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Helicobacter Pylori and the Risk of Coronary Heart Disease (Literature Review)

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ABSTRACT: The article analyzes data from foreign and Russian literature on the relationship between Helicobacter pylori infection and the risk of developing cardiovascular pathology. Variants of pathogenetic mechanisms of formation of correlation between Helicobacter pylori and the risk of IHD are analyzed. There is more and more evidence that certain microbial agents may have an etiopathogenetic role in the development of atherothrombosis.

Keywords: Helicobacter pylori, microbes, atherothrombosis, cardiovascular diseases.

Helicobacter pylori (H. pylori), a bacterium that causes peptic ulcer disease, has been proposed as one of the microbes involved in the development of atherothrombosis. This hypothesis is based on the following observations: a higher prevalence of H. pylori infection in patients with coronary heart disease, myocardial infarction, cerebrovascular diseases; the relationship between H. pylori infection and cardiovascular risk factors such as serum triglyceride and cholesterol concentrations and plasma fibrinogen; the level of H. pylori correlates with the level of acute phase proteins associated with an increased risk of coronary diseases, such as C-reactive protein; and conflicting PCR studies suggesting the presence of H. pylori infection in atheromas. Analysis of scientific data suggests that infection with H. pylori can indirectly contribute to the development and complicate atherothrombosis and cardiovascular disease. In our opinion, very large randomized trials are needed to prove the existence of a possible link between H. pylori and cardiovascular disease. Key words: Helicobacter pylori, cardiovascular risk, coronary heart disease, atherosclerosis Introduction. Currently, scientists are increasingly studying comorbid diseases. This is especially true in relation to significantly common cardiovascular diseases (CVD) (most of which are coronary heart disease (IHD) [5, 7]) or cerebrovascular diseases with a pathogenic mechanism of atherothrombosis, diseases of the gastrointestinal tract [1]. Among the combined diseases of internal organs, about 52% is accounted for by the combination of ischemic heart disease and peptic ulcer disease (PUD), which leads to an atypical course of diseases and late diagnosis [6]. Mutual aggravation and progression of the diseases under consideration is based on the combination of some pathological links [3]. Genetic predisposition and general risk factors play an important role in the occurrence of a combination of ischemic heart disease and peptic ulcer disease. In recent years, the theory of "response to injury" has been proposed as an inducer of the mechanism of atherothrombosis; Basically, this theory states that inflammatory and immunological processes caused by a viral or bacterial infection are the main cause of the atherosclerotic process [10]. A number of studies have revealed a correlation between cardiovascular risk factors, markers of inflammatory processes in atherosclerotic process and Helicobacter pylori (H. pylori), leading to the development of coronary heart disease (IHD) [12]. H. pylori infection activates both local and systemic inflammatory process and can be considered as a possible additional risk factor for the development and exacerbation of coronary artery disease.

The results of numerous studies suggest a possible pathogenetic or mediated role of H. pylori infection in the development and / or course of diseases not related to digestion. Despite the many studies that confirm the role of H. pylori in the pathogenesis of CVD, a number of studies have drawn very contradictory conclusions [9]. Main part Objective of the study: to study the available literature data on the role of H. pylori in the pathogenesis and progression of coronary artery disease and the risk of cardiovascular pathology. Materials and research methods: a review of domestic and foreign literary sources Research results and their discussion H. pylori is a bacterium that is found everywhere, the prevalence of which varies depending on the socio-economic conditions of the population [10]. It is considered an etiopathogenetic agent of both benign and malignant gastroduodenal diseases; the destruction of the bacteria leads to scarring of peptic ulcers, suppression of gastritis, a decrease in the recurrence of peptic ulcer disease, an improvement in the symptoms of dyspepsia, and regression of the growth of MALT lymphoma. It has been classified by the World Health Organization (WHO) as a type 1 carcinogen [2]. In addition, in recent years, it has been suggested that H. pylori is of great importance in the atherothrombotic process, the evidence for this is analyzed below. The study of the relationship of H. pylori infection with cardiovascular diseases (ischemic cardiopathy and ischemic cerebrovascular disease) was carried out by different investigators. Possible mechanisms of H. pylori impact on the body are: 1) activation of the inflammatory process with the production of cytokines, eicosanoids and other mediators; 2) molecular mimicry between antigens of bacteria and components of tissues of a macroorganism with their further autoimmune damage; 3) interaction with mast cells, followed by the secretion of biologically active substances that act

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on blood vessels, bronchi, and other internal organs; 4) the development of allergic reactions, predominantly of an immediate type; 5) a decrease in the barrier function of the intestine, leading to the entry of toxic products, allergens into the blood; 6) the absorption of macro- and microelements, in particular iron, for the processes of their vital activity and, consequently, the robbery of the macroorganism [2]. Research on the relationship between H. pylori serotype and cardiovascular risk factors. Factors that increase the risk of atherothrombosis, such as increased plasma fibrinogen and clotting factor VII, hypercholesterolemia, and hypertriglyceridemia, have long been studied. There are conflicting results regarding the relationship between these factors and H. pylori infection. Niemëla et al. [3] found significant differences between triglycerides and HDL cholesterol among subjects seropositive and seronegative for H. pylori. According to Rengström [9], no significant differences were found in plasma levels of fibrinogen, cholesterol, or triglycerides among seropositive and seronegative patients. In another large study, the authors showed a significant increase in fibrinogen in seropositive patients, but did not find significant differences in plasma cholesterol and triglyceride levels in some seronegative patients [5]. Coagulation factor VII was also investigated in this study, but no significant differences were found among patients seropositive for H. pylori versus seronegative. A study by Pellicano R. revealed the ability of bacteria to enhance platelet aggregation and stimulate the procoagulant activity of blood components [7]. In the work of Weydig C., the possible mechanisms of the proagregational properties of H. pylori are indicated by means of adhesion molecules (L- and P-selectins), glycoprotein Ib, and von Willebrand factor [11]. Research on the relationship between H. pylori serotype and inflammatory markers. There is growing evidence that inflammation plays an etiopathogenetic role in the development of atherosclerosis and that several markers of inflammation are associated with a greater risk of CHD. Markers such as C reactive protein (CRP), the level of leukocytes in the blood, fibrinogen in plasma, or the presence of heat shock proteins (HSP) worsen the prognosis of CHD [8, 10].

When comparing seropositive patients with respect to H. pylori with seronegative patients, Patel et al. [15] found an increase in the level of leukocytes in the blood and fibrinogen. Birnie et al. Found an increase in bacterial HSP for myocytes, in particular HSP-60 and HSP-65 [11], while an increase in C reactive protein was associated with a worse prognosis in patients with unstable angina pectoris or recent myocardial infarction. The relationship of coronary cardiopathy with TNF-α, also a marker of inflammation, was also investigated, but no statistically significant differences were found. The presence of H. pylori in atheromatous plaques. The studies were carried out using polymerase chain reaction (PCR) to detect H. pylori DNA in the tissues under study. These studies, besides being few in number (only 2 groups of researchers presented the results), are also contradictory. Cunningham et al. Found H. pylori in atheromatous plaques (First European Congress on Chemotherapy), while Blasi et al. [12], in a study conducted on surgical specimens of aortic aneurysm, found no H. pylori in any of 51 samples, despite 47 patients being seropositive. On the other hand, bacteria that resist serum, or the lytic activity of serum complement, are known to survive longer in the bloodstream, allowing it to colonize other areas of the body. In this regard, H. pylori is susceptible to the bactericidal activity of human serum (mainly due to the activation of the alternative complement pathway), and there are certain differences in the combination of different strains to the C3 compliment, which makes survival of this bacterium in the blood stream unlikely [16]. However, in a later study by the team led by Oshima T., bacteria were found in vascular biopsies [14]. Baghdad scientists in 2015. also found Helicobacter pylori specific DNA in atherosclerotic plaque from the material of the coronary arteries. In addition, they assessed the role of H. pylori virulence factor (cytotoxin associated gene (CagA)), lipid profile, and studied the level of pro-inflammatory markers (C-reactive protein) as risk factors for coronary artery disease in 70 patients with coronary artery disease and the presence of H. pylori. As a result, significant differences were obtained in the mean value of CagA, CRP and the detection of Helicobacter pylori specific DNA in an atherosclerotic plaque from the material of the coronary arteries. Its association with the positivity of anti-Helicobacter pylori therapy and clinical symptoms was interpreted by the authors as evidence of the involvement of H. pylori infection in the progression of coronary artery disease [11]. In a large meta-analysis involving more than 1000 patients, the possibility of a correlation between risk factors for coronary heart disease and H. pylori was examined. The authors suggest that the correlation between the detection of H. pylori and the identification of cardiovascular risk factors (CVS) can be explained by the predominant publication of only positive results, or coincidences, or both factors simultaneously [4].

In this regard, the large HOPE study should be noted, which did not confirm a significant association between H. pylori infection and the risk of cardiac and vascular pathology. Based on scientific evidence, we propose various mechanisms to explain the association of H. pylori infection with cardiovascular disease. Inflammatory response. A subfebrile chronic inflammatory response is produced by provoking an atherogenic process through changes in some cardiovascular risk factors, such as clotting and lipid factors, with the release of fibrinogen, CRP, tumor necrosis factor (TNF-α) and interleukin 6 (IL-6), in addition to an increase in the number of leukocytes in the blood, which can cause a prothrombotic state. In adults, H. pylori induces an active chronic inflammatory process with the presence of neutrophils, T-lymphocytes, B-lymphocytes, and plasma cells [14]. The specific cellular response is characterized by the formation of T-helper lymphocytes, leading to an increase in cytokines, especially IL-1, IL-6, IL-8, TNF-α and

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interferon-γ. The ability to induce cytokines differs among different strains of H. pylori, in particular, CagA +, CagE +, VacAs1 +, VacAm1 +, BabA2 + - genes and cultural properties [10]. With CagA + strains, the production of the most intensely released cytokines with great diversity was observed [15]. A number of researchers suggest that it is the virulent cytotoxic strains of H. pylori, in particular with CagA, that are capable of causing pathological changes in the vessels. It was revealed that CagA-associated actin modification affects its contractile activity and is expressed through a cascade mechanism that includes specific transporter proteins (in particular, CagF) and a mediator link represented by enzymatic and non-enzymatic components [16]. Anti-CagA antibodies were found in the cytoplasm of smooth muscle cells and they cross-reacted with antigens from intact and atherosclerotic vessels; binding them to antigens of damaged arteries, which can contribute to the progression of atherosclerosis in individuals infected with H. pylori [9]. Apparently CagA is one of the most important agents providing cardiopathogenicity of H. pylori. However, none of the studies denying the role of H. pylori in the pathogenesis of CHD evaluated the prevalence of virulent CagA-positive strains of H. pylori among the examined patients [9]. On the other hand, it has also been observed that soluble H. pylori secretions promote plaque aggregation in the microcirculation of the gastric mucosa [17]. Simonova Zh.G. et al. Developed an integrated circuit of the multifaceted pathogenic action of a microorganism in relation to the cardiovascular system, which we present in Fig. [eight]. It shows the main pathogenetic chains developing as a result of the implementation of a specific H. pylori virulence factor. In her opinion, the predominant role is played by antitelogenesis, the action of cytokines and modulators of systemic inflammation, and the CagA protein triggers the pathochemical cascade of molecular agents produced by the microorganism itself [8]. Rice. Pathogenetic mechanisms of development and progression of H. pylori-associated diseases of the cardiovascular system. Fig. The pathogenetic mechanisms of development and progression of H. pylori-associated cardiovascular diseases.

Research results and discussion. Changes in blood lipids H. pylori infection causes an increase in cholesterol and triglyceride levels with a decrease in HDL levels, contributing to the development of dyslipidemia, a known cardiovascular risk factor. Formation of oxidants A number of authors have suggested that the formation of oxidants is also important. A decrease in antioxidants has been observed in patients with H. pylori, which can lead to the activation of lipid peroxidation and, therefore, to the development of atherogenesis, since the oxidation of low density lipoproteins (LDL) is the first of the main steps in the atherogenic process. Anti-HSP Cross-Reactivity Another theory is anti-HSP antibodies with cross-reactivity. It was revealed that H. pylori produces HSP-60 with a high degree of sequence homology with human HSP-60 in the endothelium. Hyperhomocysteinemia Hyperhomocysteinemia is a relatively new cardiovascular risk factor as it has been observed that increased homocysteine levels are associated with an increased risk of cardiovascular disease. In this regard, in patients with chronic gastritis, usually caused by H. pylori infection, there is a decrease in the absorption of vitamin B12 and folic acid, thereby causing secondary hyperhomocysteinemia [13]. Endothelial dysfunction The studies of Rasmi Y., Raeisi S. studied the mechanism of endothelial dysfunction in the pathogenesis of cardiac syndrome X, caused by structural and functional disorders of endothelial cells as a result of inflammation and proliferative changes from H. pylori, leading to a change in the elastic properties of blood vessels through pro-inflammatory cytokines, cellular molecules adhesion, growth factors and acute phase proteins. [8]. Conclusion Thus, the mechanisms of the pathogenic action of H. pylori on CVS are multifaceted and can lead to the formation of acute and chronic diseases of the cardiovascular system. However, the role of H. pylori in the etiopathogenesis of CVD remains unclear. There are new reports in the literature about the possible relationship between H. pylori and IHD. Some researchers believe that even if a link exists and reverses after the eradication of a chronic infection, very large randomized trials are needed to prove that there is a possible link between H. pylori and CVD. Currently, the literature data on the relationship of H. pylori with IHD are scattered and contradictory, yet they allow us to supplement the fundamental concepts of the pathogenesis of diseases that develop in the framework of inflammatory and immune responses at the level of various organs and systems outside the digestive tract, in particular in the CCC. Although there is no precise data confirming the role of H. pylori in the development of atherosclerosis, the accumulated evidence indicates that, along with other factors of pathogenesis, these bacteria can contribute to the development of this disease. Contradictions about the ambiguity of the role of H. pylori in the formation of atherosclerosis and ischemic heart disease may be associated with their genetic heterogeneity. In general, the above contradictory data provide a basis for further study of this problem in order to identify reliable information.

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