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Dilzoda M. Azizova
Tashkent Medical Academy, Tashkent, 100109, Uzbekistan, dilzoda89@yandex.com

Rixsi A. Sabirova
Tashkent Medical Academy, Tashkent, 100109, Uzbekistan, sabirovara@yandex.ru

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Dilzoda M. Azizova[1], Rixsi A. Sabirova[2]

1 Senior lecturer, Department of Medical and Biological Chemistry, Tashkent medical academy, Uzbekistan
E-mail: dilzoda89@yandex.com

2 Professor, Department of Medical and Biological Chemistry, Tashkent Medical Academy, Uzbekistan
E-mail: sabirovara@yandex.ru

ABSTRACT

Despite adequate hypolipidemic therapy, the risk of cardiovascular complications remains high. This review provides a scientific overview of current LDL receptor data, the importance of PCSK9 in receptor-level regulation, and the influence of lipoprotein (a) and the role of lipoprotein-associated phospholipase A2 in the development and progression of atherosclerosis. LDL receptors play a crucial role in the exchange of cholesterol LDL in the body. It has been shown that PCSK9 is involved in the destruction of LDL receptors, being the primary regulator of its expression on the cell surface. There is strong evidence of association between a continuous and independent high-level Lp (a) and increased risk of CVD development and progression of atherosclerosis in various vascular structures.

Key words: low-density lipoprotein receptor, PCSK9, lipoprotein (a), Lp-PLA2, giperlipidemiya

INTRODUCTION

The prevalence of cardiovascular diseases (CVD) remains the leading cause of death in Europe and, despite the decline in mortality in many countries, is more than 4 million deaths per year, which constitutes half of the deaths in Europe [1]. The majority of deaths are in the CVD group, with a higher percentage among women (51 per cent) than men (42 percent). Coronary heart disease (CHD) separately causes about 1.8 million deaths, which is 20% of all deaths in Europe. At present, only 10 countries in Europe have cancer as the leading cause of death compared to the CVD (Belgium, Denmark, France, Israel, Luxembourg,

Netherlands, Portugal, Slovenia, Spain and San Marino). In 32 out of 52 countries, recent data showed that deaths from SHA are more than twice as high as those from cancer in women, and in 15 countries more than four times higher. Among men, 21 European countries have more than doubled the number of CVD deaths compared to cancer, and 6 countries have more than double the number of deaths due to cancer [1]. CVD mortality increases with age; 3 out of every 10 deaths under 65 in Europe were caused by CVD, compared to 37 per cent under 75. Recent data from Denmark and Norway show that these countries currently have the lowest level of cardiovascular mortality (180 per 100,000 men of any age, 120 per 100,000 women). Denmark has also joined countries, including France, Portugal, the Netherlands and Spain, which have the lowest IVM mortality rates. The highest mortality rates for men are found in the Russian Federation (RF) and Belarus (915 and 892 per 100,000 respectively) and among women in Uzbekistan and Kyrgyzstan. (662 and 588 per 100,000, respectively). Premature mortality from SHA among men varies almost tenfold from 65 per 100,000 under 75 years of age (age-standardized) in San Marino, France, Israel and Switzerland, to 560 per 100,000 in Russia and Belarus. Among women, the differences are roughly the same: In five countries, fewer than 25 deaths per 100,000 population under 75 years of age (France, Iceland, Switzerland, Israel, Spain), compared to 10 countries with a mortality rate of 200 per 100,000 population. The mortality rate increases with age in all countries, but given the large differences between countries, the highest mortality in one age group in one country, such as 65-69 years, may be higher or equal to that in 75-79 years group in another country.

Most CVDs are based on atherosclerosis, which stays asymptomatic for many years, and in general, manifestoes sufficiently at the time of clinical symptom [2].

Ischemic Heart Disease (IHD) is a consequence of atherosclerotic damage to the walls of blood vessels, characterized by damage to the endothelial layer with lipid deposition and the formation of atherosclerotic plaques, resulting in narrowing of the vessel’s lumen and disruption of the supply of oxygen and nutrients to the heart tissue. Therefore, lipid exchange, lipoprotein (LP), fatty acids (FA), as well as systemic inflammation and oxidative stress (OS) are considered to be the leading risk factors affecting the development and progression of atherosclerosis and associated CVD [3,4].

Inflammation is an integral component of atherosclerosis and its complications [5]. Metabolism of LDL, including oxidized LDL, is highly specific to intravascular inflammation and is involved in the formation of unstable vulnerable plaque enzyme - lipoprotein-associated phospholipase A2 (Lp-PLA2)

[5]. Higher Lp-PLA2 levels are also associated with increased risk of coronary events in older persons [6].

The enzyme Lp-PLA2 is a subtype of the superfamily phospholipase A2, which hydrolyzes phospholipids of oxidized LDL [7]. The LP-PLA2 levels are associated with atherosclerosis including CHD and MI [8].

There is growing evidence that Lp-PLA2 plays a critical role in the development of atherosclerosis. The main role of Lp-PLA2 in atherogenesis is hydrolysis of oxidized LDL in the artery wall. The result is the formation of pro-inflammatory, atherogenic by-products of lysophosphatidilcholine and oxidized fatty acids. The former act as chemoattractant for monocytes, disrupting endothelial function, causing cell death, destroying plasma membranes, and inducing apoptosis in smooth muscle cells and macrophages. The latter begin to influence OS growth [9].

The literature states that Lp-PLA2 is activated in atherosclerotic plaques [10] and strongly expressed in macrophages within the fibrous casing of lesions prone to rupture [11]. When released into the bloodstream, the LP-PLA2 is transported to the blood, mostly 80% of the LPD associated. There is some evidence that Lp-PLA2 contributes to the destabilization of plaques through inflammatory activity in atherosclerotic lesions [12,13]. It is generally believed that Lp-PLA2 can concentrate in unstable atherosclerotic plaques, especially those prone to tearing of plaques [14].

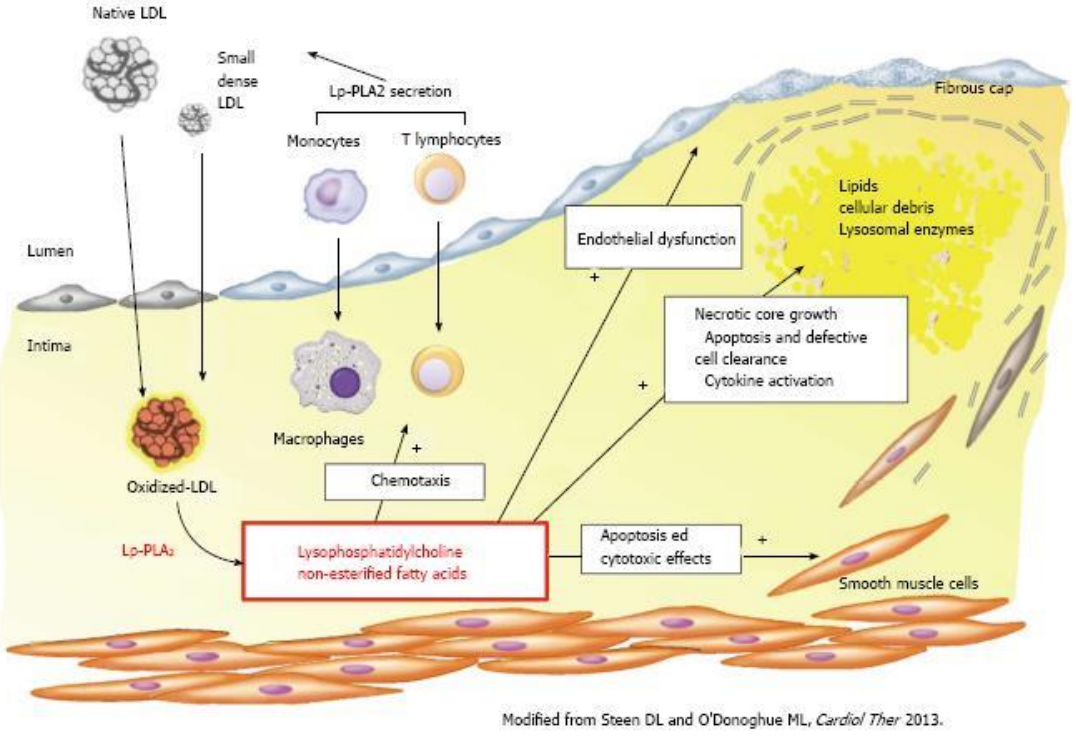

Figure 1. Mechanism of action of Lp-PLA2 [11]

The discovery of an independent connection between Lp-PLA2 activity and cardiovascular events, as well as with an increased risk of coronary events, corresponds to the majority of studies in patients with XXX [15,16-18,19]. The results of Z. Li et al. [20] show that the protective effects of omega-3 FPVC against cardiovascular events may be related to the suppression of LP-PLA2 levels. In a study performed at the E.Mayo clinic, S. Brilakis et al. [20] measured Lp-PLA2 levels in patients who had received clinical angiography. During the four-year observation, higher LP-PLA2 baselines were associated with a higher CVD risk. Finally, C. Iribarren et al. [20] studied the relationship between Lp-PLA2(mass and activity) and the calcification of the coronary artery in young people as part of the research «case-control». The mass and activity of LP-PLA2 was significantly higher in the main group than in the control group.

The relationship between Lp-PLA2and peripheral artery diseases has previously been assessed in three different cohorts: the CVD study [21], the multiethnic nature of atherosclerosis study (MESA) [22] and the Community Risk Study of Atherosclerosis (ARIC) [23]. The results of the ARIC study confirm the hypothesis that Lp-PLA2is independently related to CHD. A study of CC3 and ARIC found a link between Lp-PLA2and peripheral artery diseases, while MESA found no such association. Plasma levels of LP-PLA2(activity and mass) were found to be strong predictors for peripheral artery diseases in the studoes of S. Fatemi et al. [24], as these biomarkers remained independently associated with peripheral artery diseases, even after adjusting for the factors causing them.

LDS receptor value

The critical role of LDLP liver receptors in LDLP cholesterol catabolism was discovered in the 1970s by M. Brown and J. Goldstein [25]. For this work, in 1985, they were awarded the Nobel Prize in Medicine and Physiology. It has been shown that by localizing on the surface of hepatocytes, LDL receptors bind circulating LDL particles that transport in the composition of clatrin bubbles to endosomes inside the hepatocyte, where the LDL complex/receptor dissociates. The LDL particle is then destroyed in the cell lysosomal apparatus, while the released receptor is given the opportunity to return to the surface of the hepatocyte and participate in the capture and withdrawal of new LDL from the bloodstream (fig. 3). The importance of the LDL receptor in cholesterol control is confirmed by the fact that in people with homozygous carriers of mutations that disrupt its function, there is an elevated hypercholesterol (above 13 mmol/l), which causes early onset, aggressive CHD course and significantly, to 25-30 years, shortens life expectancy [26]. For a long time it was not clear how the re-return of the LDS receptor to the hepatocyte surface was regulated (restricted). In 2003, a protein molecule called

proprotein subtilisin/Type 9 Kexin (PCSK9) convertase was discovered, which belongs to the family of serine proteases. PCSK9 has been shown to be a major synthesis site for the liver [27,28]. PCSK9 effects on lipid metabolism

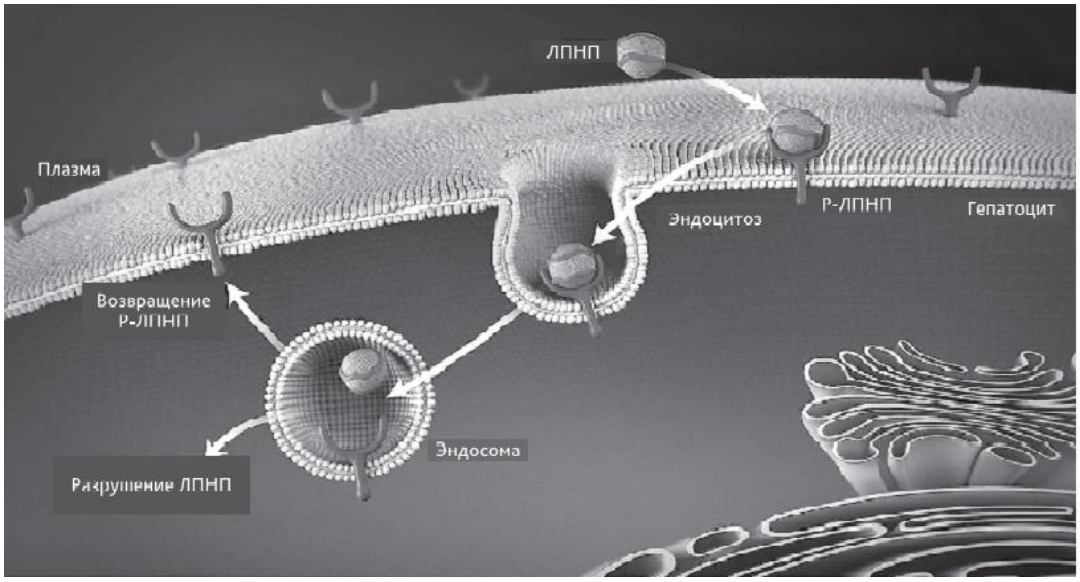

Figure 2. Role of LDS receptors in plasma LDL regulation [69]

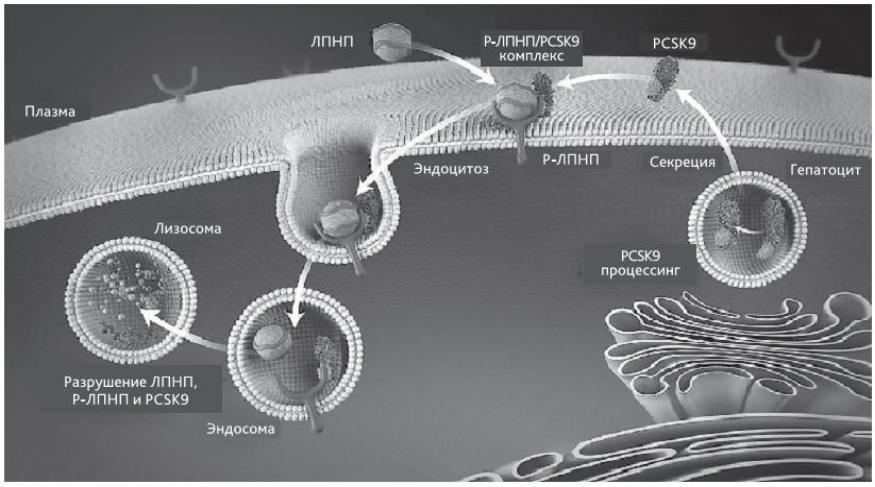

Figure 3. Involvement of PCSK9 in regulating the expression of the LDL receptor on hepatocyte [69]

The main function of PCSK9 is to regulate the density (abundance) of rLDL on the cell surface of hepatocytes, which is necessary for the elimination of cholesterol surplus along the route: hepatocyte-bile-intestinal-cal. The synthesized PCSK9 molecule interacts with rLDL on the surface of hepatic hepatocytes to form a PCSK9-rLDL complex, which is then submerged into the cell via endocytosis. This complex is then captured by lysosomes and degraded. The higher the concentration/activity of PCSK9, the greater the number of rLDL will be degraded (inactivation), which will reduce the rLDL abundance in the hepatocyte cell membrane. It has also been suggested that PCSK9, in addition to degradation of mature rLDL, disrupts rLDL formation at the post-translational level (in the

endoplasmic network and the Golgi complex) and during the transport of synthesized rLDL to the hepatocyte surface (fig. 2) [29]. The decrease of rLDL density in the plasma membrane of hepatocytes, mediated by the increased activity of PCSK9, is accompanied by a longer circulation of LDL particles in the blood and the occurrence of hypercholesterolemia. Under these conditions, there is an imbalance between the rate of delivery of cholesterol to the vessel walls and the rate of collection of cholesterol by scavenger macrophages. As a result, there is an overload of macrophages with cholesterol, transforming them into foaming cells, which is one of the key moments of development and progression of atherosclerotic vascular lesions. In addition to rLDL, other receptors are also targeted for PCSK9: the very low density lipoprotein receptor (rVLDL) and the low density oxide lipoprotein lectine receptor (LOX-1) [30-32]. PCSK9 contributes to the degradation of rVLDL in hepatocytes, fibroblasts and neurocytes. A.Roubtsova with co-aut. (2011) They investigated the role of PCSK9 in the metabolism of fatty tissue. Mice knocked out by the PCSK9 gene accumulated 80% more fatty tissue than wild mice. This indicates that PCSK9 regulates pH levels in adipose tissue and limits visceral angiogenesis [33]. LOX-1 is expressed in monocytes, vascular smooth myocytes and plays an important role in foaming cell formation and smooth myocyte migration. In LOX-1 knocked mice, inflammation is reduced, macrophage migration is reduced, weakening the atherosclerosis. PCSK9, by contrast, promotes increased LOX-1 activation and atherosclerosis [34]. Given the correlation of elevated PCSK9 concentrations with hyperlipidemia, a number of authors discussed the possibility of using PCSK9 as a diagnostic marker for atherosclerosis. Elevated serum levels of PCSK9 are associated with increased risk of CHD [35,36]. N.A.Almontashiri et al. (2014) reported that plasma levels of PCSK9 in patients with acute myocardial infarction were higher than in patients with CHD but without infarction (363.5 140.0 ng/ml versus 302.0 91.3 ng /ml, p = 0.004). These results indicate that PCSK9 concentrations increase either before a myocardial infarction or during a heart attack [37]. B.Cariou et al. (2017) in a prospectus study found that in patients with ACS (n = 174), serum levels of PCSK9 are associated with the severity of coronary artery damage on the SYNTAX scale, regardless of the concentration of LDL [38]. A recent study has shown a correlation between plasma concentrations of PCSK9 and subclinical vascular changes in the carotid artery, according to ultrasound diagnostics: Thickness of the human media, The pulse wave velocity and stiffness index β. Hence researchers suggest that it is possible to use PCSK9 as a biomarker for early vascular lesions before the manifest atherosclerosis [39].

PCSK9 non-generic functions

Some researchers have focused their research on the non-generic effects of PCSK9. There are many reports that suggest that PCSK9 functions go beyond lipid metabolism. The following are some of the most significant studies showing the presence of non-polar effects in PCSK9 that may play a role in the pathogenesis of atherosclerosis. S.Li et al. (2014) noted the association between plasma levels of PCSK9 and white blood cell count ($r = 0.167$; $p = 0.008$) in patients ($n = 251$) with stable CHD. Multiple regression analysis shows that plasma PCSK9 concentrations are reliably and independently related to both white blood cell numbers ($\beta = 0.217$; p 0.001) and their sub-populations (neutrophils $\beta = 0.152$; p 0.05 and lymphocytes $\beta = 0.241$; p 0.001). On this basis, the authors have suggested that PCSK9 is involved in the development of chronic inflammation in patients with CHD, which probably plays a role in the progression of atherosclerosis [40] Experimental studies K.R.Walley et. al. [41-43] PCSK9 is involved in the regulation of inflammatory reactions. Intraperitoneal endotoxin of intestinal coli [lipopolysaccharide (LPS)] was administered to laboratory mice. However, in the group of mice, PCSK9-knocked, plasma concentrations of inflammatory cytokines [Interleukin-6 (IL-6), tumor-alpha (TNF-a) necrosis factor, monocytokine-1 (MCP-1)] were significantly lower than wild mice [44]. Reduced PCSK9 activity leads to increased elimination of pathogenic lipids (FSC), decreased inflammatory response, improved clinical performance and survival in septic mice. The increased elimination is associated with the FSC adsorption property on LDL particles, which are then transported to the rLDL of hepatocytes of the liver, from where they are absorbed into the bile, intestines and removed from the body. The excess activity of PCSK9 in this case decreases the rLDL on hepatocytes, which reduces the clearance of FSC and promotes endotoxemia. Researchers believe that blocking PCSK9 can be a useful therapeutic strategy in sepsis patients and needs further study [45,46].

Another experimental study also shows that the increased activity of PCSK9 exacerbates the pathology of many organs, the course of inflammatory (increased concentration of inflammatory cytokines) and hyper coagulation conditions in sepsis [47]. N.Ferri et al. (2012) reported the presence of PCSK9 expression in smooth myocytes of vessels and atherosclerotic human plaques. PCSK9 secreted by smooth muscular cells is capable of reducing rLDL expression in macrophages [48].

Considering that PCSK9 contributes to the increased concentrations of inflammatory cytokines (IL-6, TNF, MCP-1, etc.) that play an important role in the etiopathogenesis of atherosclerosis, as well as the presence of PCSK9 expression

in the atherosclerotic plaque, It is likely that PCSK9 increases inflammatory reactions in the atherosclerotic plaque, which is an additional pathophysiological mechanism. However, such studies are rare and only provide indirect evidence of PCSK9 involvement in atherosclerotic inflammation pathogenesis. Recently, B.Gencer and colleagues in a large prospectus study that included 2030 patients found that PCSK9 concentrations were associated with acute inflammation (C-reactive protein) and hypercholesteronemia [49].

In a major study, ATHEROREMO-IVUS provides evidence of direct PCSK9 involvement in atherosclerotic inflammation pathogenesis. Patients underwent an intravascular ultrasound examination with virtual histology and measured the PCSK9 concentration in the serum. There was a correlation between serum levels of PCSK9 and the amount of tissue of the necrotic nucleus in blood vessels affected by atherosclerosis, regardless of serum levels of cholesterol, LDL and patient use of statins. This suggests that PCSK9 directly and independently of lipid spectrum parameters amplifies inflammatory reactions in the atherosclerotic plaque of coronary vessels [50].

Current understanding of the role of lipoprotein (a) in atherosclerosis

A number of studies have shown that for some population groups, despite reaching the target level of HC with adequate hypolipidemic therapy, the risk of cardiovascular complications (CCD) remains high at 60-80%. This risk is defined as residual (residueal)That is, the risk of macro- and micro-vascular complications that persists in most patients, despite modern treatment standards, including optimal monitoring of HS levels of LDL, blood pressure and blood glucose [51]. Lipoprotein (a) is considered to be one of the main factors influencing the rubber risk in patients with atherogenic dylipidemia, along with increased triglycerides and reduced cholesterol of high-density lipoproteins (HC LDL) - Lp (a) [52-54]. Lipoprotein (a) is a complex in the form of spherical particles consisting of a central nucleus comprising cholesterol esters (XC) and triglycerides surrounded by phospholipids, free XC and one molecule of apoprotein B 100 (apoV 100). The average diameter of these particles is 21.0-26.5 nm and the mass is 250-800 kD. The Lp (a) consists of an apoprotein (a) - apo (a) associated with a single apoB-100 molecule by a single disulfide bond. The maximum quantity of Lp (a) is contained in a fraction with a density of 1.063-1.120 g/ml. Apo (a) is a unique protein that is not found in any other lipoprotein class and has a high degree of homology (up to 90%) of the primary structure with a plasminogen molecule [55]. The presence of XC and its esters (up to 30-45% of the total mass) and one apoV molecule of 100 gives Lp (a) on the one hand, a number of properties similar to LDL; on the other hand, the presence of a molecule of apo (a) determines the participation of Lp (a)

in the thromboformation process. The nature of the structure makes it possible to consider Lp (a) as a bridge between the processes of atherogenesis and thrombogenesis [56]. Unlike other lipoproteins, the level of blood circulating in Lp (a) is under the genetic control of the apo (a) - LPA gene. The LPA gene is characterized by high polymorphism, which results in heterogeneity of size and molecular mass Lp (a). Due to its strong genetic determinant, Lp (a) is stable and not significantly influenced by gender, age or environmental factors, which makes hyperLp (a) vulnerable to lifelong CVD development, with the development and progression of the atherosclerotic process in both its early and late stages [57].

The blood content of Lp (a) varies widely, varying by a factor of 1,000, from 0.1 to 300 mg/dL. The Lp concentration (a) shows an incorrect distribution with a downward bias, without gender differences. In the European population, the median Lp (a) is 12 mg/dl (interquartile 5-32 mg/dl) [58]. In the Russian population, the average concentration of Lp (a) is 16 mg/dl (5-44 mg/dl) in men and 16 mg/dl (6-48 mg/dl) in women [59]. The level of Lp (a) above 25 mg/dl is found in about 30 per cent of Caucasians [60]. Currently, based on numerous studies, the level of Lp (a) 30 mg/dl is considered to be a «level of increased risk», as at a higher value the risk of development of CVD [61,62] rises sharply. A stratification of the risk based on the concentration of Lp (a) in the blood plasma (table.) [63] was proposed. A number of authors, on the basis of available research findings on the predictive role of Lp (a), suggest that persons at moderate risk should be classified as high risk of SSS when more than the 80th percentile [64] is included in the stratification model. High levels of Lp (a) in the blood are quite common. Thus, according to M.Graham and co-authors (2016), the frequency of detection of Lp (a) in the blood of more than 50 mg/dl reaches 20% in the total population, and even more frequently in patients with CVD and aortic stenosis [64]

The Lp level (a) 30 mg/dl is detected in 37-40 per cent of high-risk patients and only in 14 per cent of low-risk individuals [65]. According to M.V.Yezhov and co-authors (2011), in case of chronic ischaemic heart disease (CHD), the frequency of high level Lp (a) among men reaches 39 per cent, in women - 48 per cent [66]. According to the National Association of Compulsory Medical Insurance of Physicians in Germany, approximately 70 per cent of patients apply for a level Lp (a) test for hypercholesterol [66]. Over the past few decades, a number of prospective population studies have provided compelling evidence of a continuous and independent high-level Lp bond (a) with increased risk of CVD development and progression of atherosclerosis in various vascular basins. According to a major meta-analysis, which includes 36 prospectus studies (n=126 634 patients), an independent association between high Lp (a) levels has been identified with an

increase in the risk of developing a non-fatal myocardial infarction (IM) by 15-25%. At the same time, the risk of development of the CVD associated with the elevated level of Lp (a) was not associated with either high levels of inflammatory markers (C reactive protein, fibrinogen) or other traditional risk factors (arterial hypertension, family history of CHD, smoking, obesity, diabetes mellitus, concentration of LDL) [66].

In a major prospectus study, the hyperLP (a) was found to have predictive significance in the development of MI, fatalities, etc. [3]

In a retrospective study of a large multinational cohort of patients with family hypercholesterol (CGHS) (n = 388) at one lipid clinic (Vancouver, Canada), the relationship between several known CVD risk factors, Lp (a) and the age of development of the serious CVD case [32], was studied using multi-factor Cox regression analysis. The Lp (a) level of 56 mg/dl and higher was found to be an independent risk factor for the development of the CCS (p 0.001). Other important risk factors were the male sex (p 0.001) and the ratio of total XC to XC LDSP (p = 0.001). In the work of A.S.Jansen with collaborators (2004), the level of Lp (a) over 30 mg/dl increased the risk of developing ischemic complications by 50% [67].

A number of papers have shown a direct relationship between Lp level (a) and progression of coronal atherosclerosis. The elevated level of Lp (a) is significantly associated with occlusion of venous anastomoses during the first year and a threefold increase in the risk of CVC in the remote period following CABG [67].

Thus, numerous studies have shown that there is a direct, continuous and independent association between the elevated Lp (a) content and the high risk of early development of atherosclerosis and the resulting CVC.

Treatment

According to the World Health Organization (2016), hypolipigemic preparations are classified as follows: 1) statins (GMG-CoA reduction inhibitors); 2) fibres; 3) bile acid sequestration; 4) nicotine acid and its derivatives; 5) Preparations with other mechanisms of action; 6) Combination medicines containing as a mandatory component the inhibitor GMG-CoA-reduction. A number of drugs used for the treatment of dislipidemia and atherosclerosis are of low activity or have side effects [68]. The following groups of drugs are used as hypolypigemic agents: GMG-CoA reduction inhibitors (statins), fibres, anionic exchange resins, nicotine acid and its derivatives. According to the international classification, hypolipidemic drugs are agents affecting the cardiovascular system (code C) [Central Research Institute for Health Organization and Informatization [68]. Currently, the most widely used, studied and effective agents used in

atherosclerosis and dislipidemia therapy are statins [69] - competitive inhibitors of 15 GMG-CoA reductase enzymes, a key enzyme for cholesterol synthesis in the liver [69].

Despite their relatively high efficiency, long-term use of statins can cause side effects. Studies around the world confirm the existence of side effects. Hepatotoxic effects [70] and the development of myopathy, up to rhabdomyolysis, are considered risks for the use of statins and possible side effects of their use.

Conclusion

From the above one can conclude that Lp-PLA2 plays an important role in the pathogenesis of atherosclerosis. The main pathogenetic influence of Lp-PLA2is the increased oxidation of low-density lipoproteins (LOPs). These discoveries made it possible to create a new class of effective antilipid drugs, Lp-PLA2 inhibitors. In addition to the significant effect on lipid metabolism, there is evidence of Lp-PLA2involvement in inflammatory reactions, which are another important part in the ethopathogenesis of atherosclerosis. Lp-PLA2 can also be used as biomarkers to diagnose and predict CHD, assess the severity of coronary arteries and detect subclinical atherosclerotic changes in vessels. However, given the small number of such studies, there is a need for further study.

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