Review Article

Interventional Cardiology

Lowering LDL-C: What it means for atherosclerosis and how low to go

Abstract

Atherosclerosis worries scientists and doctors around the world. Being poorly diagnosed, this disease leads to severe consequences, including disability and death. Throughout history, our understanding of the cause-and-effect relationship between cholesterol levels and atherosclerosis has evolved, and more and more groups of lipids have entered the scene. So, for example, for a long time there was a "cholesterol hypothesis of atherosclerosis", which today has lost its position. Today it is known that "total cholesterol" is not a clear indicator of the disease, but the controversy continues around LDL-related cholesterol. It is considered to be "bad", atherogenic cholesterol. Indeed, its high levels are associated with cardiovascular risks. In our review, we collected data on LDL-C, its significance in atherosclerosis, and strategies to reduce it, with a particular focus on reducing the risks of ASCVD.

Keywords: Cholesterol • Atherosclerosis • Cardiovascular disease • Lipoproteins

Abbreviations: LDL: Low-Density Lipoprotein; LDL-C: Low-Density Lipoprotein Cholesterol; LDLR: Low-Density Lipoprotein Receptor; PCSK9: Proprotein Convertase Subtilisin/Kexin type 9; CAD: Coronary Artery Disease; CHD: Coronary Heart Disease; FH: Familial Hypercholesterolemia; ASCVD: Atherosclerotic Cardiovascular Disease; MI: Myocardial Infarction; hsCRP: high-sensitivity C-Reactive Protein; HMG-CoA-3: Hydroxy-3-Methylglutaryl Coenzyme A; ESC/EAS: European Society of Cardiology/European Atherosclerosis Society; HDL: High-Density Lipoprotein; HDL-C: High-Density Lipoprotein Cholesterol; ApoB: Apolipoprotein B; CVD: Cardiovascular Disease; SMC: Smooth Muscle Cell

Introduction

Often, when using terms such as LDL, cholesterol and LDL-C, people make mistakes. They can be used by replacing one with another, resulting in confusion. Cholesterol is a significant component of cell membranes. It is also a precursor of steroid hormones and bile acids. It is also important to mention that regardless of the origin (endogenous or exogenous); the delivery of cholesterol to peripheral cells occurs due to apoB-containing lipoproteins [1]. Normally, LDL particles account for about 90% of all circulating apoB-containing lipoproteins in the fasting blood. At the same time, the LDL level is mostly not directly measured. The concentration of LDL-C is most often estimated. Due to this, the therapeutic benefit is evaluated in randomized clinical trials, and cardiovascular risk can also be assessed by measuring LDL-C levels [2].

Usually, the LDL level and the LDL-C concentration are interrelated. It is because of this that LDL-C level measurement is a good alternative. However, it is important to note that under certain circumstances (for example, the presence of hypertriglyceridemia, diabetes or metabolic syndrome), the concentration of LDL

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particles may not correspond to the level of LDL-C [3]. This is due to the predominance of small, cholesterol-poor LDL. Accordingly, under such conditions, the measurement of LDL-C will not give accurate results about the concentration of LDL and the effect on cardiovascular risk. In this case, it is worth using a direct measurement of the amount of LDL. Also, given that each LDL contains one apoB molecule, measuring the concentration of apoB can also be effective [4].

Literature Review

The cholesterol hypothesis of atherosclerosis

In his 1913 study, Anichkov demonstrated that feeding cholesterol in oil to rabbits provoked the formation of atheroma [5]. This was proof of the role of cholesterol in the occurrence and development of atherosclerosis. In a study conducted in 1939, Muller focused on representatives of families who were found to have hereditary high cholesterol levels, as well as a predisposition to the development of cardiovascular diseases [6]. More recent epidemiological studies like MRFIT and Framingham will also establish a relationship between an increased risk of CVE and high cholesterol [7,8]. In the future, a direct connection between the CVD and the LDL-C level will also be confirmed. At the same time, it is worth noting that the feedback between CVD and the HDL-C level has been proven. A subsequent study, authored by Ancel Keys, found that in those countries where the average cholesterol level is lower (Japan, Southern Europe), mortality rates from CHD are lower than in countries where the average cholesterol level is higher (USA, Finland, Norway) [9]. It has been suggested that the level of cholesterol in the blood depends on the diet, namely on the amount of saturated fat. Based on this, a hypothesis was formed that it is possible to achieve a decrease in CVD by reducing the level of LDL-C.

Genetic causes of elevated LDL-C

FH is an autosomal dominant hereditary disease. It is associated with the premature development of ASCVD, and also depends on the level of LDL-C. Also, thanks to the study of FH, we can talk about the causal role of LDL-C in the occurrence and development of atherosclerosis [10].

In their study, Brown and Goldstein established the LDLR pathway [11]. Thanks to this, they were able to establish that the cause of FH is a mutation in the *LDLR* gene. Heterozygotes with the identified mutation have twice the increased cholesterol level. Also, these subjects are prone to premature manifestation of CVD. At the same time, a significantly overestimated level of LDL-C (>500 mg/dl) is observed in individuals with homozygous FH [12]. Also, often in childhood they develop supravalvular aortic stenosis and severe atherosclerosis. In the USA, the prevalence of heterozygous FH is about 1/200-250. At the same time, the prevalence of homozygous FH is significantly lower and ranges from 1/160,000 to 1/250,000 [13]. It is also worth noting that heterozygous FH is observed in 1/5 of people who have suffered a myocardial infarction under the age of 40. Based on this, we can say that FH provides an opportunity for targeted therapy aimed at preventing atherosclerosis. But it is worth noting that at the same time FH remains insufficiently studied, according to the latest data, it is known that only 1 to 10% of patients with FH have been identified [14]. Most people with significant hypercholesterolemia do not have classic monogenic autosomal dominant hereditary dyslipidemia. At the same time, it is polygenic factors that underlie the identified increase in LDL-C [15].

In one of the recent studies, people with LDL cholesterol ≥ 190 mg/dl were selected as the object of the study. Using gene sequencing, it was demonstrated that a monogenic mutation of FH is observed only in <2% of the subjects [16]. At the same time, people with the identified FH mutation are at significantly increased risk of CAD, regardless of LDL cholesterol levels. Most cases of monogenic FH occur in pathogenic variants in the PCSK9, APOB and LDLR genes [17]. In the genome-wide association study it was identified >50 individual genetic loci associated with increased risk of cardiovascular events. Many of the above loci are associated with those genes that affect cardiovascular risk and LDL-C levels: PCSK9, APOB, and LDLR [18]. At the same time, new loci were also established (for example, SORT1) that affect the risk of myocardial infarction and LDL-C. Separately, it should be noted that the Atherosclerosis Risk in Communities study demonstrated the relationship between a reduced risks of developing ASCVD and inherited low LDL-C levels, which arose during mutations and are the cause of the loss of functions of the *PCSK9* gene. Based on this, we can confidently talk about the causal role of LDL-C in atherosclerosis [19]. Also, the effect of LDL-C on the development of atherosclerosis depends on the dose and time.

Sirtuin 1 (SIRT1), which belongs to a highly conserved family of sirtuin proteins of nicotinamide Adenine Dinucleotide (NAD+)-dependent histone deacetylases, deserves special attention in the context of our review. Sirtuin 1 is linked to cardiovascular disease, NAFLD, diabetes and neurodegenerative disease [20]. SIRT1 is associated with lipid and glucose metabolism, playing an important role in them due to the deacetylation of a number of nuclear receptors and transcription factors, including peroxisome-proliferator activated receptor (PPAR)α, PPARγ, peroxisome-activated receptor proliferator-activated receptor gamma coactivator 1-α (PGC1- α), liver X receptor (LXR)α, LXRβ, forkhead box O (FOXO), AMP-activated protein kinase (AMPK) and sterol response element-binding protein-1c (SREBP-1c). Through these relationships, *SIRT1* gene variations may have an impact on inter-individual variations of plasma lipid levels, including LDL-C levels. The genotype/haplotype of the SIRT1

gene has been shown to be associated with serum LDL-C and HDL-C levels, and in a study by Inamori, et al. was shown to be associated with n-6/n-3 PUFA intake, *SIRT1* haplotype, and LDL-C and HDL-C levels [21].

Lowering LDL-C reduces ASCVD

Critical evidence for the cholesterol hypothesis has been provided through extensive randomized clinical trials of drugs that lower cholesterol levels. Also, in the period from 1966 to 1975, a project aimed at the treatment of coronary diseases was carried out [22]. According to its results, it became clear that niacin treatment has a significant effect on reducing certain non-fatal recurrent myocardial infarction by 26%. At the same time, no benefit was found with respect to the primary endpoint of total mortality. Separately, it should be noted that 9 years after the end of the follow-up (the average follow-up period was 15 years), the niacin group saw an 11% decrease in the mortality rate from all causes [23].

Another major study was conducted by Lipid Clinics Research. According to its results, it was found that lowering cholesterol levels affects the reduction of CVD [24]. Due to treatment with cholestyramine (cholestyramine is a bile acid binding inhibitor), the LDL–C level decreased by 12%. Also due to this, the CAD frequency decreased by 19% [25]. Previously conducted studies aimed at studying cardiovascular outcomes that reduce lipid levels had limitations. These limitations were associated with the lack of sufficiently effective ways to reduce LDL-C levels. At the same time, in part of the work, it was suggested that lowering cholesterol does not have an effect on reducing overall mortality. It was also said that lowering cholesterol can increase the risk of death from cancer, suicide and accidents [26].

It was possible to achieve a more effective way to reduce the level of LDL-C. This became possible thanks to the appearance of drugs of the statin class-HMG-CoA reductase inhibitors. Also, thanks to them, it was possible to overcome the concerns that were put forward by the results of studies conducted in the past [27].

One of the landmark studies of cholesterol reduction in patients with elevated LDL-C and CAD levels using simvastatin was the 4S study. It was designed with total mortality in mind as the primary endpoint. Thanks to this study, results were obtained indicating that a 35% reduction in LDL-C levels led to a 30% reduction in overall mortality [28]. At the same time, the reduction in the risk of coronary events was 34%, and the reduction in mortality from CAD was at the level of 42% [29]. Further studies have also confirmed similar results in subjects with low levels of LDL-C and CAD, as well as in people with low/high levels of LDL-C and without known CAD. At the same time, it is worth noting that in secondary prevention studies, the relationship between a decrease in CVE and a decrease in LDL-C with non-statin and statin approaches to reduce LDL-C was at the same level [30]. A large meta-analysis based on the results of 26 studies (170,000 people) was aimed at studying the effects of statin treatment [31]. According to its results, it became clear that such treatment for 5 years led to a decrease in coronary revascularization, the cumulative frequency of serious coronary events and stroke by 20% for every 1 mmol/l (38.7 mg/dl) decrease in LDL-C. Subsequently, these data were supplemented by another meta-analysis conducted on the basis of 49 studies (300,000 people; 40,000 major vascular events), in which there were examples of 9 different ways to reduce LDL-C. According to the results of this meta-analysis, it turned out that each decrease in the level of LDL-C by 1 mmol/l (38.7 mg/dl) led to a 23% reduction in the risk of major vascular events [32]. Based on these results, it was suggested that a further reduction in lipid levels would be beneficial. By the current moment, it is possible to achieve a decrease in the LDL level to 50%-70%. This was made possible by newly developed PCSK9 inhibitors. In the FOURIER trial (a randomized, double-blind, placebo-controlled clinical trial involving 27,564 patients), CAD patients who received the PCSK9 inhibitor, evolocumab, in combination with statin therapy achieved a median LDL-C level of 30 mg/dl [33]. This was due to a 15% reduction in the cumulative endpoint of cardiovascular death, stroke, MI, hospitalization for coronary revascularization or unstable angina. Similarly, during the ODYSSEY trial (randomized, double-blind, placebo-controlled trial involving 18,924 patients), it was found that in patients with acute coronary syndrome who had already received the maximum possible satin therapy, the appointment of alirocumab resulted in LDL-C values<50 mg/dl [34]. It was also associated with a 15% reduction in the cumulative endpoint of death from nonfatal MI, coronary heart disease, unstable angina or ischemic stroke. Also, in a subgroup of patients with baseline values of LDL-C>100 mg/dl, this advantage approached 24%. Based on the totality of the results obtained during these PCSK9 tests, we can say that the hypothesis that the lower the LDL-C level, the better-has been confirmed.

Despite the fact that satins show high efficacy in the prevention of CVD, CVD persists in many patients who receive therapy with satins. This phenomenon is called residual risk. In all likelihood, this residual risk is associated with inflammation. Thus, in the study of the outcomes of anti-inflammatory thrombosis with Canakinumab (CANTOS) [35], the final confirmation of this hypothesis was obtained. In the course of this study, the administration of antibodies to IL1ß in patients with elevated serum hsCRP and previous MI affected the reduction of recurrent CVD. At the same time, it is worth noting that this happened regardless of the decrease in lipid levels (>90% of patients received simultaneous statin therapy). During the secondary analysis of the FOURIER trial [36], it was found that the absolute reduction in risk when using evolocumab was greatest in patients with elevated

hsCRP. Despite the fact that the relative risk of the primary cardiovascular endpoint in different groups was at the same level. Based on these results, it can be said that targeting inflammation and LDL levels can provide the most reliable strategy for reducing the risk of ASCVD.

Discussion

How low should LDL-C levels be lowered?

To date, it has become known which lipid levels can be called too high, and also due to what it is possible to achieve their reduction, especially among people with a very high risk of recurrent cardiovascular events. This became possible due to the results obtained in the course of high-quality randomized trials of lipid-lowering drugs. In early statin trials, results were compared in the absence of treatment and when using moderate intensity statin treatment [37, 38]. According to their results, it was possible to establish a significant reduction in mortality and a decrease in cardiovascular morbidity. Then, in the course of later studies, the results of more and less intensive statin treatment were compared. According to the results, it was possible to confirm that by applying a more aggressive approach to reduce LDL, it was possible to achieve a further reduction in ASCVD cases [39]. And in the course of recent studies, it turned out that with already ongoing statin therapy, the use of additional treatment with non-statin drugs, such as PCSK9 inhibitors or ezetimibe, led to a gradual decrease in cardiovascular morbidity [40]. At the same time, the minimum LDL-C level below which the useful action stops was not determined, and no compensating security problems arose. Similarly, genetic studies have been able to establish a link between the low incidence of coronary heart disease and mutations that lead to lifelong low LDL-C levels [41]. Such mutations include a mutation of the previously mentioned PCSK9 enzyme, which results in loss of function. Based on the results of the analysis of accumulated data in this area, the assessment of atheroprotective, slightly elevated and strongly elevated LDL-C levels have changed. Thus, for people at high risk, the recommended LDL-C treatment goals gradually decreased from <3.0 mmol/L established in 1998 to <1.8 mmol/L adopted in 2011 [42]. The recommendations for dyslipidemia ESC/EAS 2016 were also changed to <1.4 mmol/L in the recommendations for dyslipidemia ESC/EAS 2019 [43,44].

Modern European recommendations suggest that it is important to use treatment goals, taking into account the overall risk of cardiovascular diseases [45]. This risk is determined by the presence or absence of cardiovascular risk factors and ASCVD. It is also quantified using a risk assessment system, such as SCORE, for example. SCORE takes into account gender, age, blood cholesterol, smoking status and blood pressure. At the same time, the higher the estimated risk of cardiovascular diseases, the lower the recommended target level of LDL-C. Such a targeted approach takes into account individual treatment with dose adjustment of the drug or combination of drugs [46]. At the same time, this individual treatment is aimed at achieving the appropriate target level of LDL-C. The advantages of this approach include better communication between the patient and the doctor, more specific, individual treatment to reduce the level of LDL-C and cardiovascular risk. We can also mention a better adherence to the recommended treatment. It has been proven that therapy, mainly aimed at reducing the level of LDL-C, as a result leads to a decrease in cases of ASCVD. But it remains less clear how the impact of a decrease in circulating LDL levels leads to changes in the atherosclerotic plaque [47].

Recently, new studies have been conducted, which were aimed at studying samples of bilateral biopsy of carotid endarterectomy at the beginning and after six months of therapy with pravastatin [48]. According to the results, a decrease in lipids caused by statins was recorded, as well as an increased content of collagens. At the same time, a decrease in the activity of metalloprotease, inflammation cells and cell death were recorded.

The recorded changes contribute to the stabilization of plaques. Also, in the course of early studies, which included coronary angiography with and without intravascular ultrasound, the advantages of satin therapy were revealed in relation to the degree of coronary artery stenosis [49]. At the same time, it is worth mentioning that in different studies, the degree of effect of statin treatment on the volume and composition of the plaque was not the same. This potentially reflects differences in the underlying substrate and the different resolution of the imaging techniques used. A study involving sequential intravascular measurement of optical coherence tomography was also conducted [50].

According to its results, it became clear that it is possible to achieve a change in the balance between the formation and destruction of capillaries by reducing the level of LDL. Such a change can cause capillary thickening. Due to this effect, the risk of rupture and thrombosis is reduced. The results of the secondary prevention study are also not unimportant [51]. They confirm the fact that when using the PCSK9 inhibitor evolocumab to reduce LDL levels, plaque volume and major coronary events decrease. At the same time, the composition of the plaques was unchanged throughout the entire treatment (76 weeks) [52]. But it is worth mentioning that the reliability of virtual histology for measuring the composition of plaques remains uncertain. In addition, this study was conducted among people who had previously received statin therapy. Based on this, it can be assumed that the apparently studied lesions were already sufficiently stabilized (before the use of evolocumab).

Implications for future prevention of atherosclerotic cardiovascular disease

The data presented on the pathophysiology of ASCVD help to expand knowledge about the causal relationship of LDL and atherosclerosis. The new data are complementary to the previous review, which was based on Mendelian randomization studies, GWAS, epidemiological studies and controlled intervention studies with pharmacological agents (targeting the LDL receptor) [53]. Together with the corresponding molecular mechanisms, the new data have an impact on the entire continuum of ASCVD prevention: Primary, secondary and tertiary. They are also consistent with the basic concept derived from genomics. According to this concept, the driving force behind the development and progression of ASCVD and its clinical consequences is the cumulative arterial burden of LDL-C [54]. In addition, due to pathophysiological data, therapeutic strategies are confirmed that are aimed at reducing and maintaining LDL-C at a sufficiently low level (<1 mmol/L or 40 mg/dl) in people with ASCVD detected, which potentially has a high predisposition to relapse. At the moment, such a low level of LDL-C can be achieved with the combined effects of statins and PCSK9 inhibitors (without the addition of ezetimibe or with it), therapeutic regimens (with proven tolerability and safety) [55]. The presence of a causal relationship between the LDL level and ASCVD was established and confirmed. Based on this, changes will be made to future international guidelines for the treatment of ASCVD-promoting dyslipidemias and atherogenic dyslipidemias. They will also be used to determine the rational use of existing treatment methods, as well as those that will be developed in the future. It is also worth mentioning that the success of modern programs aimed at the treatment and prevention of ASCVD will also be determined by patient-oriented approaches and the practice of precision medicine [56].

This thesis drew attention to the emerging mechanistic features of atherosclerosis. In theory, such features can help to re-evaluate existing therapeutic targets and identify new ones that will be an integral part of the biology of the arterial wall and the stability of plaques. The most important of them are the biology of monocytes/macrophages and SMC, inflammation, endothelial transcytosis of atherogenic lipoproteins, efferocytosis. They also include innate and adaptive immune responses to the retention of apoB-containing lipoproteins in intima and calcification. In general, this direction is quite promising, but it will take a lot of work to identify all potentially useful areas.

Conclusion

Our understanding of the role of cholesterol in the development of atherosclerosis has come a long way. The understanding that cholesterol affects vulnerability to CVD was first formulated in 1913. The starting point was the idea of an excess of dietary cholesterol. Only after many decades it became obvious that for the development of atherosclerosis and all its consequences, it is not so much the consumption of foods rich in cholesterol that is important, but it's further metabolism. So, different groups of cholesterol-binding lipids have different atherogenicity. Today, HDL is considered the main carrier of "good" cholesterol, and LDL is considered to be the "bad" one. In this regard, one of the most important indicators was the HDL-C to LDL-C ratio. Accordingly, one of the promising strategies for the treatment of atherosclerosis is the pharmacological reduction of LDL-C levels. Numerous studies, including those discussed in this review, support this approach. However, one should not forget about the complex nature of atherosclerosis, which requires an appropriate integrated approach.

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Conflicts of Interest

The authors declare no conflict of interest.

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