The Way of Cholesterol in Atherogenesis: from the Main Enemy to Complex Biomarkers

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Abstract

Since the advent of the cholesterol hypothesis of atherosclerosis, cholesterol has been perceived by the world community as a great evil. However, normally cholesterol is an important component of the plasma membrane, as well as a participant in the signaling of bile acids, steroid hormones and vitamin D synthesis, and its deficiency has negative consequences. There is a much wider understanding of the negative effects of excess cholesterol. The pathogenesis of atherosclerosis, and hence all its negative consequences, such as myocardial infarction, Peripheral artery disease, stroke, etc., is inextricably linked with cholesterol. However, it is no longer entirely correct to perceive cholesterol as an unambiguous evil. So, for example, the indicator "total cholesterol" does not have the clinical significance that has been attributed to it for decades. Today we have a challenge to measure cholesterol and assess its pathogenicity. In this review, we collected data on current approaches to measuring cholesterol in the context of its relationship with atherosclerosis.

Keywords: atherosclerosis; CVD; cholesterol; lipid; LDL

Significance | Cholesterol plays various roles in atherosclerosis - from the trigger to the biomarker

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Introduction

Atherosclerotic CVD is the prime reason for disability and mortality in the world. Atherosclerosis manifestation and development are consistently associated with such lipoproteins as apoB, low density Lp, very low density Lp, intermediate density Lp and Lp(a) (Makover et al., 2022). Apolipoproteins B, rich in cholesterol, are stored in the intima of the arterial wall vessels during the process of atherogenesis and then form an atherosclerotic plaque under influence of inflammatory and immune mechanisms (Linton et al., 2019).

Numerous studies have demonstrated a connection between CVD occurrence and the LDL levels in plasma (Barona and Fernandez, 2012; Fernandez et al., 2013). Atherosclerosis risk correlates with levels of apoB and especially LDL. Multiple trials clearly demonstrate the ability of lipid-lowering treatments to decrease morbidity and deaths considerably in individuals with coronary heart disease and without it via lowering the LDL cholesterol levels. Also, high survival rates were observed in recent trials of secondary prevention through aggressive decrease of LDL cholesterol concentrations in plasma (Jacobson, 2011). Although, even with LDL decrease after statin and other lipid-lowering therapies there are still CVD events occurring. The reason of that might be triglyceride or the cholesterol inside the Lp rich in triglycerides. After statin therapy the atherosclerosis risk was higher in individuals with excessive concentrations of triglycerides

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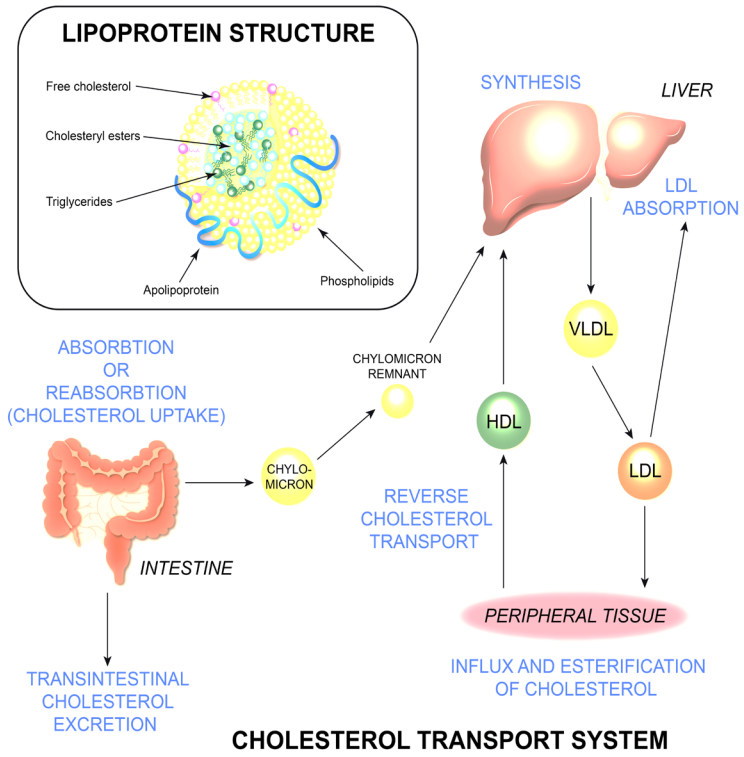

Figure 1. Schematic illustrarion of cholesterol transport system.

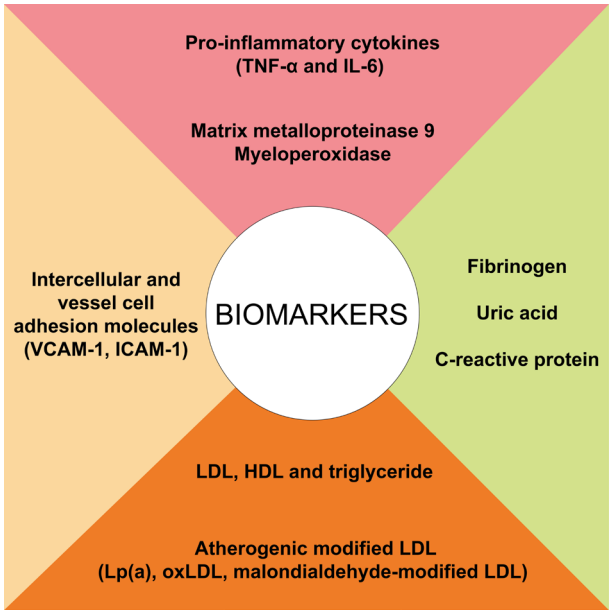

Figure 2. Biomarkers for pathophysiological and clinical implications of atherosclerosis.

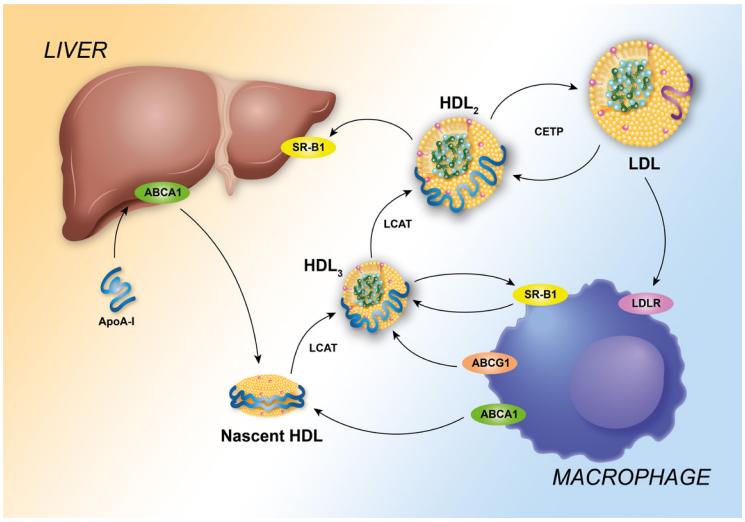

Figure 3. Schematic illustration of reverse cholesterol transport (RCT). RCT involves a series of steps. ApoA-I interacts with ABCA1, leading to the release of free cholesterol and phospholipids. This process results in the formation of nascent HDL. Simultaneously, free cholesterol is transferred from macrophages to HDL through the involvement of ABCG1. Nascent HDL undergoes modifications by plasma factors such as LCAT, lipid transfer proteins, and lipolytic enzymes. These modifications transform nascent HDL into HDL_3. HDL_3 further matures into HDL_2, which becomes enriched with cholesteryl esters due to the activity of LCAT. This enrichment helps prevent the reverse transfer of free cholesterol back to macrophages. SR-B1 selectively extracts lipids, including free cholesterol, cholesteryl ester, and phospholipids, from HDL. The extracted lipids are then processed within the liver. Abbreviations: ABCA1: ATP-binding cassette protein A1, ABCG1: ATP-binding cassette protein G1, ApoA-I: Apolipoprotein A-I, CETP: cholesteryl ester transfer protein, HDL: high-density lipoprotein, SR-B1: scavenger receptor class B member 1, LCAT: lecithin–cholesterol acyltransferase, LDLR: low density lipoprotein receptor.

(Sampson et al., 2012). Furthermore, the REDUCE-IT (Pradhan et al., 2020) study recently discovered that in the individuals with high triglyceride concentrations after statin treatment the CVD risk may be decreased to an important degree by icosapent ethyl, a highly purified ethyl ester of eicosapentaenoic acid.

In accordance with the worldwide dyslipidemia guidelines, LDL cholesterol is the major therapeutic target in primary and secondary atherosclerosis prevention, for it is a proven risk factor for atherosclerotic CVD (Bartlomiejczyk et al., 2019). In several guidelines, apolipoprotein B, a measure of the amount of atherogenic Lp particles, and non-HDL cholesterol, a measure of cholesterol concentration in a broader range of atherogenic apolipoprotein B, were indicated as secondary targets. Lipid-lowering treatment may be enhanced by their elevation (Behbodikhah et al., 2021).

Whereas in most cases there is a strong correlation between apoB, non-HDL and LDL cholesterol, in patients with mild to moderate hypertriglyceridemia, obesity, metabolic syndrome, diabetes and other related conditions, there may be a discrepancy among those measures (Lim et al., 2015). Lately the Australian guidelines for harmonized lipid reporting advised to report of non-HDL in standard lipid profile. These guidelines along with previous findings emphasize the importance of these markers in the evaluation of atherosclerotic CV risk (Blaha et al., 2008).

Cholesterol

Cholesterol is an important plasma membrane constituent. It controls fluidity and permeability, assembles various signaling molecules creating "lipid rafts" and maintains a cell barrier, in mammalian body it also acts as substrate for bile acids, steroid hormones and vitamin D synthesis (Cockcroft, 2021). A cholesterol deficiency has a negative impact on tissue formation, cell functionality and physiology of the whole organism, but elevated cholesterol and hypercholesterolemia lead to pathological conditions. Peripheral artery disease, stroke, myocardial infarction and many other CV diseased emerge due to atherosclerosis (Zaric et al., 2020). Atherosclerotic plaque development is a chronic process during which cholesterol is deposited superfluously in the intima of the arteries. Studies in animals and clinical trials demonstrated that cholesterol concentrations in plasma and the CV events are correlated (Lee et al., 2017).

In mammalian body cholesterol homeostasis is maintained by systemic and cellular mechanisms that arose as a result of evolution. Glomset and colleagues (Glomset et al., 1975) were the first to describe reverse cholesterol transport (RCT). It is a mechanism of transporting peripheral cholesterol to the liver by the HDL and a crucial part of HDL atheroprotective function. Although, in murine model knockout of apoA1, ABCA1 or LCAT did not show any impact on the content of neutral sterols in feces, even though HDL cholesterol concentrations were significantly reduced (Rosenson et al., 2012). Thus, it may be concluded that there is some other way of removing cholesterol from the organism, independent of the HDL. Reverse cholesterol transport carries out just a part of the transport and metabolism of cholesterol. General cholesterol homeostasis also includes such important processes as influx of modified lipoproteins into peripheral cells, absorption of cholesterol in the intestines and absorption of LDL particles by the liver (Temel and Brown, 2015). At present, there is no known model that could provide a description of the mechanism from the uptake of cholesterol in the intestine to the excretion in the feces. Thereby, a working model was suggested called CTS – cholesterol transport system, which involves the RCT as well as hepatic LDL absorption, intestine cholesterol uptake, transintestinal cholesterol excretion (TICE), and influx and esterification of cholesterol into peripheral cells (Temel and Brown, 2012). In Figure 1, we summarized the current understanding of cholesterol transport within the body. Extensive research indicated that the CTS regulation impairment is the main reason for atherosclerosis and hypercholesterolemia. There are multiple drugs being developed, that target the cholesterol transport system. Several of those drugs have already demonstrated the prospect of reducing the CV events in individuals with CV disease (Mahdy et al., 2012).

Cholesterol-associated risk is usually linked to individual lipid parameters, such as LDL cholesterol, non-HDL cholesterol and total cholesterol. The 2018 American Heart Association / American College of Cardiology / Multi-Society Guidelines (Powers et al., 2019) advise to use the Pooled Cohort Equations (PCE) in order to evaluate atherosclerotic CVD risk in non-diabetic patients from 40 to 75 years old with LDL cholesterol level 1.81–4.89 mmol/L. To further specificate the risk it may be useful to take into account coronary artery calcium (CAC) level and "risk enhancing factors". International Atherosclerosis Society, National Lipid Association, and European Society of Cardiology/ European Atherosclerosis Society (Visseren et al., 2021) take another approach and recommend specific non-HDL cholesterol and LDL cholesterol targets adapted to the category of risk. Nevertheless, cholesterol-associated risk is complicated and includes the interaction of multiple factors, among them are Lp rich in triglycerides, levels of cholesterol particles, and RCT.

A number of studies indicate that total cholesterol to HDL cholesterol ratio is a powerful CV risk marker. The TC/HDL-C ratio may be easily gathered from the standard lipid profile and it largely correlates with LDL-P amount, while the discrepancy between the TC/HDL-C ratio and non-HDL cholesterol or LDL cholesterol occurs in 1.3 m people (Quispe et al., 2020). In secondary prevention major adverse CV event (MACE) occurrence and atheroma development were reclassified by TC/HDL-C ratio when discrepant with apolipoprotein B, LDL

cholesterol, and non-HDL cholesterol (Bezafibrate Infarction Prevention (BIP) study, 2020). Whereas in the 2018 AHA/ACC/Multi-Society Cholesterol Guidelines (Stone and Grundy, 2019) apolipoprotein B is indicated as a "risk enhancing factor", the total cholesterol to HDL-C ratio is not. Although, TC/HDL cholesterol ratio may be figured simply from the standard lipid profile.

Biomarkers—Pathophysiological and Clinical Implications—An Arch in Time

The term of biomarker was first suggested in 1980, it is a biological measure designed to evaluate various indicators of responses to treatment and normal and pathological processes (Strimbu and Tavel, 2010). Perfect properties of a biomarker would be a possibility of easy clinical use, high repeatability and responsiveness. LDL, HDL and triglyceride biomarkers proved to be helpful only in individuals with high CV risk. It was afterwards revealed that different stages of atherosclerosis are associated with different particular molecules (Sweeney et al., 2021). During the process of atherosclerosis several biomarkers are used, such as adhesion molecules of intercellular and vessel cells, interleukin 6, matrix metalloproteinase 9 and myeloperoxidase. Two pro-inflammatory cytokines TNF-α and interleukin 6 correlate with an elevation of CVD and AS lesion development. Higher interleukin 6 concentrations in serum correlate with higher frequency of failure of invasive revascularization in individuals with T2DM (Hong et al., 2021). The oxidation of LDL (oxLDL) includes myeloperoxidase. Antiviral and antibacterial activities are mediated by myeloperoxidase along with inflammation and destabilization of AS plaques, from which it may be concluded that PVD etiology had various factors. Vascular cell adhesion protein 1 and intercellular adhesion molecule 1 are found in high amounts in atherosclerotic-prone vessels, which indicates subclinical lesions (El-Hajjar et al., 2022). There are several CV risk biomarkers or factors with diverse applications such as Lp(a), fibrinogen, uric acid and CRP. A number of researches have studied the malondialdehyde-modified LDL-C application as an atherosclerotic biomarker. The formation of organic free radicals and the active oxygen species lead to an elevation of blood concentrations of oxidized malondialdehyde-modified LDL (Adam et al., 2022). Viigimaa and colleagues (Viigimaa et al., 2010) have reported that malondialdehyde-modified LDL is correlated directly to postinfarction cardiosclerosis ($p < 0.05$), and thus may be applied as independent atherosclerosis biomarker. Alghazeer and colleagues (Alghazeer et al., 2020) also emphasize the possible malondialdehyde role in the AS plaque development. They have revealed that concentrations of malondialdehyde represent an elevation of oxygen free radicals' generation, and the atherogenic index is related to malondialdehyde as well. In individuals with dyslipidemia the antioxidant balancing is required as the oxidative stress is a major atherosclerosis risk factor. In Figure 2, we provided the summary of biomarkers described in this section.

Cholesterol as a clinical measurement challenge

The measuring of circulating cholesterol is now a standard clinical test due to its benefits in clinical medicine. Before now, TC has been the standard measured lipid and was indicated as such in the Framingham Heart study conducted in 1948. Afterwards it was discovered that different Lp kinds do not correlate with the CV risk equally. While HDL generally has positive effect, LDL effect is usually harmful. Measurement of LDL cholesterol became a standard procedure with the introduction of randomized clinical trials of cholesterol-lowering treatments (Hajar, 2017). Lately it has been revealed that dependence on levels of LDL-C alone leads to omission of triglycerides, Lp(a), oxidized LDL and other important cholesterol particles that may induce AS risk (Yanai et al., 2022). Suchwise the importance of measuring non-HDL-C has been accentuated by its supporters. Many of the comparative researches of LDL-C and non-HDL-C indicated the outperforming predictive results for the latter, however not all of them. It was lately discovered that smaller cholesterol particles demonstrate more atherogenic effect than bigger ones, and thereby the particles number and size are essential for risk assessment (Guo et al., 2021). In terms of AS risk prediction, the LDL amounts and apoB concentrations are more important than concentrations of LDL and non-HDL-C if the discordant assay is applied. Apolipoprotein B levels come in very useful in CV risk evaluation as their number of molecules exactly matches the amount of LDL particles (Behbodikhah et al., 2021).

An elevation of cholesterol in diet leads to a mild elevation of HDL-C, it is yet to investigate if this is a positive or negative effect. While HDL contributes greatly to cholesterol removal from AS lesions, its high plasma levels does not guarantee an improved cholesterol removal function. Late trials have proposed that HDL risk predictive ability may be better assessed by direct measurement of cholesterol efflux by HDL (Hill and Bordoni, 2023).

Non-HDL-C measuring tests proved to be superior to those of LDL, furthermore, at present the measuring of the apoB or LDL particle amount might be the most efficient way to evaluate CVD risk. The importance of HDL-C levels measurement in a particular patient to evaluate CVD risk is still to be discovered (Aggarwal et al., 2021).

Does high TC cause atherosclerosis?

No association between TC and degree of atherosclerosis

When we assume that elevated total cholesterol leads to AS, we may infer those individuals with elevated total cholesterol ought to have more AS compared to those with lower total cholesterol (Tharu and Tsokos, 2017). It was revealed in 1936 by Landé and

Sperry (Lande and Sperry, 1936) that, adjusted for age, patients with lower total cholesterol concentrations had the same degree of AS as those with higher concentrations, and these revelations were reaffirmed repeatedly afterwards in different researches. Several studies indicated a mild connection between AS and total cholesterol level. Although, these researchers conducted their studies in hospitalized individuals and there might have been people with familial hypercholesterolemia among them. This would mean that the bias occurred, since the proportion of patients with DH is higher in a cardiovascular hospital then among the population in general (Masana et al., 2019). In the research of Solberg and colleagues (Solberg and Strong, 1983) such connection between total cholesterol and AS was lost after the patients with total cholesterol over 350 mg/l (9 mmol/l) were withdrawn from the study.

No exposure-response

If excessive total cholesterol was the main reason for AS development, there would be observed exposure-response in cholesterol-lowering treatment studies. For instance, the most positive effect should be indicated in the arteries of patients whose lipid levels were decreased the most. Nevertheless, 16 angiographic studies of cholesterol-lowering therapies demonstrated no such correlation except for one trial, where exercise was the only therapeutic approach (Feingold et al., 1981).

Does high LDL-C cause atherosclerosis?

An idea based on selected patient groups

Assuming that LDL cholesterol is atherosclerosis-promoting, individuals with increased LDL cholesterol levels ought to have higher degree of AS then those with lower levels. More than 4 trials failed to discover a correlation between LDL cholesterol and AS, as well as there was no connection of LDL cholesterol and CAC observed in research of 304 females, except for one trial in 1779 healthy people with no traditional cardiovascular risk (Navarese et al., 2018). In this trial the researchers discovered that individuals with subclinical AS showed much higher levels of LDL cholesterol (125.7 versus 117.4 mg/dl). Although, correlation does not necessarily imply causation. For example, cholesterol concentration may be increased by 10-50% as a result of psychological stress within 30 minutes. Psychological stress may also promote AS through other ways, e.g., enhanced aggregation of platelets and arterial hypertension (Assadi, 2017).

Inverse association of HDL cholesterol and ASCVD

A causal association of lower HDL-C levels with higher AS cardiovascular risk is still disproven by summary data of genomic consortiums and individual-level MR, as well as by extended researches of candidate genes of isolated HDL-C phenotypes and by the results of multiple clinical trials (Boes et al., 2009). Since all of these data indicate the lack of causality, then how can be the phenomenon of the obvious negative correlation of atherosclerotic CVD risk and HDL-C concentrations explained? There is a possibility that HDL-C concentration is also negatively correlated to the triglyceride concentration, and that would be a marker of Lp rich in triglycerides present. These lipoproteins are also named remnant lipoproteins and they along with Lp(a) and LDL-C form the lipoproteins containing apolipoprotein B, which is atherosclerosis-promoting (Sandesara et al., 2019). Remnant lipoproteins in fact do have a causal connection to the atherosclerotic cardiovascular disease because they contain cholesterol, which was indicated in many researches of big populations. LDL and the remnant Lp both are able to penetrate the artery wall. And the remnant lipoproteins can be retained in the intima, because the fractional loss from the intima and diameter of macromolecules are negatively correlated (Si et al., 2022). Thereby, decreased HDL-C concentration can be considered as a strong marker for remnant Lp and triglycerides elevated concentration, since it, unlike triglycerides, does not depend on the diet. The same has been reported for glucose and hemoglobin A1c. MR and GWAS researches showed that Lp rich in triglycerides might in fact cause atherosclerosis, although clinical trial failed to find that connection (Qi and Qi, 2012). There were recently introduced several more candidate biomarkers which could shed light on the negative correlation of HDL levels and the atherosclerotic CV risk. Certain HDL subtypes based on protein and carrying apolipoprotein C3 can be of interest. The HDL is believed to have atheroprotective features implemented through antioxidative, anti-inflammatory and antidiabetic activity and cholesterol efflux. Some structural trials have described a model of human lipid-free apolipoprotein A1 monomer. At present such a model provides an opportunity for discovering and analyzing the properties of the HDL functionality, structure and synthesis. This sort of research could result in a better knowledge of the HDL-C levels and CV risk negative correlation (Sacks and Jensen, 2018).

Reverse cholesterol transport, cholesterol efflux, HDL cholesterol concentrations and ASCVD

Glomset and colleagues suggested the RCT theory in 1968 (Glomset et al., 1975). It is a mechanism of cholesterol transfer from the tissues to the liver and bile through the HDL. They thereafter reported that there is a connection between AS and defective RCT and that the RCT efficiency is represented in the HDL-C levels. Miller and colleagues assumed that HDL-C has anti-atherogenic properties, since its levels was lower in atherosclerotic individuals compared to a healthy group, although the HDL deficit and AS risk connection is still not proven, and a negative correlation of remnant Lp and HDL-C has been established (Rader et al., 2009; Yazdanyar et al., 2011).

We depicted the scheme of RCT in Figure 3. The initial stage of the RCT is cholesterol efflux from cells. Transporter ABCA1 binds

to the apolipoprotein A1 and thereby stimulates the development of nascent HDL, which matures and acquires a spherical shape under the influence of lecithin-cholesterol acyltransferase. It is debatable whether TC efflux has a protective action against AS. If reduced TC efflux leads to AS development, it has to represent the cholesterol efflux from macrophages, which are the cause of the AS lesion (Chen et al., 2022). In murine model 30% and 70% of the HDL-C biogenesis are associated with ABCA1-controlled cholesterol efflux from intestines and liver. Therefore, the cholesterol efflux from macrophages may account only for a small portion of levels of HDL-C and HDL biogenesis. Studies from 2008 demonstrated that TC efflux does not lead to higher AS risk. These studies included unselected patients with ABCA1 mutations causing low CEC and with and isolated low HDL and apolipoprotein A1 levels (Chung et al., 2011). The results of the studies indicated that the patients did not have elevated atherosclerotic CV risk, which has been afterwards supported by the Copenhagen studies and by Karjalainen and colleagues (Karjalainen et al., 2015). The latter studied cholesterol efflux from two different angles, analyzing non-pleiotropic single nucleotide polymorphisms in apolipoprotein A1, performing as plasmatic acceptor, and in ABCA1, performing as the cholesterol transporter from cells to apolipoprotein A1.

Whereas HDL-C level is not possibly a good indicator of macrophages-mediated CEC, another method of CEC analysis was introduced by Khera and colleagues (Khera et al., 2011; Rosenson et al., 2012). It involves a measurement of whole-body efflux from macrophages mediated by ABCG1, ABCA1, scavenger receptor B1 and water diffusion and is meant to evaluate the cholesterol efflux fraction more accurately. This research described the CEC as a potent predictor of the thickness of the carotid intima as well as HDL-C- and apoA1-independent atherosclerotic cardiovascular disease. There is such area of concern as the adaptation for phenotypes that are strongly correlated, as it was described above, when CEC is corrected for apoA1 and HDL levels. In each case there are difficulties with defining a correlated covariate as independent, as the confounding in non-genetic researches is unpreventable. Nearly 40% of the changes of HDL-C levels are accounted for by CEC, and because of this big explanatory portion of the HDL-C levels, the said CEC assay might not accurately reflect the actual efflux. A study conducted lately by Shea et al. (Shea et al., 2019) introduced another method of evaluating the variation in the cholesterol concentrations in cultured macrophages – cholesterol mass efflux capacity. Further they found the same negative correlation of this indicator and atherosclerotic CVD. Although, it is yet to investigate if those assays are correctly reflecting the efflux from macrophages. Since these researches were observational, unlike genetic and randomized clinical trials, they may not be able to provide evidence of causal conjunction. Taken together, data obtained during large-scale genetic studies of TC efflux and infusions of apoA1 and HDL mimetics in an attempt to induce cholesterol efflux do not confirm the hypothesis of a causal relationship between ASCVD and TC efflux. To establish if the cholesterol efflux from macrophages has in fact atheroprotective properties, in-vivo human trials will be required (Ganjali et al., 2021).

Currently the HDL-C level is unsuitable as a therapeutic goal, as it is long established that the negative correlation of AS and HDL-C levels is not necessarily a causal one. Although, reduced levels of HDL-C are still considered an important AS risk marker, as it indicated remnant Lp and elevated triglycerides. The European Society of Cardiology/European Society of Atherosclerosis Society in 2019 advised against interpreting increased HDL-C levels as a marker of low risk of AS, since it has been reported that excessive HDL-C might not lead to positive consequences (Kronenberg, 2018).

While decreased HDL-C levels do not necessarily make a suitable target, a number of observational researches emphasize that HDL-C could be associated with some serious disorders besides the CVD, such as dementia, lung disease, kidney disease, T2DM, cancer, AMD, autoimmune disease, infections, and mortality. It has been reported that for AMD, T2DM and kidney disease this connection might be in fact causal (Cho et al., 2020). Lately GWAS research and candidate gene researches indicated HDL-C associated genes in AD. It is yet to investigate if those new findings indicate an actual HDL-C participation in the pathological process or only a reflection of local transport mechanisms and an effect of the HDL-C structure and size (Kjeldsen et al., 2021).

TC/HDL-C ratio discordance with LDL-C and non-HDL-C

Various researches of population level have demonstrated that total cholesterol / HDL cholesterol ration is a powerful CVD marker, since its constituent elements are a part of widely used risk assessments (Upadhyay, 2015). It has been reported that back-integration of HDL cholesterol with total cholesterol in the ratio may be a marker of discrepancy between the size/amount of Lp particles and cholesterol in case of IR, obesity and other disorders that involve increased triglyceride-rich lipoproteins and decreased HDL cholesterol concentrations (Nikolic et al., 2013).

Discrepancy is pretty new and original manner of epidemiological assay which may be useful in terms of more accurate evaluation of a particular lipid score ability to predict additional risk. Thereby, for patients whose total cholesterol / HDL cholesterol parameters are discrepant with non-HDL cholesterol, LDL cholesterol and other parameters, the possible clinical benefit of total cholesterol / HDL cholesterol is most clear (Nigam, 2011).

Whereas discrepancy between apolipoprotein B, LDL particles and non-HDL cholesterol versus LDL cholesterol has been well studies, there is still little data on the discrepancy of TC/HDL cholesterol

with other lipid parameters. Research which included a modern database of over 1.3m American adults demonstrated a significant discrepancy between TC/HDL cholesterol versus LDL cholesterol and non-HDL cholesterol (Martin et al., 2009). TC/HDL cholesterol parameter in individuals with LDL cholesterol less than 1.8 mmol/L was above the population percentile equivalent TC/HDL cholesterol of 2.6 in 58% of cases (Quispe et al., 2020). The discrepancy was more apparent in individuals with increased triglycerides and reduced HDL cholesterol concentrations, which is typical for IR, in individuals with metabolic syndrome, DM and higher levels of LDL and cholesterol-poor apolipoprotein B particles. Consequent observation of individuals with CAD demonstrated that TC/HDL cholesterol reclassified the development of atherosclerosis and major adverse CV events rate at two years in case of discrepancy with non-HDL cholesterol, LDL cholesterol and apolipoprotein B as well (Wilkins et al., 2016). Among individuals whose apolipoprotein B level was less than 59 mg/dL those with above or equal percentile equivalent TC/HDL cholesterol of 2.5 showed more developed AS and higher major adverse CV event rate than patients with TC/HDL cholesterol less than 2.5. It was also reported that most of the patients with high and moderate CV risk who have reached non-HDL cholesterol goals will need aggressive therapy in order to achieve expected TC/HDL cholesterol goals. Although, currently there is no available information on evaluation of the effect of TC/HDL cholesterol discrepancy with other lipid parameters in a primary prevention group, e.g. the Atherosclerosis Risk in Communities Study (Jung et al., 2021).

The TC/HDL cholesterol ratio being applied for the risk evaluation alone might not give any additional benefit, as both total cholesterol and HDL cholesterol are included in PCE. Although, it could be of interest as a secondary therapeutic target aside from non-HDL cholesterol and LDL cholesterol. Even more so in case of diabetes and other conditions when the discrepancy is frequent and the lipid-lowering therapy is advised. We assume that application of TC/HDL cholesterol ratio as a lipid target along with LDL cholesterol and non-HDL cholesterol in order to promote statin treatment may lead to positive results in individuals with decreased HDL cholesterol and high CV risk, e.g., patients with metabolic syndrome, DM or obesity (Calling et al., 2021). It has also been reported that a TC/HDL cholesterol target of 3 is able to accurately detect patients who meet the secondary prevention target level of LDL particles for secondary prevention (less than 1000 nmol/L). Nevertheless, a more effective strategy might be to aim at secondary TC/HDL cholesterol targets of percentile equivalence to non-HDL cholesterol targets, as it is applicable for multiple levels of CV risk. Choosing TC/HDL-C as a target would require aggressive non-HDL cholesterol lowering therapy in those with decreased HDL-cholesterol concentrations, since it was proven that HDL cholesterol increase does not lead to any positive effect. This therapeutic approach requires continued examination in randomized clinical trials (Mathews et al., 2012).

Conclusion

In the process of working on this review, we analyzed a significant number of studies and reviews of different years, which clearly show a change in ideas about the role of cholesterol in the pathogenesis and determination of the risks of atherosclerosis. So, the starting point was the view of cholesterol as an "absolute evil", which is still common among the townsfolk. However, the scientific community today takes a different view. Currently, various indices are used to assess CVD risks, which better reflect the complexity of the pathogenesis of atherosclerosis, which includes both an inflammatory component and lipid metabolism disorders. To date, it is known that elevated "total cholesterol" in itself is not a factor in increased cardiovascular risk. The ratios HDL-C to LDL-c and TC to HDL-C are promising today. However, the question of the representativeness of these indicators is still not fully resolved.

Author Contributions

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