THE BIOCHEMICAL BASIS FOR THE DEVELOPMENT OF ATHEROSCLEROSIS

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ABSTRACT

The article discusses the factors affecting the occurrence of atherosclerosis at the biochemical level, as well as the pathogenesis of this process.

Keywords: *stenosis, aneurysm, chylomicrons, lipoproteins, proteoglycans, scavenger receptors, macrophages, ligands, oxidative stress, triacylglycerides.*

АННОТАЦИЯ

В статье рассматриваются факторы, влияющие на возникновение атеросклероза на биохимическом уровне, а также патогенез этого процесса.

Ключевые слова: *стеноз, аневризма, хиломикроны, липопротеины, протеогликаны, скавенджер-рецепторы, макрофаги, лиганды, оксидативный стресс, триацилглицериды.*

INTRODUCTION

Atherosclerosis is a disease that affects the arterial blood vessels (arteries) throughout the body. This disease causes fat, mainly cholesterol, to deposit in the inner lining of arterial vessels, which leads to narrowing of the blood vessels up to and including complete blockage. Atherosclerosis is the basis for the development of cardiovascular disease, the leading cause of premature death worldwide.

Aim. Analysis of the onset and development of atherosclerosis at the biochemical level.

MATERIALS AND METHODS

A review of the scientific literature on the biochemical basis of the development of atherosclerosis.

RESULTS

Atherosclerosis is a chronic disease. The problem with atherosclerosis is that it is asymptomatic for a long time and does not manifest itself clinically until the blood flow to the organs involved is impaired. As a rule, ischaemia symptoms appear when the lumen of a vessel narrows by more than 50% (so-called haemodynamically significant stenosis). Atherosclerosis is most common in the arteries of the aorta, heart, brain, lower limbs and kidneys. As a result, coronary heart disease (CHD), myocardial infarction, ruptured aortic aneurysms and ischaemic or haemorrhagic stroke are the leading causes of death.

Atherosclerosis is a multifactorial disease, and the risk of its development is determined by several combinations of factors. The main processes leading to the formation of fatty streaks are unknown, but animal experiments suggest that early endothelial dysfunction occurs under stress conditions. In this case, denatured lipids enter the lining layers of the inner membrane. They mediate inflammation, leading to leukocyte mobilisation and foam cell formation, a characteristic pathology of the fat chain. Atherosclerosis comes from the Greek word 'Athero' meaning mush; Marchand coined the term 'atherosclerosis' to describe the relationship between fatty degeneration and vascular stiffness. It is a mottled intravascular thickening of the subintimal lining. The earliest lesions are fatty streaks. Fatty streaks develop into fibrotic plaques, and unstable plaques cause a range of clinical symptoms. Damage to the arterial wall endothelium is an early pathological event in atherosclerosis. The arterial wall is a dynamic regulatory system. However, damaging factors can disrupt normal homeostasis and provide the onset of atherosclerosis.

It is important to note here that the arterial wall is a dynamic regulatory system. However, damaging factors can disrupt normal homeostasis and allow atherosclerosis to develop. For example, vascular endothelial cells and smooth muscle cells actively respond to inflammatory mediators such as IL-1 and TNF-a. These mediators also activate vascular endothelial cells, which start producing IL-1 and TNF-a. This fact is inconsistent with the previous view that only cells of the immune system can synthesise these cytokines. Based on the evidence that immune cells are not the only source of inflammatory mediators, further research was initiated into the role of "activated" endothelial cells and smooth muscle cells in the pathogenesis of atherosclerosis. These basic studies have identified several key components involved in the process of atherosclerotic inflammation. These components include endothelial dysfunction, lipid accumulation in the intima, mobilisation of leukocytes and smooth muscle cells to the vessel wall, foam cell formation and formation of extracellular matrix deposits. The cells present at the site of the atherosclerotic lesion interact with

each other in a continuous, disorganised and competitive manner, leading to the formation of fibrotic plaques after several decades, forming one of several possible profiles. Three pathologically important steps can be distinguished in this process: 1) fatty streak formation, 2) fibrotic plaque formation 3) atherosclerotic plaque destruction.

The underlying processes leading to the formation of fatty streaks are unknown, but animal studies suggest that early endothelial dysfunction occurs under stress conditions. In this case, denatured lipids enter the lining layers of the endothelium. They mediate inflammation, leading to leukocyte mobilisation and foam cell formation, a characteristic pathology of the fat chain.

Other factors include cholesterol, triglycerides and lipoproteins. Elevated serum concentrations of low-density lipoproteins (LDL) and triglycerides are associated with the formation of atherosclerotic lesions. Lipid metabolism occurs through exogenous and endogenous pathways. The exogenous pathway begins with the synthesis and secretion of chylomicrons in the small intestine from absorbed exogenous fat. Chylomicrons contain large amounts of triglycerides (about 85%) and apolipoproteins (Apo): apolipoprotein B-48 (Apo B-48), apolipoprotein C-II (Apo C-II) and apolipoprotein E (Apo E). Apo C-II is an important cofactor for the enzyme lipoprotein lipase, whose function is to catabolise (lipolysis) triglycerides in chylomicrons into fatty acids, thereby facilitating the entry of fatty acids into adipose tissue. After the action of lipoprotein lipase, the chylomicron residues are relatively enriched in cholesterol due to the loss of triacylglycerides and are transported to the liver via apolipoprotein E (Apo E) for absorption. The endogenous pathway starts with the synthesis of very low density lipoprotein (VLDL) particles, which are rich in triglycerides and contain apolipoprotein B-100 (Apo B-100), Apo C-II and Apo E. After removal of triglycerides in adipose tissue, some of the remaining HDL is metabolised into LDL particles by lipoprotein lipases, which carry complex cholesterol esters and small amounts of triglycerides. Small LDL particles pass through the endothelial barrier and are deposited in the extracellular matrix of the subendothelial space due to Aro B-100 binding to proteoglycans, one of the most important molecules for lipoprotein retention Deposition of LDL particles in the vessel wall is considered to be the first step in the development of atherosclerosis.

Lipoprotein abnormalities caused by obesity are evident in a study conducted by the Federal Research Centre of the Institute of Cytology and Genetics, Siberian Branch, Russian Academy of Sciences, a federal state-funded scientific institution. The study focused on the prevalence of hypercholesterolemia (hyperC) and low-density lipoprotein hypercholesterolemia (LDL hyperC) in the context of abdominal

obesity (AO) in a Novosibirsk population aged 25-44 years. A one-stage population-based study was conducted in a population aged 25-44 years in Novosibirsk, Russia: 1415 individuals, including 670 men (47.3%) and 745 women (52.7%, pregnant women and those on maternity leave were not included in the study); the presence of AR, hyperCH and LDL hypercholesterolemia was assessed. Results showed that individuals with AR had higher mean total cholesterol and LDL cholesterol levels; the prevalence of hyperC in those with AR was 1.3 and 1.2 times higher than in those without AR; women with AR had 1.2 and 1.3 times higher prevalence than those without AR; men with AR had 1.4 and 1.2 times higher prevalence than men without AR. Logistic regression analysis showed that AR was statistically significantly associated with the presence of atherogenic hypercholesterolemia in both men and women in the younger age group below 45 years. Significant associations were observed for AR with both hypercholesterolemia and LDL hypercholesterolemia in men and only LDL hypercholesterolemia in women.

In the second stage of atherosclerosis, accumulated subendothelial LDL is oxidised by resident vascular cells to oxidised LDL (ox-LDL), causing the production of monocyte chemoattractant protein-1 (MCP-1) and macrophage colony-stimulating factor (M-CSF) in vascular cells. In addition, the presence of risk factors such as smoking, hypertension, hyperglycaemia and hyperlipidaemia increases the production of reactive oxygen species (ROS) and therefore suppresses the protective endogenous antioxidant response. Oxidative (oxidative) stress further accelerates LDL oxidation and reduces endothelial function, contributing to endothelial dysfunction. Chronic oxidative stress is a stronger risk factor for atherosclerosis formation: in the early stages of LDL modification, lipid components interact with AOS and multiple types of lipid oxidation products are formed. Lipid oxidation products such as hydroperoxides and lysophospholipids can bind to and modify apolipoprotein B (Apo B) protein. Non-enzymatic oxidation of Apo B leads to changes in the amino acid side chains with damage to the peptide bonds, significantly altering the composition and structure of Apo B. When the ApoB protein is modified, oxLDL becomes the ligand of the scavenger receptor. OxLDL then recognises and interacts with the two major scavenger receptors on macrophages - the class A scavenger receptors and the class B scavenger receptors, also known as cluster differentiation 36 (CD36). Class A scavenger receptors recognise modified Apo B proteins on oxLDL particles and oxidised phospholipids are recognised by CD36. Macrophages interacting with the scavenger receptors are activated and take up the oxLDL particles. Macrophages overloaded with lipoprotein particles become frothy (xanthom) cells and eventually die by apoptosis, releasing accumulated lipids and cytokines and attracting new

monocytes/macrophages to the focus. After the death of the foamy cells, the connective tissue framework ('fibrous cap') of the atherosclerotic plaque is formed by fibroblasts.

CONCLUSION

To summarise the data analysed, lipid metabolism disorders and lipid modification are important for the initiation and progression of atherosclerosis. Hyperlipidemia as well as other risk factors that increase oxidative stress (production of reactive oxygen species) lead to the accumulation of oxidized low density lipoproteins, which is the first step in the development of atherosclerosis. With the development of endothelial dysfunction, the regulation of vascular tone is impaired, endothelin-1 levels are increased and nitric oxide levels are decreased. The complex, multicomponent interaction between impaired lipid metabolism, endothelial dysfunction and inflammatory mechanisms of atherosclerosis requires further elucidation to improve therapeutic and diagnostic strategies for the treatment of atherosclerosis and cardiovascular disease.

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