Chapter 6

Role of Cholesterol as a Risk Factor in Cardiovascular Diseases

Eyup Avci, Ahmet Dolapoglu and Didar Elif Akgun

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Abstract

Cardiovascular disease is the most common cause of death in adult population in the world. The disease includes numerous problems, many of which are related to a process called atherosclerosis. Atherosclerosis is a condition that develops when a substance called plaque builds up in the walls of the arteries. This plaque narrows the arteries, making it harder for blood to flow through. If a blood clot forms, it can stop the blood flow. This can cause a heart attack or stroke. There are many risk factors associated with cardio vascular disease (CVD). While some risk factors cannot be changed, such as family history, some of them can be modified with treatment such as abnormal blood lipid and sugar levels, obesity, smoking, and high blood pressure. Research makes it clear that abnormal blood lipid (fat) levels have a strong correlation with the risk of coronary artery disease, heart attack and coronary death. Cholesterol plays detrimental roles in the pathogenesis of atherosclerosis and CVD. In this chapter, we aim to summarize the relationship between blood cholesterol levels and CVD.

Keywords: cholesterol, cardiovascular disease, atherosclerosis

1. Introduction

Atherosclerotic cardiovascular disease is a group of disease which contains coronary artery disease, carotid artery disease, upper and lower extremity disease, and renal arterial diseases. The main cause of atherosclerotic cardiovascular diseases is the atherothrombotic process that occurs with atherosclerotic plaque rupture. Atherosclerosis is a chronic lipid-associated inflammatory disease concomitant with intimal thickening, especially involving bifurcation regions where endothelial damage is particularly high. Hypertension, hyperlipidemia,

diabetes, and smoking are the main risk factors for atherosclerosis. Fibrinogen, hsCRP, and interleukin-6 (IL-6) which are markers for inflammation have been found elevated in atherosclerosis. Atherosclerotic diseases are also common with systemic inflammatory diseases such as lupus and rheumatoid arthritis.

2. Pathogenesis of atherosclerosis

Atherogenesis starts early in life. Subintimal lipoprotein accumulation and leukocyte adhesion occurs as a result of increased endothelial permeability due to endothelial damage. Intimal neovascularization is seen with the migration of vasa vasorum into the intima. There is a structure in the luminal side of the atherosclerotic plaque that is called fibrous cap which contains molecules such as smooth muscle, collagen, and elastin. External elastic lamina is placed adjacent to the atherosclerotic plaque and tunica media and the lipid core is found between these two structures and it is made from the cholesterol crystals, smooth muscle cells, vascular structures, and foam cells.

Atherosclerotic plaques create luminal stenosis in the advanced stage. The first study in this subject was conducted by Glagov et al. in autopsy material of a patient with 136 left main coronary artery (LMCA) lesions. In this study, there is a positive correlation between internal elastic membrane area and plaque area, and luminal stenosis is prevented by expansion of the compensator at the atheromatous load of less than 40% [1]. In the REVERSAL trial, statin therapy was performed in patients with asymptomatic coronary artery disease. Atheroma volume, percentage of atheroma volume, and atheromatous change in the diseased segment were evaluated and progression of coronary atherosclerosis was observed in the pravastatin receiving group compared to baseline but no progression of atherosclerosis was observed in the atorvastatin group [2].

3. Lipoprotein structure

The lipid core that carries triglycerides and cholesterol esters has a hydrophobic structure and is coated with polar capsules which contain apolipoproteins, phospholipids, and nonesterified cholesterol crystals. When the lipoproteins were classified according to their migration rates in lipoprotein electrophoresis, the band closest to the origin formed the chylomicron band; low-density lipoprotein (LDL) in the beta band, very-low-density lipoproteins (VLDL) in the pre-beta band, and high-density lipoprotein (HDL) in the alpha band, respectively.

Chylomicron is synthesized in liver from dietary fat molecules. Since chylomicrons and VLDL molecules larger than 70 nanometers cannot reach the subintimal region through the transcytotic transport system, chylomicrons do not have atherogenic potential. But chylomicron remnants are atherogenic and cannot be removed from circulation when they are present in high quantities [3]. Hydrolysis of the chylomicrons with lipoprotein lipase results in the formation of VLDL. The majority of VLDL is converted to LDL. Chylomicrons are attached to ApoB48. Chylomicron remnants, LDL, and VLDL are connected to apoB100 and are called non-HDL cholesterol.

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4. Atherosclerosis and cholesterol hypothesis

The hypothesis of cholesterol suggests that lipids play a major role in the development of atherosclerosis. The 4S trial (Scandinavian Simvastanin Survival Study) showed that while there was significant reduction in total cholesterol level, LDL cholesterol level, and decrease in major coronary events, HDL cholesterol level was elevated in simvastatin receiving group [4]. After 4S study, REVERSAL, ASTEROID, and SATURN studies revealed that parallel plaque regression was observed with aggressive lipid-lowering therapy and reduction in major cardiovascular events was achieved. These similar studies have proven the relationship between hyperlipidemia and atherosclerosis [2, 5, 6].

Statins reduce macrophages and extracellular lipid accumulation in atherosclerotic plaque region and increase the content of collagen in the extracellular matrix which result in intimal calcification. Statins also stabilize inflammation and coagulation cascade after plaque rupture.

5. LDL and total cholesterol

LDL is the particle that is responsible for transporting cholesterol to tissues. Cholesterol transportation is achieved by binding of the LDL receptor and apoB. There are three separate fractions of LDL: LDL (large/floating), IDL, and small dense LDL. The most atherogenic LDL is small dense LDL.

In the WOSCOP trial and the AFCAPS/TeXCAPS trial which used pravastatin and lovastatin, respectively, the effect of hyperlipidemic therapy on the primary prevention of coronary artery disease was shown [7, 8]. The ASCOT-LLA study was terminated early in hypertensive individuals because atorvastatin significantly reduced nonfatal MI and CAD-induced mortality [9]. Similarly, the CARDS study was terminated early in diabetic individuals because atorvastatin decreased 37% in major cardiovascular events and 48% in stroke [10].

LIPID study compared low-dose and high-dose atorvastatin in patients with stable coronary artery disease and mortality was similar in both groups, but there was a significant decrease in major cardiovascular events in the high-dose atorvastatin group. The HPS study has shown that statin therapy protects high-risk patients with LDL cholesterol levels below 116 mg/dL [11]. CARE study with pravastatin in acute MI and MIRACLE study with atorvastatin in USAP or MI have shown early initiation of statins have a positive affect [12, 13].

In the ASTEROID trial, high-dose statin therapy (rosuvastatin 40 mg/day) was shown to reduce 53% LDL cholesterol, 15% increase in HDL cholesterol, and regression in 78% atheroma [5].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors inhibit the PCSK9 protein, which is effective in LDL receptor synthesis and provide 50–70% reduction in LDL-C levels.

In the ACCELERATE study, it was shown that the CETP inhibitor (Evacetrapib) did not reduce major cardiovascular events despite a 39% reduction in cholesterol level [14].

6. HDL

HDL is a molecule that is antioxidant, antiinflammatory, antiapoptotic and increases macrophage cholesterol excretion and endothelial healing. The removal of cholesterol from the body by the liver via HDL is called reverse cholesterol transport. ABCA-1, ABCG-1, and SR-B1 are effective in reverse cholesterol transport.

ApoA1 and ApoA2 are mainly found in the structure of HDL, and also HDL includes apoCs, ApoE, apoD, apoJ, lecithin-cholesterol acyltransferase (LCAT), serum paraoxonase (PON1) and platelet-activating factor acetylhydrolase (PAF-AH) molecules. Enzymes carried by HDL prevent oxidative modification of LDL.

Pentraxin 3 (PTX-3) in HDL controls leukocyte level. Defective PTX-3 was associated with large atherosclerotic plaques and higher level of inflammation [15, 16].

The association between low HDL and atherosclerotic cardiovascular disease was first shown by the Framingham study. Hypertension, diabetes mellitus, elevated total cholesterol, low HDL cholesterol, smoking, and age is considered as risk factor for coronary artery disease. The association between a low HDL cholesterol and atherosclerosis has been proven, but the increase in HDL has not been associated with a reduction in the incidence of atherosclerotic cardiovascular disease. Due to HDL being a molecule that prevents inflammation, some changes in HDL structure occur in chronic inflammatory processes.

7. Lipoprotein (a)

Lipoprotein (a) (Lp (a)) consists of an LDL molecule bound to apolipoprotein (a). Lipoprotein (a) is structurally similar to plasminogen and is thought to play a role in atherothrombosis with antifibrinolytic properties. In a study with patients with normal LDL and elevated Lp(a) levels, it was determined that increased Lp(a) levels was associated with high cardiovascular risk [17].

Cholesterol ester transfer protein (CETP) is responsible for transferring cholesterol esters. CETP inhibitors are associated with increased HDL and decreased LDL levels. In the study conducted with anacetrapib, there was no significant difference in mortality despite a significant increase in HDL and a significant decrease in non-HDL cholesterol compared to placebo [18].

8. Atherogenic dyslipidemia

In atherogenic dyslipidemia which is the result of an increase in triglyceride levels, triglyceride content is increased. The primary source of triglycerides is the VLDL. While LDL molecules are more easily oxidized, HDL molecules are more easily eliminated from the kidneys. Metabolic syndrome, type 2 diabetes, insulin resistance, abdominal obesity, and polycystic ovary syndrome are associated with atherogenic dyslipidemia.

In the case of atherogenic dyslipidemia, since chylomicrons have no effect on atherosclerosis, non-HDL cholesterol level is used rather than triglyceride level. Although levels of

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LDL, VLDL, and chylomicron residues can be determined by detecting Apo B levels, there is limited access and standardization for the detection of Apo B level. In the ESC dyslipidemia guide, non-HDL cholesterol calculation is recommended instead of measuring ApoB levels in the presence of hypertriglyceridemia. (Class 2a) In a study conducted by Puri et al., the level of non-HDL cholesterol rather than LDL cholesterol significantly correlated with atheromatous progression when the triglyceride level rises above 200 mg/dl. In the NICE guideline, all individuals are focused on evaluating non-HDL cholesterol exclusively from LDL cholesterol.

9. Familial hypercholesterolemia

Familial hypercholesterolemia is a metabolic disorder that occurs as a result of the absence or lack of LDL receptors in the liver. Since LDL molecules are removed from the circulation, very high LDL levels and premature atherosclerosis are observed. Familial hypercholesterolemia is thought to be approximately 1/500 of the homozygous form and approximately 1/1 million of the heterozygous form. Tendon xanthomas are pathognomonic signs for familial hypercholesterolemia. There is also an increase in the frequency of corneal arcus, xanthelasma.

10. Sitosterolemia

Sitosterol is a plant-derived molecule and its structure resembles cholesterol. Cytosterolemia is a progressive disease with an increase in the absorption and a decrease in biliary secretion of cholesterol and sitosterol molecules. Sitosterolemia is also called pseudohomozygous familial hyperlipidemia.

Recommendations for ESC 2016:

- Total cholesterol should be used to predict cardiovascular risk via the SCORE system. (1-C)
- LDL-C should be used primarily in screening, diagnosis, risk estimation, and treatment. (1-C)
- HDL-C should be used in the Heart Score algorithm. (1-C)
- TG provides additional information in the risk estimation. (1-C)
- Non-HDL cholesterol should be considered as a risk indicator, especially in individuals with high triglyceride levels. (1-C)
- ApoB should be considered as an alternative risk marker in patients with high triglyceride values. (2a-C)
- Lp (a) may be considered in individuals with high-risk, early family history of CVD and in the reclassification of individuals with borderline risk. (2a-C)
- ApoB1/ApoA1 ratio can be considered as an alternative analysis in risk prediction. (2b-C)

- The ratio of non-HDL cholesterol/HDL cholesterol can be considered as an alternative, but the HDL cholesterol used in the HEART SCORE provides a better risk estimate. (2b-C)
- LDL cholesterol is the main treatment target. (1-A)
- When available, apoB should be an alternative to non-HDL-C. (2a-C)
- Lp(a) should be recommended in selected case at high-risk, for reclassification at borderline risk, and in subjects with a family history of premature CVD. (2a-C)
- TC may be considered but is usually not enough for the characterization of dyslipidemia before initiation of treatment. (2a-C)
- HDL cholesterol and non-HDL cholesterol/HDL cholesterol levels are not recommended as treatment targets (Class 3).

11. Epidemiology

More than 30% of worldwide deaths are thought to be cardiovascular based and the frequency tends to increase due to changes in lifestyle and prolonged life. According to AHA 2016 statistics, in the United States, one in every 42 seconds loses his/her life due to cardiovascular reasons [19]. In Europe, the cardiovascular mortality rate is 4.1 million a year. A total of 1.8 million deaths, in other words 20% of all deaths, are due to ischemic heart disease. This is followed by cerebrovascular events with an annual death of 1.1 million. According to ESC data, 1.5 million deaths before the age of 75 and 710,000 deaths before the age of 65 are cardiovascular sources; half is due to coronary artery disease [20]. Deaths in all age groups, 51% of women and 42% of men are cardiovascular.

12. Coronary artery disease and cholesterol

Acute coronary syndrome is a clinical event that occurs when the coronary blood flow is reduced by thrombus on the rupture plaque and the myocardial oxygen requirement cannot be met. Acute coronary syndrome is broad spectrum which contains STEMI, nonSTEMI, unstable angina pectoris, and sudden cardiac death. In many cases, the thrombosis process begins with plaque rupture. Up to 25% of cases of acute coronary syndromes can begin with plaque erosion. Lymphocyte and macrophage activation and the inflammatory response is accompanied by atherothrombosis. There are clinical differences according to coronary collateral reserve and obstruction severity. This process occurs after a plaque rupture and is called Type 1 MI.

Atherosclerotic plaques that play an essential role in acute coronary syndrome are divided according to their structural characteristics: Plaque structure is with thin fibrous cap, dense necrotic core, high inflammatory cell density, and low smooth muscle content; it is called vulnerable plaque. Vulnerable plaque increases with hypertension, diabetes mellitus, elevated LDL, decreased HDL, and elevated ACE. Conversely, stabilized plaques with thick fibrous caps, poor necrotic cells, and dense extracellular matrix with low inflammatory content are observed in individuals with low risk factors (**Figure 1**).

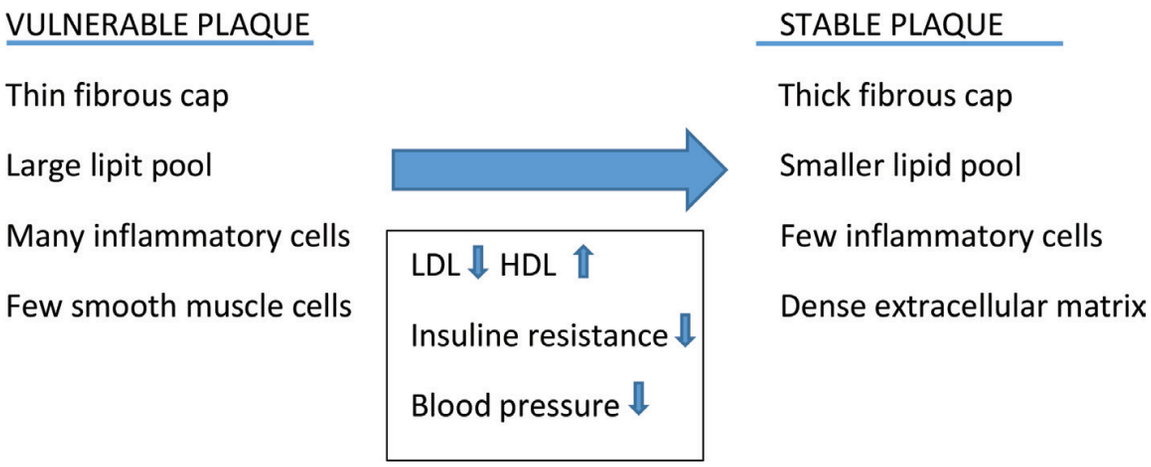

Figure 1. Structural differences between vulnerable and stable plaques.

In a meta-analysis involving 90,056 patients, a reduction of 38.6 mg/dl in LDL was shown to be associated with a 20% reduction in major cardiovascular events [21]. In MIRACLE study: increased plaque stability with statin therapy reduces death, incidence of acute coronary syndrome and frequency of recurrent coronary ischemia [13]. In the PROVE IT TIMI-22 trial, atorvastatin 80 mg and pravastatin 40 mg were compared and it was determined that high-dose statin therapy was more effective than low-dose statin therapy in reducing cardiovascular events. The 2017 ESC STEMI guidelines recommended that high-dose statin therapy was independent of cholesterol level. In the FOURIER study, it has been shown that the addition of the evolocumab in patient with LDL level ≥ 70 mg/dl, despite the use of high dose statin, is associated with a decrease in cardiovascular deaths [22].

13. Coronary calcium score

The coronary calcium score began to be used in the 1990s and the method was prepared by Agatson et al. Zero coronary calcium score has a high negative predictive value. It is the most commonly used method. In the 2016 ESC Guidelines for Cardiovascular Disease Prevention, the use of coronary calcium scoring has been proposed for predicting cardiovascular risk in individuals with a SCORE risk threshold of 5–10%.

CARDIA study showed a correlation between elevated LDL or non-HDL cholesterol and coronary calcium score [23].

14. Peripheral arterial diseases and cholesterol

Peripheral arterial disease is a concept that involves diseases of arteries other than coronary arteries. It most commonly occurs as a result of atherosclerotic process. In addition to atherosclerosis, vasculitis, and injuries, trapping syndromes are also effective in the formation of peripheral arterial disease. Approximately one-third of the individuals with peripheral artery

disease are accompanied by coronary artery disease. Peripheral artery disease should be considered as equivalent to coronary artery disease risk. Deaths are mostly of cardiac origin.

According to the REACH study, 3-year vascular-induced deaths were more common in patients with peripheral arterial disease than in those with coronary and carotid artery disease [24]. The use of statin has reduced both symptoms and cardiovascular mortality in a variety of studies on peripheral arterial disease [25, 26].

15. Carotid diseases, stroke, and cholesterol

Ischemic stroke should be investigated in two groups as embolic and thrombotic stroke.

Smoking and age are the most important risk factors for carotid atherosclerosis. The atherosclerotic plaque is located in the bifurcation area and often extends on the outer wall of the carotid bulb.

When stenotic plague increases, the risk of emboli increases. Carotid stenosis is defined as a stenosis of 50% or more in the extracranial portion of the internal carotid artery. In addition to the luminal narrowing, the lesion's edge irregularity, the presence of intraplate plaque hemorrhage, whether the lesion is unilateral or not, also determines the severity of the disease. Symptomatic carotid stenosis is the occurrence of symptoms related to carotid stenosis in the last 6 months.

In the heart protection study with simvastatin, a reduction of 39 mg/dL at the LDL level resulted in a 20% reduction in major cardiovascular events, 25% reduction in stroke, and 38% reduction in ischemic stroke [11].

In the SPARCLE trial (stroke prevention by aggressive reduction in cholesterol levels), patients who had stroke and TIA within the last 1–6 months were evaluated for 5 years. In patients receiving high-dose atorvastatin, a reduction of 43% in LDL levels resulted in a 20% reduction in major cardiovascular events and a 16% reduction in stroke. Despite the increase in hemorrhagic stroke rates in the high-dose statin group, there was no difference in lethal hemorrhagic stroke [27, 28].

It has been suggested that statin therapy initiated after stroke also improves neurological function with a decrease in infarct area. According to the information obtained from the meta-analyses, the use of statin before and after stroke is associated with improvement in neurological function. However, there was a relationship between statin therapy and hemorrhagic transformation in cases treated with thrombolytic therapy [29].

Carotid intima media thickness is a subclinical atherosclerosis indicator and it is recommended to use it in addition to classical cardiovascular risk indicators, especially in individuals with hypertensive middle cardiovascular risk (SCORE risk 1–5%). Values above 0.9 mm or values above normal 75th percentile should be considered pathological. According to the American Society of Echocardiography, these individuals should be considered as having increased CV risk. Individuals between 75 and 25% have expected cardiovascular risk. Individuals below the 25th percentile have low cardiovascular risk [30].

16. Renal artery stenosis hypertension and cholesterol

Renovascular hypertension is about 5% of all hypertension cases. In the presence of peripheral artery disease, the frequency of renal artery stenosis reaches up to 14%. There is an increase in the frequency of renal artery stenosis and peripheral artery disease association in the presence of diffuse peripheral artery disease [31]. Atherosclerotic renal artery disease is the most common cause of renovascular hypertension. Atherosclerotic renal artery disease is often defined as having ≥60% stenosis in the osteal or proximal one-third of the renal artery. The second most common cause is fibromuscular dysplasia in younger individuals with no atherosclerotic risk factors. There is a "string of beats" view at the distal one-third of the renal artery. Renal artery stenosis can be tolerated by autoregulation mechanisms until the renal perfusion pressure reaches 70 mmHg. Renal revascularization has not been shown to reduce hypertension, renal, or cardiovascular events. Antihypertensive therapy, antiplatelet therapy, and statins are the main treatments.

17. Lower extremity peripheral artery diseases and cholesterol

A common cause of lower extremity peripheral artery disease is atherosclerosis. It is common in men who have cigarette use at a young age. Diabetes and smoking are the most common causes of amputation in peripheral artery diseases. In the atherosclerotic process, progressive narrowing of the vessel wall occurs. Clinical signs are observed in the later stages of the disease. Clinical disease severity is determined by Fontaine and Rutherford classifications. There are studies that argue that the ankle brachial index (ABI) used in lower extremity diseases should be used as a risk factor for coronary artery disease. When ABI is above 0.9, it is considered normal but below 0.40 is considered as serious disease.

The 2017 ESC guidelines for peripheral arterial disease recommended LDL cholesterol lowering to 70 mg/dL or 50% reduction in LDL levels in patients with an initial LDL level of 70–135 mg/dL. Studies in lower extremity arterial disease patients have shown that statin therapy decreases all-cause mortality and cardiovascular mortality.

18. Aortic aneurysm and cholesterol

Aneurysm is defined as enlarging the diameter of artery, local or diffuse, by 50% or more relative to normal. According to localization, it is divided into thoracic and abdominal. Aortic aneurysms are 80% in abdominal location [32]. It is a chronic disease associated with inflammation of the aortic wall. It is suggested that the vessel is formed as a result of elasticity and power loss of the aortic wall after occlusion of vasa vasorum.

In the population with abdominal aortic aneurysm, association with other atherosclerotic cardiovascular diseases was frequently observed. The presence of abdominal aortic aneurysm was frequently associated with other atherosclerotic cardiovascular diseases. Smoking, age,

and male sex increases the risk of aortic aneurysm. While intimal atheroma and thrombosis process are present in both diseases, elastin fragmentation and adventitial chronic inflammation are limited to aortic aneurysms [33, 34].

In the tromsø study, there was a relation between the intima media thickness and the incidence of coronary artery disease and abdominal aortic aneurysm, but no correlation with aortic diameter [35]. The relationship between lipid level and aortic aneurysm has not been clearly elucidated [36]. The data for the studies are based on the similarity of risk factors for atherosclerosis and aortic aneurysm risk factors.

19. Retinal vascular diseases and cholesterol

Hyperlipidemia is associated with retinal vascular diseases. In old age, structures called "druzen" in tissue are similar to atherosclerotic lesions. Ischemic optic neuropathy can be seen as a result of stenosis in the retinal arteries and venules. In the ACCORD Eye trial, although strict treatment for diabetes and hyperlipidemia was beneficial, there was no significant benefit from strict blood pressure regulation [37, 38].

Author details

Eyup Avci[1]*, Ahmet Dolapoglu[2] and Didar Elif Akgun[1]

*Address all correspondence to: dreyupavci@gmail.com

1 Faculty of Medicine, Department of Cardiology, Balikesir University, Turkey

2 Cardiovascular Surgery Clinic, Balikesir Ataturk State Hospital, Turkey

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