflammatory effects.

The Physiologic Role of HDL in Protection from Atherosclerosis

HDL physiology is complicated and a decreased atherosclerosis risk is associated with HDL cholesterol levels. Moreover, a more thorough assessment of specific subfractions of HDL suggests different effects on the risk within circulating subforms [12]. There are diverse HDL particles circulating in the bloodstream, their density varying from 1.063-1.21 g/cm3. Apolipoproteins were shown to be involved in receptor recognition, structural stability, and enzyme activation.

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Apo A1 is an important, although not the only, apoprotein constituent of high-density apoprotein. Apo A1 was shown to induce efflux of cholesterol from peripheral depots into the circulatory system, followed by transfer to the liver for elimination [13]. Enzyme Lecithin Cholesterol Acy Ltransferase (LCAT) contributes to the cholesterol esters development in the vascular compartment and another factor for it is apo A1, which was also shown to have a stabilizing effect on prostacyclin. Prostacyclin is a vasodilator; it has a strong antiplatelet action and may potentially decrease the risk of occlusive intravascular thrombus formation [14]. HDL is also related to such apoproteins as apoC-II and apoC-III, which modulate lipoprotein lipase activity. Furthermore, there is a connection between apoE and mature subfractions of HDL, which provide recognition and removal from the plasma by the Lipoprotein of Low-Density (LDL) (Apo B/Apo E) receptor. Additionally, the HDL particle is linked with such enzyme systems as acetylhydrolase, a platelet-activating factor [15, 16]. Acetylhydrolase is the foundation of intravascular coagulation modulation and HDL cooperation with lipoprotein metabolism. The relative concentration of apoproteins, cholesterol, and enzymatic composition of HDL may differ in HDL particles, they also contribute to the classification and evaluation of the HDL subfraction's role in atheroprotection and risk assessment. We summarized the atheroprotective effects of HDL in Figure 1. The HDL's main role in atheroprotection is assumed to be mediated by the reverse transport of cholesterol. The two main sources of HDL circulating levels are primary synthesis in the ileum and liver along with interconnection in the plasma compartment with very low-density lipoproteins, chylomicrons, and other triglyceride-rich lipoproteins [17]. The resulting HDL are precursor particles that mainly consist of apo A1 and phospholipids. The nascent HDL synthesis exerts the ability to gradually store cholesterol and yields the original lipoprotein particle, which takes part in the HDL maturation cascade. The initial stage of reverse transport of cholesterol is the cholesterol accumulation by nascent HDL. Apo A1 enables the interaction of nascent HDL particles with lipid-rich foam cells as well as cholesterol extraction from intracellular stores [18]. However, the ways cholesterol is extracted from the monocyte-macrophage system are complex and include such processes as ATP binding cassette transporter A1 (ABCA1) interaction, the Scavenger Receptor class B type I (SR-B1) interaction, and passive diffusion. The gradual cholesterol accumulation in the HDL particle leads to a molecule configuration alteration to a more spherical shape. The subforms of HDL have been categorized according to their size and relative cholesterol concentration into several categories: Nascent, very high-density, HDL-3, HDL-2, and HDL-1. In plasma HDL-3 and HDL-2 are the main circulating subfractions [19]. Numerous methodological issues make it arduous to quantify the correlation between different HDL subfractions and the reduction of the risk. However, epidemiologic studies suggest that the risk of coronary artery disease is more associated with HDL-2 concentration than HDL-3 concentration. HDL-2 is richer in cholesterol and bigger in size, which suggests that higher concentrations show increased reversed cholesterol transport. However, as experimental studies have shown, HDL-3, which is small, dense, and rich in protein, might be more potent in protecting LDL from oxidative free radical injuries in the vascular wall [20].

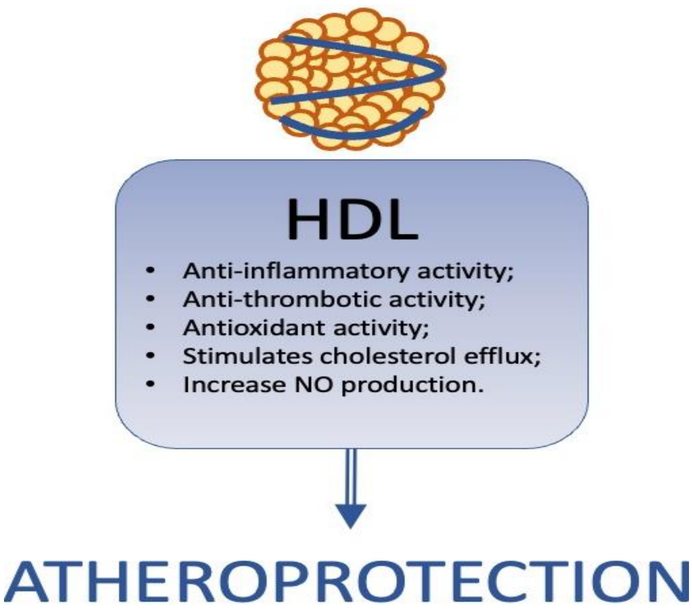

Fig. 1: Atheroprotective effects of HDL

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Transfer of cholesterol stored inside HDL to the liver ensures following release into the pool of bile acids and excretion from the body. Cholesterol delivery to the biliary system in the liver may be carried out by a double mechanism in the case of mature HDL. HDL particles are able to obtain apoE, which ensures the clearance of the particle from plasma after recognition and internalization by the apoB or apoE receptor. Another mechanism for receptor-mediated and metabolic utilization of cholesterol is ensured by the scavenger receptor B1, expressed by hepatic tissues [21]. There is a third mechanism for the HDL to work with lipoproteins comprising apoB, which are formed in the internal pathway of lipid metabolism, for example, Very Low-Density Lipoprotein (VLDL). Once removed from peripheral depots by HDL particles, cholesterol can be moved to the internal pathway using a cholesterol ester transfer protein [22]. That protein modulates the triglycerides and cholesterol equimolar movement between VLDL and HDL. Genetically mediated cholesterol ester transport protein deficiency leads to difficulties with cholesterol transport to particles containing apoB. That may result in higher levels of HDL cholesterol and a statistical connection with lower CVD risk [23].

The way that HDL cholesterol works with platelets and coagulation systems at numerous levels causes a decrease in the intravascular thrombus formation risk. Hypercoagulability was shown to be a new acute coronary syndrome risk factor. In subjects with ACS and vascular blockage risk platelet activation was indicated after the plaque rupture. Antiplatelet treatment is an important therapeutic step in reducing the risk after the acute coronary syndrome manifestation. Endothelial function is an important part of platelet function. It plays a key role in the balance between thrombosis and degradation [24]. Both coagulation and vascular tone depend to a great extent on the nitric oxide, a potent antiplatelet agent and vasodilator produced by the endothelium. Endothelial dysfunction is linked with multiple CVD factors, such as diabetes, obesity, dyslipidemia, smoking, and others. With these factors present the imbalanced processes of regulation of development and degradation of blood clots lead to a rise in the CVD risk [25]. The nitric oxide production mediated by the endothelium is controlled by the nitric oxide synthase. Its activation is mediated by numerous aspects such as the local HDL availability. The arginine catabolism to citrulline and nitric oxide is mediated by the activation of nitric oxide synthase. The antiplatelet and vasodilatory action was displayed as a result of HDL acting as a nitric oxide synthase agonist. The nitric oxide production by HDL was also shown to be an important part of the restoration of blood vessels by modulating the synthesis of endothelial progenitor cells [26]. Local prostacyclin is a substantial part of reendothelialization and angiogenesis. Its concentration controls the vasodilatory balance along with the endothelium. The human prostacyclin receptor and the HDL receptor (SR-B1) are linked through adapter proteins, which also may connect the prostacyclin and HDL reparative action. HDL concentration may partially regulate the coagulation protein balance. The essential capacity of the vascular system to control fibrinolytic and procoagulant parameters cooperation is complicated [27]. It depends on local concentrations of plasmin derived from plasminogen and plasminogen activator inhibitor-1. In patients showing symptoms of metabolic syndrome at an early age plasminogen activator inhibitor concentration and circulating HDL cholesterol levels were inversely related. HDL cholesterol concentration was statistically correlated with a relative enhancement in interactions of fibrinolysis markers and the concentration of natural inhibitors that link dyslipidemia and clotting disorders [28].

HDL-Cholesterol Levels (U or J Curve)

A number of studies show the reduction of the HDL-C protective action in such cases as individuals with Coronary Artery Bypass Graft (CABG) or coronary artery disease. Observational cohort studies provide limited information that suggests the plateau effect presence as well as higher cardiovascular risk and mortality in patients with exceedingly elevated concentrations of HDL-C. As displayed by Angeloni and colleagues, in individuals going through isolated primary elective coronary artery bypass surgery the preoperative concentration of HDL-C did not lead to a decrease of the CVD risk, on the contrary, it caused an increase in MACE appearance (HR, 1,43; p = 0,11) [29]. Thus, this emphasizes the necessity for interferences that enhance the beneficial effect of HDL-C rather than raise its concentration. Analysis of combined data from six populations demonstrated that coronary heart disease cases and HDL-C levels were inversely correlated and linear for men and women HDL-C values. However, in men with HDL-C concentration over ninety mg/dL and in women with HDL-C concentration over 75 mg/dL there was not revealed any additional CHD risk decrease. Furthermore, unadjusted models demonstrated a higher overall risk of mortality in males with extremely high HDL-C concentration, which decreased following the traditional risk factors adjustment [30]. Moreover, according to Li and colleagues’ study, an extremely high HDL-C level (>80 mg/dL) has been significantly interrelated to an elevated risk of mortality from any cause in patients under the age of 65 [31]. This connection did not depend on other CV factors in this study. In order to stratify the risk of death the authors propose taking into account the role of age in HDL-C levels, assuming that the rise of the HDL-C concentration does not necessarily lead to a favorable outcome. Another analysis of nine Japanese groups of people involved 43,407 patients from 40-89 years old, from which were formed five separate groups depending on their HDL-C concentrations. This study demonstrated that very high HDL cholesterol levels (≥2.33 mmol/L/≥90 mg/dL) raise the risk for ischemic stroke and CHD and the risk of CVD death (HR = 2.37; 95% CI, 1.37-4.09 for total) [32]. Among patients with very high levels of HDL cholesterol, the elevated risk was associated with ongoing alcohol consumption. Several studies revealed the possible presence of a U-curve linking HDL-cholesterol concentration and the risk of CV death and CVD. Thus, HDL-C appears to have both beneficial and adverse effects on atherosclerosis. Some studies yield evidence that lower HDL-C concentration causes endothelial injuries, as does exceedingly high levels of HDL-C. In addition, according to Takaeko and colleagues' study, in individuals not getting lipid-lowering treatment very high HDL-C concentrations were to a large extent related to the dysfunction of the endothelium after adjusting for covariates [33]. Another analysis of pooled data from 68 longitudinal prospective groups included more than 300 thousand individuals from all over the globe. This analysis proved the inverse linear relationship of HDL cholesterol levels and unfavorable CV events. Although, grouping on the basis of HDL cholesterol quintiles allowed to discover significant diminution of the inverse correlation of HDL cholesterol levels and unfavorable CV events in cases of the highest quintile [34]. Multi-Ethnic Study of Atherosclerosis (MESA) analysis shows signs of this kind of correlation as well, this study involved 5,5 thousand patients, both male and female, with low CVD risk [35]. Another study of HDL-C levels above 2,07 mmoL/L showed elevated CV risk in comparison to the HDL-C reference range (HR, 2.59; 95% CI, 1.11-6.02). That study revealed that SNP in SCARB1 is largely connected to higher risk of subclinical AS and myocardial infarction [36]. Moreover, CANHEART conducted research of more than 500 thousand patients without CVD, originating from Ontario, Canada. This study demonstrated a noticeable increase in overall mortality risk in men with more that 2,07 mmoL/L and less than 0,78 mmoL/L HDL-cholesterol concentrations, after adjustment for covariates, e.g., excessive alcohol consumption [37]. In comparison to the reference group (HDL-C, 41-50 mg/dL), males with lower HDL cholesterol level (≤30 mg/dL) had markedly increased cancer mortality (HR, 1.61, CI, 1.32-1.97), cardiovascular mortality (HR, 1.81; 95% CI, 1.45-2.25) and other mortality hazard ratio (HR 2.01, confidence interval 1.63-2.47).

This connection of extremely high levels of HDL cholesterol and enhanced risk of CVD was also indicated in the study of 2 general population groups the Copenhagen general population study and the Copenhagen City heart study. To get the information about more than 50 thousand men and 60 thousand women with low CVD risk, these two long-term separate groups were analyzed together and observed for 6 years. A significant U-curve shaped interdependence between all-cause death (male and female) and HDL cholesterol levels was discovered in this analysis as well [38]. In males and females with HDL-C levels above 2,51 mmoL/L the overall mortality risk was the clearest (HR 1.36; 95% CI, 1.09-1.70 and HR 1.68; 95% CI, 1.09-2.58 respectively) in comparison to the lower risk groups of patients. CV death was proved to make a U-shaped connection to HDL cholesterol levels in this analysis as well. The studies mentioned above involved predominantly individuals with lower CVD risk. Thereby, there is little information on patients with higher risk [39]. Van der Steeg and colleagues carried out an a posteriori analysis of two prospective researches [40] (Van Der Steeg et al., 2008). The first one-the IDEAL (Incremental Decrease in End Points through Aggressive Lipid Lowering) study [41]. Included around 9 thousand individuals, who had experienced CV events before. These individuals were randomly divided into two groups, to get high-intensity and medium-intensity statin treatment.

The IDEAL study revealed that high HDL-C levels (<1.04 and >2.07 mmoL/L vs the lowest risk HDL-C range, 1.55-1.80 mmoL/L) proved to be a significant risk factor for serious cardiac events, e.g., non-fatal myocardial infarction, reanimation after heart failure and coronary death, after correction for tobacco use, sex, age, apolipoproteinA-I and apolipoproteinB. In the EPIC-Norfolk study an analogous connection was observed in the case of HDL cholesterol particle size. 5965 patients have been studied, all of them either had coronary artery disease or had elevated CVD risk, including in the cardio-vascular biobank. Lately, preliminary information about those patients demonstrated a U-shaped correlation between HDL cholesterol and non-fatal myocardial infarction, cardiovascular death and overall mortality. In this analysis, risk for all-cause mortality, cardiovascular death and non-fatal myocardial infarction in patients with HDL-C level less than 30 mg/dL and higher or equal to 50 mg/dL was much higher (hazard ratio, 1.62; 95% confidence interval = 1.16-2.26, p = 0.005 and hazard ratio, 1.44; 95% confidence interval = 1.01-2.06, p = 0.04, respectively) corrected for race, gender, age, BMI, LDL cholesterol, triglycerides, hypertension, tobacco use, history of heart failure, diabetes, history of MI, angiotensin-converting enzyme inhibitors use, angiotensin II receptor blockers use, statins, aspirin, beta-blockers, obstructive CAD and estimated glomerular filtration rate. A combined analysis of 37 group studies, that included 3,524,505 patients and over 612,027 cases of death, estimated mortality risks and HDL-C concentrations. This analysis displayed J-shaped dose-response relationship between all-cause mortality, CVD, cancer and HDL cholesterol concentrations. Individuals with the concentration of HDL-C between 54 and 58 mg/dL, 68-71 mg/dL, 64 and 68 mg/dL had the lowest risk, respectively.

The combined HR for mortality of all causes was 1,03 (95% CI, 1.01, 1.05) and 1.10 (95% CI, 1.09, 1.12), respectively, for every 10-mg/dL rise and reduction in HDL-Cholesterol concentration, in comparison to 56 mg/dL concentration of HDL cholesterol [43]. Thereby, the study leads to a conclusion that concentration of HDL-C is connected to all-cause mortality, CVD and cancer in a J-shaped dose-response relationship. That indicated that exceedingly high as well as exceedingly low HDL cholesterol concentrations are associated with an increase of the mortality risk.

The results of the foregoing studies might be partially inaccurate due to additional impact of habits and demographics on the concentration of HDL cholesterol.

One of the reasons for the HDL cholesterol and cardiovascular risk U-shaped correlation might be gene mutations, which result in increased HDL-C level leading to higher cardiovascular risk. On the other hand, exceedingly high levels of HDL-C might I some cases indicate an HDL-C dysfunction, that could lead to an increased cardiovascular risk. Feng and colleagues assume that the U-shaped correlation of HDL cholesterol and CVD may be based on transport of free cholesterol to HDL cholesterol during lipolysis of triglyceride-rich lipoproteins by lipoprotein lipase [43].

Presently it appears that the functionality of HDL cholesterol and not its level could be causally associated with protection against atherosclerosis. HDL cholesterol has been established to be a compound of subfractions that vary in characteristics and composition and not a homogeneous group. In order to find the possible causative association of HDL cholesterol and CVD the researchers have turned their attention to the HDL cholesterol molecule/subspecies function. The HDL cholesterol beneficial action against atherosclerosis may be related to its numerous characteristics. As a means to understand the HDL cholesterol impact on evaluation of cardiovascular risks, academic interest should turn to the analysis of multiple subfractions of HDL cholesterol, their functioning and quality [44]. The TRIUMPH study [45] involved 2,465 individuals with acute MI, the IHCS study [46] involved 2,414 individuals that went through coronary angiography. A combined analysis of high-density-Lp cholesterol concentrations stratified into tertiles and the main subclasses HDL2-Cholesterol and HDL3-Cholesterol in those two complementary prospective groups showed an elevation of myocardial infarction and mortality risk by more than 50% in patients with decreased level of HDL3 cholesterol. Although, for HDL-C and HDL2-C there was not found any considerable connections. That, in turn, could mean that the HDL-C concentrations alone may not represent the HDL-C atheroprotective capacity correctly.

The HDL cholesterol functionality is harder to determine than its concentration. Definitely, the measuring of the HDL-C functionality provides a better prediction of cardiovascular risk in comparison to measurement of HDL-C levels. Presently, there are two major validated HDL-C functionality analyzes: CEC and the HDL-C inflammatory index [47]. The dynamic evaluation of the HDL cholesterol rapidity and ability to transfer the excess cholesterol from macrophages and other peripheral cells to the liver underlies the cholesterol efflux capacity analysis. HDL-C efflux mediated by scavenger receptor class B, type I, ABCG1 and possibly other structures may be induced by mature HDL cholesterol. Although, nitrosylation and oxidative modification of some remnants on arterial apoA1 and plasma could be induced by proinflammatory myeloperoxidase. In turn, that would result in HDL-C function impairment and an elevation of CV risk. This particular modification was proved to be connected to an increased CAD risk as it renders inflammatory pathways active and deteriorates ABCA1 macrophage transfer [48]. The detection of impaired CEC could indicate the HDL malfunction and the CVD risk may be increased in carriers of dysfunctional HDL cholesterol. In multiple pathological conditions the HDL cholesterol may get deprived of antioxidative and anti-inflammatory proteins and possibly obtain pro-inflammatory proteins, which would lead to its dysfunction. The HDL cholesterol beneficial protective characteristics to a great extent rely on the enzymes function, such as HDL-associated phospholipase A2 (HDL-LpPLA2) and paraoxonase-1 [49]. Moreover, in preclinical models HDL-associated S1P is thought to contribute to the HDL cholesterol protection on endothelial cells. Sattler and colleagues showed that it inversely correlates with the total severity of coronary artery disease and that its lower concentrations seem to be able to predict the degree of CAD [50]. They also made it possible to distinguish single-vessel from multi-vessel disease. Relative values of bound apoA1 and apoA4 also influence the HDL cholesterol functional characteristics. It has been presumed that the anti-inflammatory and antioxidant capacity of HDL-C rich in C3, SAA, and other pro-inflammatory proteins might be impaired. Soria-Florido and colleagues revealed that lowered concentrations of apoA1 and S1P in apoB-depleted plasma as well as decreased CEC indicate HDL cholesterol dysfunction, which in turn leads to an elevation of acute coronary syndrome risk regardless of common risk factors and levels of HDL cholesterol [51]. The negative correlation between unfavorable CV events and cholesterol efflux capacity was proved by numerous studies, which also displayed that this criterion is a better marker for unfavorable CV events than the HDL-C concentration measurement.

Another HDL cholesterol functional evaluation is its inflammatory index, which is a measurement of the low-density-Lp-mediated MCA and the extent of oxidation of LDL by a Cell-Free Assay (CFA). The anti-inflammatory and anti-oxidant characteristics of HDL cholesterol particles decrease CFA and MCA levels (<1.0) in comparison to control LDL whereas the reverse HDL cholesterol characteristics increase these figures (>1.0) [52]. Ansell and colleagues conducted a study proposing that MCA and CFA figures are not influenced by HDL-C concentrations. The MCA and CFA levels were significantly raised in individuals who had had incident coronary heart disease, while the HDL-C concentration was within normal limits in comparison to a control group. Furthermore, this rise was also found in patients with extremely high HDL-C levels (>2.18), which suggests the presence of HDL cholesterol dysfunctional state in individuals with confirmed CVD [53].

HDL-C Raising Strategies: Therapeutics to Stimulate Reverse Cholesterol Transport by HDL

Treatment strategies for elevating the concentration of HDL involve CETP inhibitors, niacin (vitamin B3, nicotinic acid), and recombinant HDL strategies. In the past niacin has been typically used to elevate HDL concentration by 15-25%. Niacin inhibits the β-chain of ATP synthase (ATPase-B1), which is able to endocytose HDL in hepatic cells via apoA1 recognition. The wide application of niacin was associated with some clinical trials, which showed that niacin therapy was connected to CIMT stabilization and reduction and had a positive effect on CVD risk [54].

However, it was afterward refuted by the two randomized double-blind multicenter studies: HPS2-THRIVE (second heart protection study treatment of HDL to reduce the incidence of vascular events) [55] and AIM-HIGH (Atherothrombosis intervention in metabolic syndrome with low HDL/High triglycerides: Impact on global health outcomes) [56]. These studies did not indicate any decrease in CVD risk with niacin during statin treatment. On the contrary, niacin was correlated with an elevated CV events risk and consequently was later withdrawn in 2013 by the EMA.

Numerous inhibitors of CETP, that mediated the cholesterol esters transport from HDL to lipoproteins comprising apoB (VLDL, LDL) and acquirement of triglycerides and the beneficial effects of their HDL-C increasing function were also explored in different studies. However, no sign of CVD risk reduction was indicated in these studies. The ILLUMINATE study [57] was canceled early on the grounds of torcetrapib toxicity and off-target effects. Due to the absence of any clinical positive effect of evacetrapib and dalcetrapib, the accelerated study (assessment of clinical effects of cholesteryl ester transfer protein inhibition with evacetrapib in patients at high risk for vascular outcomes) [58] and the dal-OUTCOMES study (Study of RO4607381 in stable coronary heart disease patients with recent acute coronary syndrome) [59], respectively, were also stopped early. Notwithstanding a decrease in the frequency of serious CV events that was shown in the reveal study (randomized evaluation of the effects of anacetrapib through lipid modification) [60] the anacetrapib development was canceled due to its very little positive effect on CV events.

Moreover, infusion of HDL and ApoA1 mimetics, enhanced synthesis of apoA1 by small molecules, and other strategies of direct HDL modulation are presently being researched [61]. However, early clinical results showed almost no significant clinical benefit. Overall, the theory that improved HDL function might matter more than the concentration of HDL cholesterol is confirmed by the neutral impact of HDL-C increasing treatment on CV outcome. At present, HDL-C should be used as a CVD risk marker rather than as a therapeutic target.

Conclusion

Views on the causes and starting mechanisms of atherosclerosis have changed as the number of studies devoted to this issue has increased. One of the fundamentals for a long time was the concept of cholesterol, proposed about a hundred years ago by Nikolai Anichkov. However, with the accumulation of knowledge, it became obvious that one elevated cholesterol content in the blood is not enough for the development of atherosclerosis. This concept was replaced by the idea of impaired lipid metabolism and damage to the endothelium. Different types of lipids also have different properties and affect atherogenesis in different ways. HDLs have demonstrated atheroprotective properties in a wide variety of studies and have become one of the targets for the development of potential therapeutic agents.

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Author’s Contributions

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Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and that no ethical issues are involved.

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