VASCULAR ENDOTHELIAL DYSFUNCTION AS A PREDICTOR OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract. Systemic lupus erythematosus (SLE) is a systemic autoimmune rheumatic disease of unknown etiology with an ambiguous course and prognosis, developing on the basis of a genetically determined defect in immunoregulatory mechanisms, leading to overproduction of a wide range of organ-specific autoantibodies to various components of the nucleus and immune complexes that cause damage to tissues and immune-inflammatory disorders functions of internal organs. Pathology of the cardiovascular system, kidneys and central nervous system in SLE is one of the most frequent manifestations of the disease and largely determines its prognosis, and the pathogenetic structures of lesions of the myocardium, coronary, renal and cerebral vessels remain insufficiently studied. SLE is characterized by the development of vasculitis of varying severity. Activation of pro-inflammatory mediators, monocytes, T cells leads to endothelial damage. In recent years, the contribution of endothelial dysfunction (ED) (due to chronic inflammation) to the progression of systemic lupus erythematosus has been discussed.

Keywords: Systemic lupus erythematosus, endothelial dysfunction, vascular endothelial growth factor

Currently, the determination of predictors of an unfavorable outcome of the disease is of great relevance, since they allow a more rational approach to the selection of more adequate therapy. Systemic lupus erythematosus (SLE) is a particularly significant problem in clinical rheumatology, since the survival rate of this group of patients remains very low [55]. Therefore, all attempts aimed at finding predictors that affect life expectancy in a given disease are of leading importance and this is of practical interest. Over the past decade, there have been major changes in the approaches to the management of SLE patients, which have significantly

improved treatment outcomes and achieved a 5-year survival rate of 93% -94%. However, problems remain associated with the early development of atherosclerosis in patients with this pathology. Thus, according to [39], the development of myocardial infarction in SLE is observed 10 times more often than in the general population. Therefore, in recent years, many studies have been devoted to the contribution of endothelial dysfunction (DE) to the pathogenesis of the development of atherosclerosis due to chronic inflammation in this disease, since early atherosclerotic vascular lesions, primarily coronary and cerebral arteries, belong to the genesis of the most common causes of premature death in SLE patients. [43].According to the literature [33], the early development of atherosclerosis develops as a result of a complex interaction between traditional risk factors and factors directly related to the disease itself and its treatment. However, the role of traditional and non-traditional risk factors for atherosclerosis in SLE is still under discussion. It is well known that SLE is characterized by the development of vasculitis of varying severity and the activation of pro-inflammatory mediators, monocytes, T cells leads to damage to the endothelium and increases the stiffness of the artery wall. Consequently, the problem of studying the functional state of the endothelium is of great interest in the study of possible key causes in the development of premature complications of the disease and predicting SLE [34]. Modern research methods make it possible to identify groups of patients with a high risk of atherosclerosis. However, this circumstance does not completely solve all the problems, since there remain controversial questions about the degree of endothelial damage in various situations, in particular, depending on the clinical variants of the course of SLE and the state of homeostasis of the body. This is due to the fact that the vascular endothelium is currently considered as an organ of internal secretion with a complex mechanism [48]. The vascular endothelium is very sensitive to various changes in the body, primarily to immunological shifts. One of the most important factors ensuring the vital activity of the endothelium is the vascular endothelial growth factor (VEGF). It promotes endothelial proliferation, stimulates trophic functions, serves as the main regulator of physiological angiogenesis, and is

considered as a mediator of DE [36]. In a number of studies [32], in systemic diseases of the connective tissue, in particular in SS, an increase in serum VEGF, TNF α, interleukins (IL) 1β, 6, 8, 10, which play an important role in the pathogenesis of vasculopathy, was noted. Thus, newly recruited macrophages produce TNF-α and other cytokines during the interaction of VEGF, or during cellular contact with activated endothelial cells. This increases the ability of macrophages to synthesize VEGF, creating a vicious cycle of inflammation.

The manifestations of DE are also associated with a lack of production or bioavailability of nitric oxide in the arterial wall, which provides vasodilation, inhibition of the expression of adhesion molecules, platelet aggregation, antiproliferative, antiapoptotic and antithrombotic effects. In atherosclerosis, the balance between humoral factors that have a potential protective effect (nitric oxide, endothelial hyperpolarization factor, prostacyclin) and factors damaging the vessel wall (endothelin-1, thromboxane A2, superoxide anion) is disturbed. Criteria for endothelial dysfunction may be some humoral factors associated with the activity of endothelial cells, such as endothelin-1, von Willebrand factor, E-selectin, intercellular adhesion molecules, vascular cell adhesion molecules, and others [30]. DE is detected in SLE both in the early and late stages of the disease, regardless of the activity of the disease and the presence of cardiovascular risk factors. However, the mechanisms of DE development are currently not fully understood and are of considerable interest.Studies have shown [25] that in SLE, there is an increase in the levels of intercellular adhesion molecules, vascular cell adhesion molecules, E-selectin, von Willebrand factor, which is reliably associated with the presence of atherosclerotic plaques in the vessels or signs of preclinical atherosclerosis [23]. On the other hand, some authors point out that [L.S. Tam et al.] Hyperhomocysteinemia affects endothelial function in women with SLE; others believe [15] that an increase in the stiffness of the vascular wall of the common carotid artery, aorta, and femoral arteries in young women with SLE is associated with immune inflammation and metabolic changes, which can lead to to a higher prevalence of cardiovascular diseases in this category of patients and an earlier development of atherosclerosis. There is also an

opinion [51] that men with SLE are a high risk group for the development of atherosclerosis, and an increase in the level of C-reactive protein in the blood serum is associated with a thickening of the intima-media complex in the carotid arteries. There are only separate studies on the detection of DE in SLE by ultrasound imaging of the brachial artery, which are controversial [49]. Magadmi E.I. et al. (2004) described the negative effect (in SLE) of high systolic blood pressure and thickening of the intima-media complex on the expansion of the brachial artery during reactive hyperemia [32]. Lima D.S. (2002) et al. revealed DE in SLE patients regardless of risk factors, while Soer J.B. (2004) found no such changes in SLE [29]. The development of atherosclerosis is associated not only with traditional risk factors in the general population (age, male sex, heredity, hypertension, etc.), but also with the disease itself, timely diagnosis of atherosclerosis risk factors in patients with SLE and more aggressive therapy can prevent its progression [31].The literature of recent years indicates that the degree of DE is associated with the degree of activity of the inflammatory process in SLE. According to some data [37], there is a correlation between the degree of endothelial dysfunction and the duration of SLE disease. In patients with rheumatic diseases, including SLE, irrespective of the presence of hypertension, impaired left ventricular diastolic function, changes in left ventricular geometry, dilatation and hypertrophy, decreased myocardial elasticity, and increased pressure in the right ventricle were revealed [38]. Changes in the valvular apparatus of the heart were also noted in patients with SLE. Other authors [40] have identified signs of myocardial cardiosclerosis at autopsy and myocardial biopsy in SLE patients without clinical and anamnestic manifestations of heart disease. But at the same time, the data on the role of impaired left ventricular diastolic function in the interaction of factors of pathogenesis and development of the disease are ambiguous.The balance between pro-inflammatory and anti-inflammatory cytokines and other molecular factors of inflammation, as discussed above, may be crucial for the progression of atherosclerosis. Pro-inflammatory and, therefore, proatherogenic are: CRP, E-selectin, endotoxin, TNF, IL-1b, IL-6, IL-8, IL-12, IL-18, macrophage chemoattractant protein, leukotriene P4, lipoxygenase degradation products ... Anti-

inflammatory, or atheroprotective, are IL-4 and IL-10. Of the mediators of interleukocyte interaction, the greatest importance in atherosclerosis is given to IL-1, IL-6 and TNF. IL-1, IL-6 and TNF increase the adhesion of blood cells to the vascular endothelium and their procoagulant activity, increase the mobility of neutrophils, for a number of cells are a chemoattractant, promote the activation of cells in the focus of inflammation, The production of other cytokines, as well as prostaglandins, collagen synthesis and fibronectin, stimulate phagocytosis, the generation of superoxide radicals, cause degranulation of mast cells, and cause the synthesis of proteins in the acute phase of inflammation. All this contributes to the development of exudative and proliferative components of the inflammatory response. TNF has the ability to induce apoptosis in cells, as well as to stimulate the synthesis of metalloproteinases and proteolytic enzymes (tryptase and chymase) [41]. Many researchers have shown an increase in the levels of IL-1, IL-6 and TNF in SLE patients compared with the control group, and their increase was associated with the initial signs of the development of atherosclerotic vascular lesions in this category of patients [five]. Inflammatory cells infiltrating the plaque participate in the degradation of the extracellular matrix by phagocytosis and secretion of proteolytic enzymes (plasminogen activators, matrix metalloproteinases), which can cause thinning of the fibrous coating and cause rupture of atherosclerotic plaques [3]. An increase in the levels of matrix metalloproteinases in patients with SLE compared with healthy patients has been established, which indicates an increased risk of instability of atherosclerotic plaques in these patients [7]. In patients with SLE, hyperhomocysteinemia was established, which was associated with a thickening of the intima-media complex and an increased level of coronary calcium, and in patients with stable and unstable plaques, the concentration of homocysteine was significantly different [8].

It has been proven that the risk of coronary heart disease (CHD) in SLE patients is 5-6 times higher than in the general population, and in young women with SLE aged 35-44 years - 50 times [13]. According to prospective studies, approximately 10% of patients with SLE have clinical manifestations of atherosclerosis (angina

pectoris, myocardial infarction, lesions of the cerebral and peripheral arteries), and at autopsy, atherosclerosis is detected in more than half of patients [46]. Existing ideas about heart damage in SLE patients do not allow an unambiguous interpretation of this phenomenon. Structural changes in the myocardium, pericardium, or valvular lesions are often detected only by echocardiography and are rarely accompanied by hemodynamic disturbances; these changes cannot lead to high cardiovascular mortality in SLE [20]. What is the basis of such a dramatic situation? Several possible causes and their interrelationships are discussed, leading to an increased risk of cardiovascular catastrophes against the background of accelerated atherosclerotic vascular lesions in SLE. These include the accumulation of classic cardiovascular risk factors; general immune-inflammatory mechanisms underlying the pathogenesis of rheumatic diseases (RD) and atherosclerosis, which is currently considered as a probable "inflammatory" human disease [21,44]; side effects of drug therapy (non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids, basic anti-inflammatory drugs); insufficient attention to the need to prevent cardiovascular complications in these diseases and factors associated with the progression of RHs themselves [26].

Several atherosclerosis-associated autoantigens have been identified, including oxygenated low density lipoprotein (LDL), heat shock proteins, cardiolipin, beta2-glycoprotein-1. The most pronounced atherogenic properties are possessed by oxygenated LDL, heat shock proteins 60/65, which induce a strong local immune response in the plaque. In addition, oxygenated LDL can stimulate apoptosis, which is involved in the processes of plaque destabilization [24]. Studies have been carried out to study the levels of autoantibodies (to oxygenated LDL, heat shock proteins, cardiolipin, β2-glycoprotein-1, cardiolipin) as factors in the progression of atherosclerosis in SLE. An increase in the levels of autoantibodies and immune complexes in this category of patients compared to healthy patients has been proven, which was associated with preclinical manifestations of atherosclerosis according to ultrasound examination of the thickness of the intima-media complex in these patients [27].

All of the above mechanisms involved in the development of SLE are, to one degree or another, involved in the realization of renal lesions in lupus nephritis (FN) [16]. The leading component of the formation and development of FN is considered to be the deposition of immune complexes (IC) in the renal structures, in particular in the vascular endothelium, with the activation of cascade inflammatory systems and the development of immunocomplex damage to renal tissues [54]. A number of factors contribute to the deposition of IC, including their overproduction, disturbances in composition, defects in the systems of erythrocyte and phagocytic clearance of IC, and violations of the complementary cascade [52]. An important role in FN is assigned to the deposition of ICs in the kidneys, including autoantibodies to native / double-stranded DNA [35]. These ICs are characterized by high tropism for glomerular structures and significant nephropathogenic potential [18]. In recent years, a significant place in the development of LN has also been established for other variants of autoantibodies, in particular, antinucleosomal and antibodies to α-actinin [14].

Significant morphological, serological, and prognostic heterogeneity, which distinguishes LN, led to the emergence of ideas about the polymorphism of the pathogenesis of various variants of renal lesions. So M.M. Schwartz et al (2008) believe that the mechanisms of development of focal and diffuse proliferative FN may differ [42]. In the first of them, these authors assign a more significant place in the development of glomerular lesions to the immunocomplex mechanism; in the second, they believe, the basis of lesions of the renal structures are processes similar to those in pauci-immune variants of systemic vasculitis. J.S. Hill et al (2005) note that with diffuse segmental FN, compared with diffuse global FN, there is a higher degree of severity of T-cell disorders; a number of features of pathogenic autoantibodies to DNA are also presented, which may indicate the differences in the pathophysiology of these LN variants.

A significant contribution to the progression of FN is made by various changes in the systems of polymorphonuclear leukocytes and monocytes / macrophages, which contribute to the infiltration of renal structures by these cells with aggravation of their

damage [17]. These changes include defects in the expression of surface proteins that regulate the chemotaxis of these cells; increase in the production of substances that enhance their proliferation; violation of the production of humoral chemotactic factors [53]. On the other hand, a certain place in the development and progression of FN (which, first of all, concerns the processes of glomerular sclerosis and tubulointerstitial fibrosis) is assigned to non-immunological mechanisms, including oxidative stress, activation of the renin-angiotensinal aldosterone system, the endothelin-1 system, changes in lipid balance [45]. In recent years, among such nonspecific mechanisms of progression of FN (as well as other glomerulopathies), particular importance has been attached to disorders in the system of metalloproteinases (MMPs) of the glomerular matrix (in particular MMP-2 and MMP-9) and tissue inhibitors of MMP (TIMP) (especially TIMP- 1) [47]. The MMP / TIMP system is a complex system of zinc-containing enzymes and their inhibitors, providing, in particular, the maintenance of the structural composition of the basement membrane of the glomerular capillaries and the extracellular glomerular matrix. Correction of disorders in the MMP / TIMP system, regardless of the mechanisms of their development, is considered as a possible promising therapeutic approach for FN [28].

In recent years, when studying the mechanisms of acute renal failure, it was shown that, along with changes in intrarenal hemodynamics, a significant role belongs to the damage to the endothelium of the renal tubules [22]. Endothelial damage makes a significant contribution to the occurrence of intrarenal vasoconstriction and its consequence - acute renal failure [19]. It is believed that 30% of the entire endothelial lining of the body's vessels is localized in the kidneys [16]. The endothelium synthesizes, as mentioned above, such vasoactive hormones as endothelin, NO, prostacyclin, thromboxane, as well as coagulation and inflammation factors, which cause the participation of the endothelium in the regulation of kidney function, inflammation, and further possible sclerosis and nephron death [11]. In various variants of acute renal failure, DE were revealed, manifested by a violation of the synthesis of vasoactive hormones, primarily of a constrictor orientation, altering

renal blood flow and renal function. In chronic glomerulonephritis, a decrease in NO synthesis is observed, due to a chronic decrease in blood flow in the renal vessels and an increase in the level of pro-inflammatory cytokines, free radicals, and endothelin. In addition, the involvement of DE in the progression of FN is associated with imbalance in the hemostatic homeostasis system [12]. In diabetic nephropathy, work has been carried out to study the level of prostacyclin and NO; as kidney damage progresses, the balance of vasoactive endothelial factors is shifted towards increased production of vasoconstrictors [13]. S. Aiello et al. and E.S.G. Stroes et al. believe that treatment aimed at increasing the formation of NO or the introduction of selective antagonists of receptors for endothelin-1, causes a slowdown in the progression of renal failure [9].

Damage to the central nervous system is observed in almost all patients with SLE [6]. During histological examination of the brain, productive vasculitis is observed in the vessels [4]. According to the data of radionucleotide studies in SLE, cerebrovascular accident was revealed in 92.9% of cases, which indicates the dominance of the vascular factor in the pathogenesis of the nervous system lesions [2]. Violation of the vascular reactivity of the extracranial part of the bracheocephalic vessels and peripheral arteries was noted, both at rest and during exercise tests [50]. In the study of cerebral hemodynamics, high linear velocities of blood flow in the cerebral arteries, their interhemispheric asymmetry, a significant decrease in the indices of peripheral resistance and spectral expansion were revealed at rest [41]. The decrease in cerebral vascular resistance is associated with an increase in the content of NO in the blood. This may be indicated by the presence of a correlation between the content of NO and disease activity, as well as the severity of neurological complications [1].

Conclusion

The presented analysis of domestic and foreign literature indicates that the assessment of the degree of DE in SLE is an important link in predicting as a predictor of an unfavorable outcome of this disease. Based on this, it can be

concluded that the quantitative determination of VEGF in the blood serum of SLE patients in the practice of rheumatologists can be attributed to the main biomarkers characterizing the processes of turning on "angiogenesis" in this disease. It should also be noted that the prospect study of VEGF in patients with SLE and their relationships with clinical manifestations of the disease, immunological parameters, kidney damage, severity of organ damage, clinical form and activity of SLE will be of practical importance. Therefore, this makes it possible to detect the early development of both vasculitis and atherosclerotic changes in patients with SLE.

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