BIOCHEMICAL BASES OF A THEROSCLEROSIS DEVELOPMENT

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Abstract. *The problem of pathogenesis of atherosclerosis persists for more than 200 years. Ideas about the etiology and pathogenesis of atherosclerosis are highly controversial. The aim is to further investigate the causes of vascular damage and develop ways to treat them.*

Keywords: *pathogenesis, atherosclerosis, etiology, significant, development.*

Actuality: the problem of pathogenesis of atherosclerosis persists for more than 200 years. Ideas about the etiology and pathogenesis of atherosclerosis are highly controversial. The aim is to further investigate the causes of vascular damage and develop ways to treat them.

Materials and research methods. Review of literature on etiology and pathogenesis of atherosclerosis.

Results: Atherosclerotic lesion is an artery disease caused by lipid and protein metabolism disorders, accompanied by the deposition of cholesterol and lipoproteins in the vascular lumen. Deposits are formed in the form of atheromatous plaques with subsequent growth of connective tissue in them and calcification of the walls of vessels, which leads to deformation and narrowing of the clearance of the vessels up to obturation (blockage of vessels).

Pathomorphological changes in the walls of the arteries, characterized by accumulation of fat and sclerosis, inflammation of the inner lining of the arteries were described more than 200 years ago. The problem of pathogenesis of atherosclerosis is still relevant today. Further research into the causes of vascular damage and the development of treatments are required. The content of the term «atherosclerosis» has undergone a number of significant changes over the decades.

There are various and contradictory theories and hypotheses about the causes and mechanism of atherosclerosis development.

Anichkov N.N. [1] assumed that atherosclerosis was Vascular damage caused by lipoid infiltration. His position «without cholesterol there is no atherosclerosis» can be expressed in the words «without atherogenic lipoproteins there can be no atherosclerosis». According to his theory, atherosclerosis is a form of arterial disease. Anichkov N.N. formulated the infiltration theory of atherosclerosis pathogenesis, based on the fact that the main point in this disease is lipoid[cholesterol] infiltration of the inner lining of arteries [lipoidosis] with subsequent development of connective tissue.

The greatest scientific achievement of the late 20th century was the discovery by J. Goldstein and M. Brown of the low density lipoprotein receptor (LDL). The authors were awarded the Nobel Prize [6]. It is on the receptor theory of lipid exchange that the most effective direction of pharmacotherapy of atherosclerosis is based by GMG-CoA-reductase inhibitors. Gerontological theory of I.V. Davydovsky [3] believes that atherosclerosis is both an aging problem and an organism’s reaction to damage.

A.N. Klimov, T.N. Lovyagina, V.A. Nagoriev developed autoimmune theory of pathogenesis of atherosclerosis [7]. According to this theory, very low density lipoproteins [VLDL] can form in the blood of humans and animals, as well as possibly low density lipoproteins

[LDL] possessing autoimmune properties against which immune complexes are formed: VLDL antibody and LDL-antibody antibody in excess of antigen. The cytophagic effect of the complex on the vascular wall is manifested in the violation of the endothelial barrier permeability, which is accompanied by the deposition of the complex in the inner vessel wall. Increased permeability of the arterial wall under the influence of the immune complex is a favorable factor for infiltration by atherogenic lipoproteins with autoimmune properties.

The membrane hypothesis of R. Jackson and A. Gotto states that cholesterol alters the membrane and cellular metabolism of smooth muscle cells, increasing their proliferation and, apparently lipoprotein binding.

The mutagenic monoclonal hypothesis of E.Benditta indicates the existence of a clone of smooth-brain cells that reproduce in response to the formation of fibrous plaques, which are considered to be a tumor for smooth-brain cells.

Khalatov S.S. and Kukharchuk V.V. [8] identified atherosclerosis as a lipoid-infiltration process based on lipoid-cholesterol and protein exchange changes. Atherosclerosis affects middle and large arteries, which can lead to myocardial infarction [2]. Lesions occur first in the inner layer of the arteries and then capture the media. Myasnikov A. L.[12] viewed atherosclerosis as a systemic lesion, as a result of cortico regulation of protein-fat, especially cholesterol exchanges. As early as 1965 he proposed the following classification of atherosclerosis [pathogenetic aspects]: Hemodynamic form [arterial hypertension, angiospasms, vascular neurosis];

Metabolic form [cholesterol metabolic disorder, hereditary, nutritional factors, obesity, endocrine diseases];

3.Mixed forms of atherosclerosis. Academician Chazov E. I. [17] defined atherosclerosis as a pathological process that develops due to biochemical and biophysical changes in the exchange of lipoproteins and thrombotic properties of blood.

Leites S.M. believed that lipid deposition in the artery wall depended on the lipotropic substance choline.

Rokitansky-Duger’s trombogenic theory links atherosclerosis to the formation of constricted thrombose and their subsequent organization, leading to the formation of towering plaques. The role of the immune system in the development of atherosclerosis was investigated. In patients with coronary atherosclerosis, a high level of circulating immune complexes (CIC) has been established, which can cause disruption of the monolayer of endothelial cells [6]. There are three layers in the vessel wall of medium- or large-sized arteries with a diameter of 1 to 25 mm: the center clearance of the vessel, the outer envelope and the inner envelope. In the lumen is the elastin protein most exposed to atherosclerosis. The inner envelope is called the intima, the middle envelope is called the media, and the outer envelope is called the adventic.

Normally, the endothelial membranes of the vascular wall allow only a stream of macromolecules to pass through, which intersect the cells in the form of microkinocytic bubbles. When the endothelium is damaged, this barrier disappears, resulting in plasma proteins and lipoproteins infiltrating the vascular wall. The researchers define atherosclerosis as chronic focal lesion of large and medium-sized arteries, deposition and accumulation of low-density lipoprotein arteries [LDL] and very low-density lipoproteins [LDL] with the development of structural changes and reactive growth of connective tissue. There are two main lipoprotein cholesterol-carrying lipoproteins - low density lipoproteins [LDL] and high density lipoproteins [HDL]. LDL transport two-thirds of cholesterol [C] blood plasma. They are rich in cholesterol [they contain up

to 45-50% C]. Particle sizes [21-25 nm] allow LDL, along with HDL, to penetrate the vascular wall through the endothelial barrier. However, unlike HDL, which are easily removed from the wall due to its small size, HDL are retained in the walls of the vessels because they have a molecular weight of 2-4 million daltons. HDL have a molecular weight of 200-400,000 Dalton, as well as a selective affinity for glucosamine glycans and smooth-headed cell walls. The latter is due to the presence of Apo-B in the LDL and receptors on the cell walls. Atherogenic LDL interact with specific receptors on cells, resulting in receptor-mediated LDL capture and cholesterol [C] transport to cells. For these reasons, LDL are the main transport form of C for the needs of the cells of the vascular wall, and in pathological conditions - the source of accumulation of C in the walls of vessels. C Low Density Lipoproteins [LDL-C] is correlated with the risk of developing atherosclerosis and ischemic heart disease [IHS]. High risk of developing these diseases at serum concentration of LDL-C above 4.27 mmol/l [at norm - 1.7-3.5 mmol/l]. Cell

Antiatherogenic HDLs in contact with cell membranes are able to remove excess cholesterol from them, convert cholesterol esters into cholesterol esters with the help of the enzyme lecitysyncholesterol transferase [LCAT] and transport it back to the liver, where cholesterol esters under cholesterol ester are released from fatty acid and free cholesterol molecules are used to synthesize bile acids [4]. The decrease in C concentration of high density lipoproteins, [HDL-C] below 0.9 mmol/l [at 1.0-2.07 mmol/l] is associated with an increased risk of developing atherosclerosis and IBS. In patients with atherosclerosis, the concentration and duration of LDL in the blood plasma is increasing. The result is an increase in the number of LDL particles that are filtered into the artery intake, where LDL is oxidized and converted into modified particles [m - LDL]. Antibodies are formed against autoantigens LDL and an immune complex [LDL antibody in excess antigen] is formed, which is deposited in the intestine of the vascular wall with endothelial barrier permeability violation and infiltration by atherogenic lipoproteins.

Subsequent studies [16] suggest that the basis of atherosclerosis is deficiency of polyunsaturated fatty acids [poly-LC]: omega-3 and omega-6. The cause of the deficiency is cellular impairment of uptake of LDL through the apo-B-100 receptors. The function of LDL is to actively transport to the poly-LC cells, which they transport in the form of cholesterol-etherized poly-ECC. The plasma membrane produces a gradient of poly-LC, deficiency of poly-LC in cells and accumulation of poly-LCD and LDL in the blood. The functional blockage of absorption by cells of LDL [apo-B- 100-endocytosis] develops when the transition of poly-EC from high-density lipoproteins [HDL] to LP of intermediate density [LPP] is blocked. In this case, the C cycle is disrupted and transport to the poly-LC cells, the LPP does not turn into LDL and does not interact with the apo-B-100 receptor. This process can be blocked by acute phase protein. Amyloid A, which is synthesized by hepatocytes during the formation of inflammation syndrome, associating in the blood with HDL, inhibits the transition of poly-EX to LDL.

Poly-LC deficiency plays a major role in cell life. For millions of years all living things lived in the aquatic environment [cold-blooded animals], where all functional systems of the organism were formed. At low temperature, FL membranes contained mainly omega-3-LC, had the maximum possible liquid content and minimal viscosity. There was a shortage of poly-LC and the dominance of omega-6-arachidonic acid at land access. As a result, peanut acid became the main poly-LC due to long-term adaptation. As a result, eicosanoids, formed from peanut acid, will manifest the function of vasodilator, reducing resistance in the vessels; thromboxanes activate platelet aggregation and leukotriene have no anti-inflammatory effects. Probably because of this

on land warm-blooded began to have higher blood pressure, active platelet aggregation, shortened blood clotting time, high levels of insulin and acute phase proteins, including fibrinogen and prothrombin. With poly-LC deficiency, the function of highly differentiated cells that used omega-3- LCD and omega-6-LC as precursors to the synthesis of the most complex lipids, which largely determine the functional specificity of cells, phospholipid composition of the membrane and charge on its surface [5]. Not all cells in the body normally have an apo-B receptor on the membrane, and many cells do not require active poly-LC input. Such omega-6-poly-LCD cells are passively introduced from HDL. About 20% of the body's cells have apo-B-100 receptors on the membrane. For these cells active absorption of omega-6 and omega-3-LCD is a prerequisite for their normal function [5].

Under normal conditions, LDL is carried in the blood, except cholesterol, the main amount of essential polyunsaturated fatty acids. Hepatocytes first synthesize LDL, which do not contain poly-LC. Further, during the transition of poly-ESTs from HDLs to LDLs, poly-ESs are gradually accumulated in the LPP instead of the triglycerides, with LSTDs being converted into LDLs. The more poly-LCD comes with food, the faster the LDL turns into LDL and is absorbed by the cells, the lower will be the blood level of poly-ECC, which is defined in the blood as total cholesterol [C]. Under the conditions of the apo-B-100-endocytosis blockade, circulating in the blood LDP and LPP become essentially «foreign bodies». Long-term circulation of LDL and LDL, as well as all protein macromolecules and enzymes [creatine kinase, lactatdehydrogenase] causes the activation of neutrophils that denature macromolecules of LPPP and LPPP by adhering to the apo-B-100 sialic acids and enhancing peroxidation of poly-LC in complex lipids. Moreover, LPP neutrophils are denatured more actively than LPP. As a result of denaturation, pathological epitopes are formed in PL, Immunocompleted cells need to recognize the «foreign» molecules of LDL and LDPP and remove them from the bloodstream. Reticuloendothelial [SES] cells, monocytes and macrophages remove LPPP and LDP from the blood by unspecific phagocytosis. On the macrophage cell membrane, modified SLPs and SLPs interact with the scavenger receptor [scavenger receptor]. Receptors - scavengers are involved in the absorption of modified lipoproteins and glycosylated proteins, apoptotic damaged cells, modified erythrocytes, that is, are involved in absorbing «debris» formed in the blood and removing them from the bloodstream. Monocytes capture denatured lipoproteins, penetrate the vessel wall and give rise to lipid spots and later atherosclerotic plaques. This ensures stability of homeostasis, strengthening of the immune system, recovery metabolism.

Therefore, processes related to receptor scavengers are key factors in pathogenesis of various diseases, including atherosclerosis, obesity, diabetes mellitus, and tumor diseases. Therefore, direct targeted action on these receptors is a promising area of data therapy disease. So, atherosclerotic lesion forms macrophages. The higher the immune status of the body, the more active the macrophages are absorbed.

According to the macrophage theory proposed by Leary, lipids in the vessel wall selectively accumulate loose cells connective tissue. The cells of loose connective tissue are located in the intercom of all major vessels, intraorgan arteries of the lungs, liver, kidneys, cerebral vessels. Lipid deposition in the vascular wall also occurs mainly in loose connective tissue, collagen and elastic fibers. Loose connective [mesenchymal] tissue includes blood and bone marrow cells, endothelium cells, fibroblasts and fibroblasts, smooth brain cells, adipocytes, monocytes, macrophages, cells, fibroblasts, platelets, and highly differentiated brain cells, retinas, cells of

adenohypophysis, glomerular membrane. There are three layers in the vessel wall of medium- or large-caliber arteries with a diameter of 1 to 25 mm: centre clearance of the vessel, outer shell and inner shell.

Atherosclerosis starts with an irritant: nicotine, LDL, hypertension, hyperlipidemia, diabetes mellitus. The irritants act on the inner cell layer, the endothelium, under which the basal membrane is located. Endothelium cells act as a protective barrier. When the endothelium is damaged and the endothelium cells are destroyed, a breach, a void forms. In the resulting void, the intuition enters LDP, bringing a lot of fat and cholesterol. The immune system has macrophages that patrol endothelium preservation. In the event of endothelium damage, they follow the LDL, devour it with fats. Macrophages filled with fats and LDL are converted into large foam cells containing EC droplets in the cytoplasm, resembling foam foam. The takeover kills the macrophages. Thus, foamy cells and dead macrophages accumulate in the intima of vessels. All molecules merge to form a lake of fat in the receptacle's intimacy, with the appearance of fat vein in the arteries with the development of atherosclerosis. Platelets are also produced here, which, together with macrophages, produce cytokines that stimulate the proliferation and migration of smooth muscle cells into the inner vessel. Smooth-headed chicks migrate to the center of events. They form a fibrous plaque, like a crust, over a lake of fat. Fibrous plaque consists of collagen and elastin fragments.

The absorption of macrophages of LDL and LPPP and the formation of foamy cells occur where loose connective tissue cells are located. Internal intimate boundary elastin is a barrier to LP diffusion and macrophage cell migration. Because of this, the formation of foam cells and subsequent destructive changes capture the deeper layers of the vessel wall. Arterial trunks are affected by atherosclerosis at such a distance as loose connective tissue is located in their wall. Foamy cells are also formed in organs where loose connective tissue is located. After the macrophages have absorbed the denatured LPP and LPP, these LP fall into lysosomes. Therefore, when they fall into lysosomes, acid proteases perform apo-B-100 proteolysis, but neither monocytes nor macrophages can hydrolyze poly-EC to the free LCD and free XX. Therefore, esterified C poly-LC accumulates in lysosomes in the form of poly-EC crystals and turns into intracellular foreign bodies, causing hypertrophic lysosomes, forming penis cells and necrosis. The destruction of the cell membrane and the release of cell contents into the intermembrane space cause reactive changes of surrounding cells, their hypertrophy of the intercellular matrix [collagen and elastin] and trigger non-specific inflammation syndrome [18,19]. Under conditions of poly-LC deficiency, fibroblasts and smooth muscle cells synthesize omega-9-leukotrienes, which activate inflammation syndrome and protein molecule synthesis that enhances neutrophil migration. The lysis of adjacent cells and the synthesis thereof of interleukin lead to an increase in the synthesis of acute phase proteins by hepatocytes: S-reactive protein, fibrinogen, and prothrombin. Accumulation in the lysosomes of the crystals of esterified C poly-LC [linoleic peanut] is a phenomenon of pathological accumulation. On this basis, it is believed that atherosclerosis is based on pathological compensation syndrome. So, of course, atherosclerosis is inflammation, it is a two-way process associated with atherosclerotic plaque, it is a process of damage and reaction to it [15]. The key point in atherosclerotic inflammation is considered by many researchers to be the reduction of receptor absorption by low density lipoprotein [LDL] cells due to blocking, reducing the number of receptors. As a result, there is an accumulation in the

blood and tissues, in the walls of arterial vessels with deficiency in the cells of essential polyunsaturated fatty acids.

Omega-3 polyunsaturated fatty acids [omega-3-PNC] cleans the vascular walls of bad cholesterol, prevent the formation of cholesterol plaques, improve blood viscosity, normalize arterial pressure, increase the level of HDL reduce the level of LDL, strengthen the walls of vessels, making them elastic. The scarcity of poly-LCD in cells occurs because their transport system is LDL. And due to a lack of poly- LC, this system becomes untenable. Reducing the amount of poly-LC in cells compensator strengthens the synthesis of own eicosatrienic acid and proinflammatory leukotrienes. Excess accumulation of LDL through phagocytosis by blood and tissue monocytes [macrophages, Kuepfer cells liver] are subjected to modification with subsequent binding to immunoglobulins. This process requires the involvement of neutrophil leukocytes, which release a large number of active radicals involved in lipid peroxidation reactions[11]. These changes, as well as the complement system and the number of sialic acid receptor-related changes, have led to the oxidation of lipoproteins. In monocyte lysosomes, proteolysis of these structures occurs, but they cannot hydrolyze them. This requires that the monocyte membrane has appropriate receptors. Non-hydralized structures accumulate first in lysosomes, then take up the cytoplasm of monocytes, impair their functions and determine their death. These products of inflammatory leukotrienyare are excellent for strengthening atherosclerotic inflammatory process. The construction of atherosclerotic plasheo is formed by cells not of «local origin». They migrate to the formation via the mechanism of positive chemotaxis. These are the breakdown products of destroyed «foamy» monocytes, inteleykin-6, the factor of necrosis, cytokines, which stimulate the synthesis of acute phase proteins [9,10]. Modified LDL [m-LDL] can regulate gene expression for colonies macrophage stimulus [19]. This increases inflammatory response in vascular wall [14]. Specific inflammation mediators enhance LDL binding to cells enhance the transcription of the receptor gene LDL. In addition, m-LDP brings foreign antigens [lipopolysaccharides, bacteria, xenobiotics] to the intimate. The activation of macrophages leads to inflammatory and immune activation of endothelium and to an increase in the expression of adhesion molecules on the surface of endothelial jagdesins and blood-contacting cells. It turns out that in the formation of atherosclerotic plaque the whole system of blood cells is involved, starting with the system of stem cells. These are neutrophils, basophils, eosinophils [mast cells in tissues], monocytes [macrophages], fibroblasts, immunocompromised T- and B-lymphocytes, and smooth muscle cells. The first function is to dispose of damage products at the site of damage. And the function of the rest - the formation, ripening and organization of the connecting frame of the plaque. Smooth muscle cells migrate into the intima of the vessels and form a fibrous plaque, as if a crust over the «lake of fat».

Neutrophils, monocytes, immunocompromised cells come to the site of damage from peripheral blood. They and their predecessors, the fibroblasts have intramedullary ancestry. So, atherosclerotic plaque-this is cholesterol-encapsulated vascular wall [20]. The plaque, acting in the lumen of the vessel, causes its constriction and impedes normal blood flow. The plaque consists of an accumulation of intracellular and extracellular lipids, fibrin, cells, connective tissue, intermediates [glycosamine glycan, etc.] and calcium. Atherosclerotic plaque, increasing in size and ulcerating, can hold blood cells and blood clots on its surface, saturated with calcium salts, and when it is ruptured, plaque contents can get into the blood and cause thrombosis of the heart arteries, brain and other organs. It’s been shown that children have atherosclerosis for the first

time. Symptoms depend on the stage of the disease and the location of the localization cholesterol plaque.

In defeat children have shortness of breath, pain, lower extremity edema. Studies in recent years have shown that children have the first signs of atherosclerosis already before the age of 10, and plaques form by the age of 12-15. With age, fat densities increase, and then appear atherosclerotic changes, heartily vascular system. Pediatricians are tired of warning about the danger of «fast food», sodas, sedentary lifestyle when working with mobile phones, computers. It was determined that in children the number of risk factors for the development of atherosclerosis and cardiovascular system increases from 30% at the age of 11 years to 55% at the age of 15-17 years. At age 10, lipid spots cover 10% of the aortic surface, and at age 25, up to 30-50%. In children, the lipid stage of atherosclerosis development is the stage of thickening of the intimate layer of the vessels, arising after birth in coronary vessels involving smooth muscle cells, elastic and collagen fibers. This is particularly true for boys. Thus, the development of atherosclerotic lesion is an artery disease resulting from lipid and protein metabolism disorders, accompanied by the deposition of cholesterol or polyproteins in the vascular clearance [14]. The deposits are formed in the form of atheromatous plaques, followed by the growth of connective tissue in them and the calcification of the walls of vessels. This leads to deformation and narrowing of the clearance of the vessels up to obturation [of the blockage of the vessels]. Pathogenesis of atherosclerosis undergoes several stages: accumulation and modification of lipoproteins, migration of leukocytes and formation of penile cells, development of atherogenic disorders of lipid exchange: increasing the level of general blood cholesterol, an increase in the level of atherogenic lipoproteins [LDL], a decrease in the level of antiatherogenic lipoproteins [HDL]. Experimental scientists Research and clinical experience have come to three concepts on pathogenesis and atherosclerosis etiology: firstly, it is clear that atherosclerosis is a multifactorial disease, and it is impossible to link its development to any single factor. Its etiology is due to the interaction of genetic and external factors, none of which is an independent cause of the disease.

The second concept states that atherosclerosis and all related diseases are related to lifestyle and habits, the main elements of which are: a diet with a high content of saturated fat, cholesterol, calories, table salt; Smoking, alcohol abuse; low physical activity. Different combinations of these components lead to those biochemical and physiological changes that are combined under the name «risk factors» and can be transformed into atherosclerosis.

Finally, the third conceptual position is that in the development and atherosclerotic artery lesions two morphofunctional systems are interacting, constituting two key elements of atherogenesis - vascular wall and blood (plasma factors).

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