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ENDOTHELIAL DYSFUNCTION AS A LINK IN THE PATHOGENESIS OF ANKYLOSING SPONDYLITIS AGAINST THE BACKGROUND OF A NEW CORONAVIRUS INFECTION

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ABSTRACT

The main purpose of this work was to substantiate the feasibility and possible directions of the influence of means of pharmacological correction of endothelial dysfunction for the prevention of pathological conditions associated with a new coronavirus infection. Theanalysis of the available literature on the functions of the endothelium was carried out, the study of foreign and domestic experience on the possible directions of pharmacological correction of endothelial dysfunction was carried out. A review of the available literature data on endothelial dysfunction with substantiation of the role of vascular endothelial damage as one of the central links in the pathogenesis of acute respiratory distress syndrome is presented. The phases of the formation of stages of endothelial dysfunction are shown, the mechanisms of endothelial damage in a new coronavirus infection are determined. Possible directions for the pharmacological correction of endothelial dysfunction are proposed, which will prevent the risk of complications from a new coronavirus infection, including through the development of path genetically grounded directions of pharmacotherapy.

KEYWORDS: *Ankylosing spondylitis, Asymmetric dimethylarginine, homocysteine, endothelial dysfunction, cardiovascular pathology, COVID-19.*

INTRODUCTION

Endothelial dysfunction is defined as a pathological condition characterized by progressive damage of endothelial cells and accompanied by a violation of its functions. Endothelial

dysfunction is an important pathogenetic link in a wide range of diseases, which determines the high practical significance of the development of methods for its diagnosis.

Among the reasons that can initiate endothelial dysfunction, it is necessary to highlight systemic inflammation and activation of lipid peroxidation processes. According to researchers, inflammatory mediators can cause activation and damage to the endothelium, leading to impairment of its function, which has been convincingly proven in particular pathology, in particular, in osteoarthritis [8].

Analysis of the literature data showed that the main causes of ED are the association of inflammatory markers (asymmetric dimethylarginine, homocysteine, endothelin 1-21, type 1 vascular endothelial adhesion molecule, type 1 intercellular adhesion molecule, reactive hyperemia index), impaired adsorption-rheological properties of blood, as well as persistence, contributing to the development of endothelial dysfunction, is asymmetric dimethylarginine (ADMA), which inhibits nitric oxide synthase. The main functions of nitric oxide in the cardiovascular system are associated with its vasodilatory effect, inhibition of smooth muscle cell proliferation, as well as platelet aggregation and adhesion [10]. That is why, with an increase of ADMA in the blood plasma, insufficient vasodilation of blood vessels occurs, the function of the endothelium worsens, which contributes to the development of cardiac pathology.

Ogawa T. et al. have investigated the pathways of metabolism of ADMA [11]. After intravenous administration of labeled ADMA to rats, 2% of the molecules were excreted with exhaled carbon dioxide, 14% was excreted in the urine, and 86% was accumulated in the liver, pancreas and kidneys in the form of citrulline. In subsequent works of these authors, two enzymes were isolated that participate in the hydrolysis of ADMA. These enzymes were found to be dimethylargininedimethylaminohydrolase (DDAG) [12] and alanine glyoxylate aminotransferase 2 (AGAT2) [13]. DDAG is the main enzyme that hydrolyzes about 80% of ADMA to form dimethylamine and citrulline. DDAG is divided into two main isoforms: DDAG1 and DDAG2 [14]. DDAG1 is synthesized in the digestive, respiratory, excretory systems, the central nervous system and the male reproductive system. DDAG2 is synthesized in the bone marrow, digestive system, excretory system, and the female reproductive system [15].

In rheumatological patients, a change in endothelial function is a unique "crossroads" of pathogenetic pathways, on the one hand, determining the progression of the immune-inflammatory process (traffic of immunocompetent cells to target organs, antigen-presenting function and cytokine production by activated endothelial cells), on the other hand, leading to accelerated progression atherosclerosis and an increase in the risk of its complications (decrease in the antithrombogenic potential of the endothelial lining, subendothelial accumulation of oxidative low density lipoproteins, foam cells, inflammatory cells) [9].

A.L. Maslyansky et al., 2015, assessed the functional state of the endothelium in patients with rheumatological diseases [9]. Researchers studied the effect of various markers of inflammation on ED, as well as the increase in the level of markers of ED, depending on the nosological form. Based on the examination of 286 patients with rheumatological diseases, the researchers came to the conclusion that in patients with ankylosing spondylitis, the levels of such markers as type 1 intercellular adhesion molecule, type 1 vascular endothelial adhesion molecule were increased, in addition, in ankylosing spondylitis, the greatest increase in the level of homocysteine was observed. Compared with other groups of rheumatological patients. At the same time, with

ankylosing spondylitis, the level of ADMA was lower than in patients with systemic scleroderma, rheumatoid arthritis, systemic lupus erythematosus, but higher than in the control group. There is also evidence that the well-known association of increased homocysteine levels with the development of cardiovascular disease is mediated by mechanisms involving ADMA.

The research results of E.D. Egudina et al., proved that in addition to markers of inflammation, there are also other factors that contribute to the development of ED in patients with ankylosing spondylitis. According to the authors, ED develops in 53% of patients with ankylosing spondylitis and in the presence of vascular pathology is accompanied by an increase in the blood concentration of cGMP and a decrease in the content of prostacyclin [29].

In the work on the role of systemic inflammation and endothelial dysfunction in patients with ankylosing spondylitis, D.A. Poddubny et al. provided evidence that patients with ankylosing spondylitis have significantly increased levels of circulating endothelial cells, which are a marker of endothelial damage, as well as increased levels of von Willebrand factor. Endothelium-dependent vasodilation is reduced in 47% of patients [30]. The study shows the relationship between systemic inflammation and endothelial dysfunction.

The presence of ACE2 on the endothelium and smooth muscle cells of blood vessels is the reason for the involvement of the cardiovascular system in systemic damage, which is observed in almost all patients with COVID-19.

The endothelium is one of the tissues involved in the defeat of the SARS-CoV-2 virus, and therefore in some works even use the term "endothelitis" [20]. In this case, there is a pronounced endothelial dysfunction associated with the introduction of the virus into cells. This is accompanied by endothelial damage, endothelial dysfunction, and perivascular inflammation, which exacerbates endothelial damage [21].

Despite the high density of expression of ACE2 on endothelial cells, there is evidence of organ features of the distribution of the ACE2 protein on the endothelium. Currently, there is the only work in which clinical material obtained from a biopsy or autopsy was investigated. In total, the distribution of ACE2 in the tissues of 15 organs from 93 patients with various diagnoses was investigated [9]. The authors noted that ACE2 is present on the endothelium of both arterial and venous vessels of almost all organs. Moreover, smooth muscle cells of arterial vessels showed ACE2-positive staining. ACE2 was found even on the endothelium and smooth muscle cells of the cerebral vessels, while it was not found in other brain cells. However, ACE2 is not expressed on the endothelium of the sinusoidal capillaries of the liver. Thus, the presence of a receptor on the vascular endothelium for the introduction of the virus makes it one of the most important targets for SARSCoV2. In addition to endothelium and smooth muscle cells, ACE2 is expressed in significant amounts on the pericyte membrane, which also contributes to the development of vascular disorders [10].

The introduction of the SARS-CoV-2 virus into endothelial cells has been proven by numerous studies. Microscopic examination of tissues of patients with COVID-19 in several studies revealed damage to the endothelium of various organs. So, in a patient with COVID-19, pneumonia, when examining the pulmonary arteries of medium diameter, endothelial damage with vacuolization of the cytoplasm, signs of desquamation of endothelial cells was found [22]. The SARS-CoV-2 virus was also detected in the endothelium and extracellular space of lung

capillaries [23]. In a patient with COVID-19, complicated by mesenteric ischemia followed by resection of a section of the intestine, histological examination of the resected area revealed pronounced "endotheliitis" of the vessels of the submucosal layer with signs of direct lesion of endotheliocytes by the virus, phenomena of apoptosis, perivascular inflammation, and mononuclear infiltration [20]. The authors suggest that COVID-19-induced endothelial damage may explain the systemic impairment of microcirculatory function in various organs in patients with COVID-19 [20].

CONCLUSION

Thus, the presented analytical review on the influence of the functional state of the endothelium on the course of ankylosing spondylitis and the formation of pathological processes initiated by exposure to the body of the coronavirus from the SARS-CoV-2 family makes it possible to single out endothelial damage as one of the central links in the pathogenesis of the development of cardiovascular complications. Due to AS and other severe complications of COVID-19. Timely differentiated prescription of drugs for the pharmacological correction of endothelial dysfunction will most likely improve the prognosis of a new coronavirus infection, especially against the background of concomitant chronic diseases complicating the course of COVID-19. The study and understanding of the causes of endothelial dysfunction in rheumatic diseases seems promising, since it will reveal the mechanisms of the rapidly progressive atherosclerotic process and high cardiovascular mortality.

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