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A LOOK AT THE MECHANISMS OF THE DEVELOPMENT OF THE CARDIOVASCULAR MANIFESTATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

KASIMOVA M.B

PhD, associate professor of Department of internal disease №2 with endocrinology of Tashkent Medical Academy of Uzbekistan.

AKHMEDOVA N.A

PhD, associate professor of Department of internal disease №2 with endocrinology of Tashkent Medical Academy of Uzbekistan.

ALIQULOV I.T

Senior lecturer of Department of Propaedeutics of Internal medicine №1 of Tashkent Medical Academy of Uzbekistan.

SOLIKHOV M.U

Senior lecturer of Department of Propaedeutics of Internal medicine №1 of Tashkent Medical Academy of Uzbekistan.

XAYTIMBETOV J.SH

Senior lecturer of Department of Propaedeutics of Internal medicine №1 of Tashkent Medical Academy of Uzbekistan.

NARZIYEV N.M

Senior lecturer of Department of Propaedeutics of Internal medicine №1 of Tashkent Medical Academy of Uzbekistan.

Abstract

Systemic lupus erythematosus (SLE), atherosclerosis and coronary heart disease (CHD) share common pathophysiological mechanisms associated with systemic and chronic inflammation. At the same time, traditional risk factors, such as hypertension, elderly age, smoking, hypercholesterolemia, obesity, and male sex, cannot fully explain the mechanism for the accelerated development of atherosclerosis in patients with SLE. Specific risk factors, such as its duration, glucocorticoid use, anti-doublestranded (native) DNA autoantibodies and antiphospholipid antibodies, create conditions for the accelerated development of atherosclerosis in this group of patients. The available facts indicate that a rheumatologist can reduce the risk of cardiovascular disease (CVD), by controlling the activity of SLE. Traditional CVD risk factors should be also modified with smoking cessation, weight loss, and blood pressure control. It is necessary to keep in mind the role of anti-inflammatory therapy, in particular the positive effect of drugs, such as anti-malarial drugs and mycophenolate mofetil, and the adverse prognostic effect of prolonged glucocorticoid use. Further studies should assist in elaborating effective risk scales and specific therapeutic programs for the prevention and treatment of CVD in patients with SLE.

Keywords: Systemic Lupus Erythematosus; Atherosclerosis, Nontraditional Cardiovascular Risk Factors; Treatment

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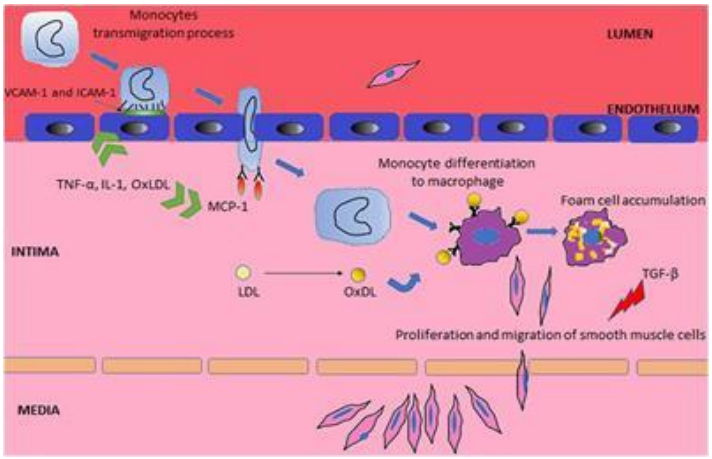
Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of a wide range of pathogenic autoantibodies, multivariable manifestations, course and prognosis, development of exacerbations and remissions [1–3]. The prevalence of the disease varies from 1.4 to 11 cases per 100,000 population [4]. Along with a diverse clinical picture during the course of the disease, a characteristic "bimodality" can be distinguished. Thus, in the first three years after diagnosis, the predominant cause that determines the severity of the disease and the mortality of patients is kidney damage and infectious complications against the background of high disease activity. However, the second peak in mortality, 4–20 years after diagnosis, is predominantly caused by cardiovascular disease (CVD) [5, 6]. It should be noted that, while all-cause mortality in SLE has significantly decreased over the past decades due to the increase in the effectiveness of therapy, mortality from cardiovascular diseases remains at a high level and they remain the leading cause of death in patients [7, 8]. At the same time, it should be noted the high prevalence of CVD in patients with SLE, which significantly exceeds that in the general population [9–11] (pic.1).



Picture 1: The main stages of the pathogenesis of atherosclerosis in SLE.

In the Canadian Hopkins Lupus Cohort study, coronary artery disease (CHD) was reported in 8% of patients, peaking at 8 years from diagnosis, and was responsible for 30% of deaths at a 3-year follow-up [12]. In Hopkins Lupus Cohort, the overall risk of SLE-related CVD is 2.66 times higher than in the general population, with the same severity of traditional cardiovascular risk factors [13]. The risk of developing coronary artery disease is especially high in women with SLE, exceeding the population by 5–9 times [14, 15], and according to S. Manzi et al. [16, 17] - 50 times. In Colombia, the prevalence of CVD among SLE patients was 36.5%, and in North America it was 6–10% [9, 14, 18]. In addition, in the Italian study by A. Doria et al. [19] reported subclinical atherosclerosis in 10–40% of patients with SLE. A.E. Ilyina et al. [20] examined 62 patients with SLE and found carotid artery involvement in 58% of cases. Clinical manifestations of atherosclerosis occurred in 42% of patients, including angina pectoris diagnosed in 37% of patients. In fact, SLE is an independent risk factor for the accelerated development of atherosclerosis [14, 21, 22]. However, its pathogenesis needs further study. The role of autoantibodies in the accelerated development of atherosclerosis in SLE remains unclear

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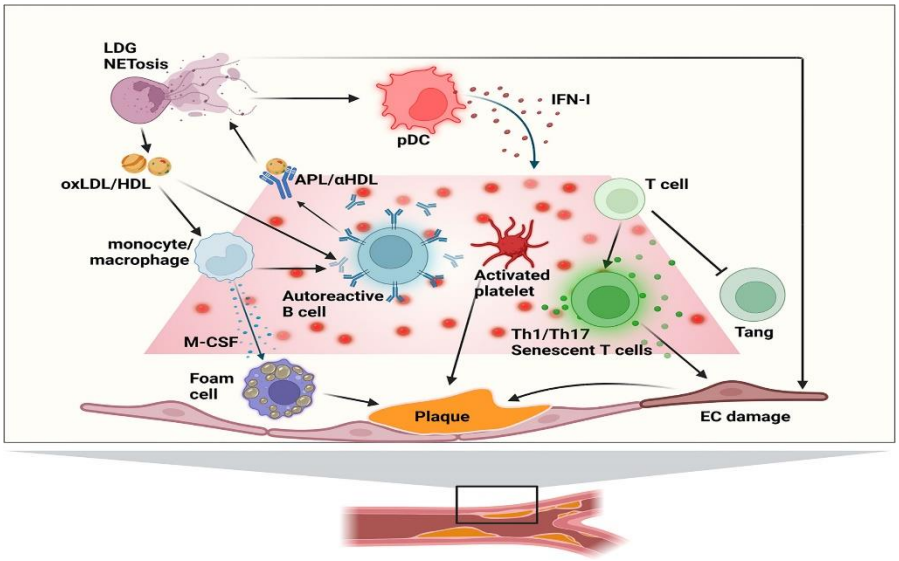
at present [23]. Antiphospholipid antibodies (APAs) are frequently found in patients with SLE and have been considered as possible predictors of atherosclerosis, although studies evaluating their role have shown mixed results [24–27]. At the same time, there is a significant increase in the subclinical marker of atherosclerosis - the thickness of the intima-media complex (IMC) in patients with primary antiphospholipid syndrome (APS) compared with the control group [25]. Antibodies against apolipoprotein A1, high density lipoproteins (HDL) [28], and heat shock protein 60 [29] may be involved in the development of CVD. In a recent report reviewing the Hopkins cohort, based on an analysis of a follow-up of 2000 patients with SLE, it is concluded that lupus anticoagulant is the only APA associated with myocardial infarction (MI). Neither lupus anticoagulant nor antibodies to cardiolipins are associated with atherosclerosis [27, 30]. Some studies consider AFA as a stimulator of tissue factor (TF) expression on the surface of peripheral blood mononuclear cells in SLE, which correlates with the risk of developing peripheral arterial atherosclerosis [31]. Given the role of TF in atherogenesis [32], as well as in APA-induced thrombosis [33], the authors suggest that TF may play a triggering role in the development of CVD in SLE [31]. Endothelial cells in SLE are damaged under the influence of circulating immune complexes and proinflammatory cells, acquiring prothrombotic properties [3]. The damaged endothelium expresses adhesion molecules that attract lymphocytes and monocytes that infiltrate the subendothelium. One of the confirmations of the existence of this process is the increase in the number of endothelial cells noted in the blood of patients with SLE [6]. In turn, monocytes in SLE showed altered mitochondrial membrane potential and increased oxidative stress. The analysis performed confirmed the pronounced associations between autoimmunity activation, oxidative stress, inflammation, and increased risk of atherothrombosis in SLE [7]. In recent years, much attention has been paid to type I interferons (IFN I) as an important mediator of SLE pathogenesis [30]. The ability of IFN I to initiate endothelial damage and atheroma formation, the presence of which correlates with SLE activity, has been noted [4] (pic.2).



Picture 2: Main immune mechanisms of atherogenesis involvement in SLE patients.

The Seybold Report
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APL, antiphospholipid antibody; EC, endothelial cell; (ox)HDL, (oxidized) high density lipoprotein; IFN-I, type I interferon; LDH, low density granulocytes; (ox)LDL, (oxidized) low density lipoprotein; pDC, plasmacytoid dendritic cell; Tan, angiogenic T cells.

In 2004, a new form of programmed cell death, the formation of a neutrophil extracellular trap (NEC), was described [2]. NILs are extracellular chromatin combined with neutrophil proteins and are designed to trap and destroy pathogens [3]. In patients with SLE, a violation of the formation of NVL was noted [6]. Neutrophils in SLE have the ability to intensively form NIs that stimulate the production of IFN I and autoantibodies such as anticatelicidin-LL37 and antiribonucleoprotein [8]; in addition, lupus neutrophils are able to secrete NVL, which have a damaging effect on the endothelium in vitro [18]. Activated platelets play an important role in the development of atherothrombosis [19], as well as mediators of immunity and inflammation. They not only release cytokines, but also express the CD40 ligand (CD40L/CD154), FcγRIIa, and Toll-like receptors on their surface [30]. In patients with SLE, platelet activation is significantly increased compared to the control group [31]. Platelets in SLE, in response to activation of CD40L on their surface by immune complexes, activate dendritic cells, participating in increased production of IFN I. In turn, increased production of IFN I contributes to vascular damage. Apparently, it is the effect on this mechanism by blocking platelets that explains the improvement in the course of nephritis and the decrease in inflammation activity after the use of clopidogrel in a model of SLE in rats [22]. A number of genetic studies have shown a possible link between genetic disorders and an increased incidence of CVD in patients with SLE. In a large group of SLE patients, 23% of patients had a history of thrombosis and a predictive single nucleotide polymorphism (SNP) in the factor V and methylenetetrahydrofolate reductase genes was identified [23]. Elevated levels of matrix metalloproteinase 2 (MMP2) and MMP9 were previously reported in the blood of SLE patients [24]. A promoter genotype associated with high MMP2 activity, development of CVD, and elevated cholesterol levels has also been identified in patients with SLE HDL usually play a protective role in atherosclerosis by reverse transport of cholesterol and by protecting low-density lipoproteins (LDL) from oxidation. However, in SLE, the so-called pro-inflammatory HDL was found in 45% of patients, and their presence correlates with increased formation of oxidized LDL, the number of carotid atherosclerotic plaques, and an increase in the thickness of IMT [26]. Thus, in addition to traditional CVD risk factors, the association between SLE and atherosclerosis may be due to additional risk factors, such as inflammation and autoimmune processes [1, 16, 27]. Given the complex mechanism of SLE pathogenesis, doctors often face the question of how to prevent and treat CVD in SLE patients. In the practice of a cardiologist, the Framingham risk scale is widely used, which makes it possible to determine the categories of CVD risk for the choice of subsequent prevention of coronary artery disease. However, this scale strictly depends on the age of the patient and its use is not effective enough in young patients with SLE [9]. Therefore, the assessment of only traditional risk factors for coronary artery disease in patients with SLE may lead to an underestimation of their risk of developing CVD. A number of large prospective studies have shown the dependence of the development of CVD in SLE patients on both classical (older age, smoking, hypercholesterolemia, obesity, male sex and hypertension) and new specific risk factors, such

The Seybold Report
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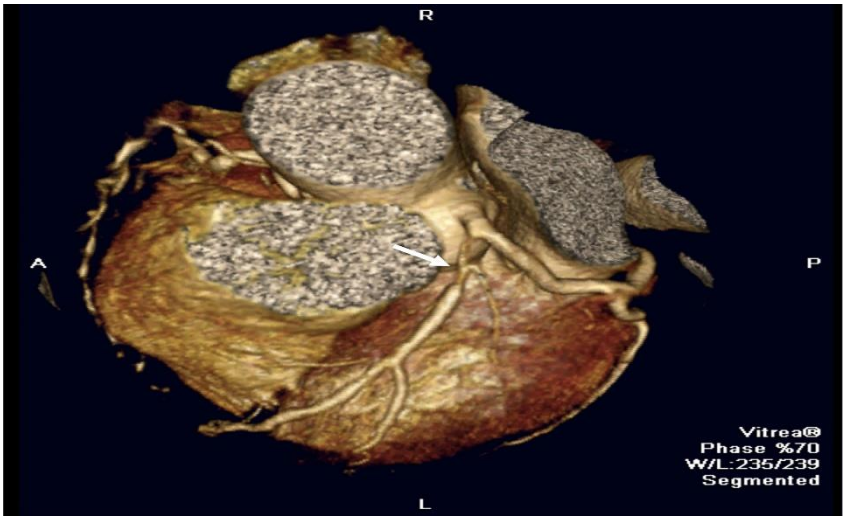
as the duration of SLE, the use of glucocorticoids (GC) , the presence of autoantibodies to double-stranded (native) DNA, the presence of APA and neuropsychiatric lupus [9, 10]. Epidemiological data in the work of S. Schoenfeld et al. [1], who analyzed 28 studies on this issue, confirm the fact that patients with SLE are at an increased risk of developing CVD. The overall risk of MI, heart failure, cerebrovascular disease, and CVD mortality is at least doubled among patients with SLE compared with the general population. Young patients with SLE have an extremely high risk of developing CVD compared to their peers, and it increases with age. In recent years, much attention has been paid to highly sensitive C-reactive protein (hsCRP). Based on a number of studies, and in particular the results of the JUPITER study [2, 3], CRP is recognized as a major risk factor for CVD and a secondary goal of statin therapy. In contrast to the general population, where CRP levels were associated with an increased risk of CVD, this relationship is less pronounced among patients with SLE. In the LUMINA study [4], as well as in a smaller study including 208 Swedish patients with SLE [5], an increased risk of CHD in SLE patients was observed at CRP levels between 1.5 and 3.3 mg/l. Given the high prevalence of coronary artery disease, a risk analysis for coronary artery disease was performed in 472 patients with SLE at the University of Toronto Clinic. In a prospective study, CRP and the 10-year Framingham index effectively predicted the development of coronary artery disease (MI or angina) in patients with SLE at a CRP level >1.6 mg/l. The authors provide strong arguments in favor of the use of CRP as a predictor of CVD, since the determination of its level was sufficient to select patients at risk for CAD in the general population [16]. In the study of A.E. Ilina et al. [20] found a significant correlation between the CRP level and IMT thickness in SLE patients with and without APS.



Picture 3: Cardiovascular manifestations in SLE. Coronary computed tomography image showing a severe stenosing lesion in the proximal segment of the left anterior descending coronary artery (white arrow) in a patient with SLE

However, the role of CRP in predicting CAD among SLE patients currently needs further study. Currently, the IMT thickness - the distance between the inner surface of the intima and the

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outer surface of the media - is a sonographic marker of early atherosclerotic lesions of the vascular wall and coronary artery disease. It not only reflects local changes in the carotid arteries, but also indicates the prevalence of atherosclerosis. Local thickening of IMT >1.3 mm is considered evidence of the presence of an atherosclerotic plaque.

G.C. Wu et al. [27] conducted a meta-analysis of 71 studies assessing IMT thickness (4814 SLE patients and 3773 controls) and 44 studies examining the prevalence of carotid atherosclerotic plaques (4417 SLE patients and 3528 controls). Compared with the control group, patients with SLE had a greater IMT thickness (p140 mmHg, smoking, SLE activity index (SLEDAI), the presence of lupus anticoagulant, and a low level of the C3 component of complement. Despite certain limitations, its further development seems to be In addition to autoimmune mechanisms, modern treatment can have an adverse effect on the cardiovascular system. Drug therapy for autoimmune diseases is accompanied by the development of a wide range of adverse reactions (AR) [10]. –310 307 Glucocorticoids, which are traditionally used for the treatment of SLE, can induce: arterial hypertension (62%), diabetes mellitus (18%), dyslipidemia (66%) and thromboembolic complications [1, 12]. development of CVD, although some authors do not confirm this assumption [21].On the other hand, recent studies in patients with SLE and rheumatoid arthritis (RA) suggest that GCs can reduce the number of cardiovascular complications, probably by reducing autoimmune activity and severity of inflammation [14].

In recent years, antimalarials have attracted the most attention in terms of evaluating their possible cardioprotective properties. Indeed, the use of antimalarial drugs in SLE has been correlated with reductions in vascular stiffness [25], carotid atherosclerotic plaque growth [7], and total cholesterol levels, especially in patients treated with GCs [17]. Animal studies on SLE models revealed an antithrombotic effect of these drugs [27]. Hydroxychloroquine has been shown to reduce the risk of both arterial and venous thrombi in SLE, especially in patients with APS [19]. Hydroxychloroquine improved the lipid profile in patients with SLE, but the possibility of preventing the development of CVD could not be confirmed [20]. At the same time, with the use of hydroxychloroquine, adverse reactions were observed, mainly associated with impaired conduction, such as prolongation of the QT interval and, in rare cases, the development of atrioventricular blockade [15].

The wide prevalence of CVD in patients with SLE naturally raises the question of the use of antiplatelet agents, and in particular, acetylsalicylic acid. M. Iudici et al. [22] analyzed the results of treatment in a group of 167 patients with SLE, of which 146 regularly took aspirin and 21 refused to use it. Follow-up was carried out for an average of 8 years. In the group treated with aspirin, 5 cases of coronary artery disease were registered, in the group without aspirin - 4. Against the background of the use of acetylsalicylic acid, there was no HP. Based on the data obtained, the authors conclude that it is advisable to prescribe low doses of aspirin to patients with SLE for the prevention of coronary artery disease. Mycophenolate mofetil (MMF) is able to reduce the activity of T-lymphocytes in atherosclerotic plaques, slow down the processes of atherogenesis in animals that are a model of SLE and atherosclerosis [11, 23]. Despite these interesting experimental data, a two-year study investigating the effect of MMF

The Seybold Report
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on IMT thickness showed no positive effect in SLE patients [18]. Nevertheless, the already available data allow us to hope for positive results and justify the continuation of the study on larger cohorts of patients and with longer follow-up periods. Methotrexate. The positive effect of methotrexate in the prevention of CVD in patients with RA is widely known. However, the available data do not allow conclusions regarding the protective effect of imuran and methotrexate on the development of CVD in SLE [4]. Thiazolidinediones such as rosiglitazone and pioglitazone alter gene expression as peroxisome proliferator-activating receptor agonists, regulators of adipocyte differentiation, lipid and carbohydrate metabolism, and inflammation. In a study in a lupus/atherosclerotic mouse model, rosiglitazone reduced autoantibody production, renal pathology, and the development of atherosclerosis [15]. Pioglitazone had a positive effect on endothelial function and regeneration [26].

The use of pioglitazone in a small group of young women with SLE for 3 months resulted in an improvement in the lipid profile and a decrease in the levels of inflammatory markers such as CRP and serum amyloid A [30]. Statins may play a role in preventing the accelerated development of atherosclerosis in SLE. Their use leads to a decrease in the content of prothrombotic factors in APS and a decrease in the number of cardiovascular complications in patients with SLE [8]. They also have an immunomodulatory effect. Treatment of patients with SLE with fluvastatin for 1 month reduced the SLEDAI activity index, lipid levels, oxidative stress, and vascular inflammation [31]. Statin therapy in the LUMINA study (LXXVI) resulted in a significant reduction in the SLAM-R activity index and significant clinical improvement in patients with SLE [89].

In a model of SLE in NZB/W F1 mice, treatment with atorvastatin reduced the level of antibodies to native DNA [20]. In a lupus/atherosclerotic animal model, simvastatin therapy reduced the area of atherosclerotic damage [21]. In a study conducted in 27 patients with SLE who received 20 mg of fluvastatin per day for 1 month, a decrease in the SLEDAI activity index, a decrease in lipid concentration, oxidative stress and inflammation of the vascular wall were noted. Available data have shown that the use of fluvastatin in patients with SLE seems to suppress the oxidative-inflammatory mechanisms involved in the development of atherogenesis [32].

At the same time, the LAPS study noted that, despite the reduction in cholesterol levels during treatment with atorvastatin, the risk of developing CVD in patients did not decrease [22]. In addition, the use of atorvastatin in pediatric patients with SLE for 36 months did not affect the thickness of the IMT, although the level of CRP and the lipid profile did improve [13]. These contradictions seem to be explained by the insufficient number of patients included in the study, the heterogeneity of patient groups, and the relatively short duration of observations. In this regard, despite the potentially anti-inflammatory, immunomodulatory and antithrombogenic effects of statins, there are currently no standard indications for their use in SLE [18]. Atherosclerosis and its complications are the main cause of late mortality among patients with SLE. SLE and CAD share common pathophysiological mechanisms associated with systemic chronic inflammation. At the same time, traditional risk factors cannot fully explain the mechanism of the accelerated development of atherosclerosis in SLE. The presence of specific

The Seybold Report
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risk factors, such as the duration of the course, the use of GC, the presence of autoantibodies to double-stranded (native) DNA and APA, create conditions for accelerating the development of atherosclerosis in this group of patients. Evidence suggests that a rheumatologist can reduce the risk of CVD by controlling SLE activity. Correction of traditional CVD risk factors should also be carried out, starting with smoking cessation, control of body weight and blood pressure. It is necessary to take into account the role of ongoing anti-inflammatory therapy, in particular the positive effect of drugs such as antimalarials and MMF, as well as the prognostically unfavorable effect of long-term use of GCs. Further research should help develop effective development risk scales and specific therapeutic programs for the prevention and treatment of CVD in patients with SLE.

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