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ASSESSMENT OF CLINICAL AND DIAGNOSTIC ASPECTS OF ATHEROSCLEROSIS IN PATIENTS WITH SYSTEMIC SCLERODERMA

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Abstract. Systemic scleroderma (SS) is a diffuse connective tissue disease in which one of the main targets of the pathological process is the vessels of the microvasculature. Involvement of vessels of a larger caliber, including arteries of small diameter of the extremities and internal organs, is noted in many patients, but its significance has been studied much less. At the same time, the proportion of mortality in patients with SS from cardiovascular complications is steadily increasing.

Aim. To determine the frequency of detection of atherosclerosis, to clarify the nature of atherosclerotic lesions of brachiocephalic arteries in patients with systemic scleroderma (SS), to identify the main factors influencing this process.

Material and methods. 40 patients with SS were examined. The indicators of vascular stiffness in the area of the carotid artery - femoral artery, lipid spectrum, glucose, uric acid, and the concentration of cytokines in the blood serum were determined.

Results. An increase in the thickness of the intima-media complex (TIM) was recorded in 75% (n=30/40) of the examined patients with SS. Various degrees of stenosis of the arterial lumen (25-75%) — in 50% (n=20/40) of patients. The relationship between aterosclerosis and certain classical risk factors (RF) was determined. Among non-classical risk factors, a relationship has been found between TIM and IL-6.

Conclusion. In patients with SS in the genesis of atherosclerosis, a certain proportion belongs primarily to inflammatory mediators, as well as metabolic disorders characteristic of SS (uricemia). This may indicate the existence of a special combination of pathogenetic mechanisms of arterial wall

Received: April 04, 2023 / Revised: May 22, 2023 / Accepted: June 28, 2023 / Published: July 15, 2023

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damage in patients with SS, and may qualify for a re-evaluation of the state of patients with SS, using a larger sample of patients and additional research methods.

Keywords: atherosclerosis, systemic scleroderma, atherosclerosis, cytokine.

Progressive systemic sclerosis or systemic scleroderma (SS) is a chronic autoimmune connective tissue disease characterized by generalized microangiopathy, immune dysregulation, and activation of fibrogenesis processes. The main clinical signs of SS are due to widespread microcirculation disorders, fibrosis of the skin and internal organs [1].

It has been established that patients with SS are characterized by an accelerated development of the atherosclerotic process, and high cardiovascular risk in SSc is associated with traditional risk factors (hypertension, dyslipidemia, hypertriglyceridemia, TIM, endothelial dysfunction) and factors associated with the activity of the disease itself [2,4].

In a study conducted by Nordin A. et al. (2013) in Stockholm (Sweden), it was found that the highest risk of developing cardiovascular complications (CVD) and signs of subclinical atherosclerosis were noted in the group of patients with SS with positive antibodies to the centromere [3]. In Australia, Ngian G.S. et al. (2012) found that patients with SS were significantly more likely to develop coronary artery disease associated with pulmonary hypertension, and the incidence of cardiovascular risk factors such as obesity, hypercholesterolemia, and diabetes mellitus did not differ from those in the control group. The latest data from ongoing cohort studies show an increase in mortality from cardiovascular complications in SS by 3.5 times [5-7].

In addition, recent studies show that patients with SS have a higher in-hospital mortality from atherosclerosis-related CVD compared with patients with systemic lupus erythematosus and rheumatoid arthritis (Dave, A.J., 2014) [8].

An increase in the level of interleukin 6 (IL6) correlates with the risk of developing coronary heart disease, is a predictor of the occurrence of cardiovascular events in patients with clinically stable coronary disease, proven angiographically. In addition, in unstable angina and myocardial infarction (MI), an elevated level of IL6 is associated with an unfavorable prognosis (Gumanova N.G., 2019). With an increase in the concentration of IL6 by 1 pg/ml, the relative risk of developing recurrent MI or sudden death increases by 1.7 times. An elevated level of IL6 before coronary artery bypass grafting is associated with graft occlusion in the early postoperative period, and also predicts the development of delayed cardiovascular events [9-10].

Udachkina E.V. et al. (2013) found that in arteries affected by atherosclerosis, the levels of IL6 mRNA expression are 10–40 times higher than in arteries without signs of atherosclerosis. In the thickened intima of the atherosclerotic defect, the presence of the IL6 gene transcript was noted. In addition, IL6 was found to be an independent biomarker of carotid atherosclerosis in patients with moderate and severe coronary disease [11].

They also showed that IL6 concentrations, regardless of traditional risk factors, positively correlated with the presence of atherosclerotic plaques in the carotid and femoral arteries according to

duplex scanning. The level of IL6 is significantly higher in patients with IIa- and IIb-type dyslipidemia than in the control group of healthy people and correlates with TIM [12].

Khripunova A.A. (2012) studied the frequency of macrovascular complications and the prognostic value in their development of traditional cardiovascular risk factors and immunoinflammatory mechanisms in SS[13].

Literature data on intima-media thickening of the carotid arteries in patients with SS and subclinical atherosclerosis are contradictory. Macedo R. et al. (2012) revealed thickening of the intima-media of the carotid arteries in patients with SS, however, no relationship was found between TIM of the carotid arteries and the severity of the disease [14-16].

Thus, the analysis of such clinical situations substantiated the need for a more in-depth study of the state of the cardiovascular system in patients with SS. Thickening of the aortic walls, which is an independent factor of cardiovascular risk, was diagnosed in patients with SS, regardless of the severity of skin and pulmonary fibrosis, and also significantly differed from the control group[15].Of interest is the data that the decrease in the reserve of coronary arteries according to the results of Doppler echocardiography with contrast in patients with SS was determined with a higher frequency when compared with the control group [16]. A recent study showed a significant decrease in endothelium-dependent vasodilation as an early marker of atherosclerosis with a trend towards an increase in the thickness of the intima-media complex in patients with SS compared with the control group, while the groups did not differ in cardiovascular risk factors [17].

Along with the data of instrumental examination, confirming the diagnosis of atherosclerosis, clinical signs of atherosclerosis against the background of SS are also described. According to the results of the Edinburgh epidemiological study, the diagnosis of intermittent claudication was established in 22%, coronary heart disease (CHD) in 15%, cerebrovascular disease in 6.5% of patients with SS [19].

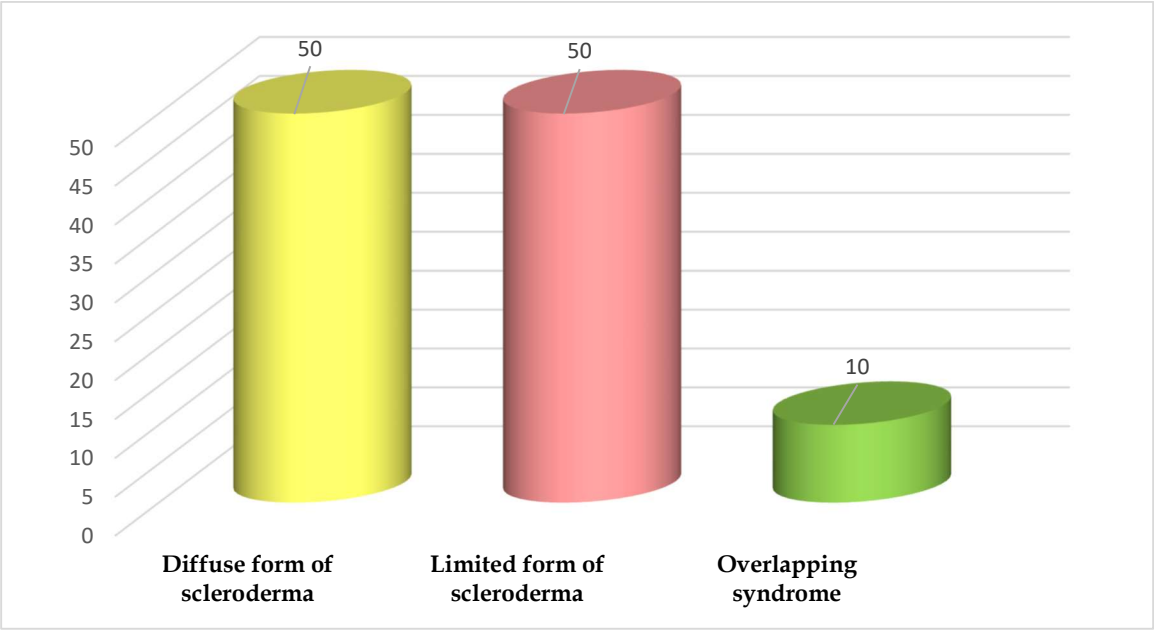
According to various studies, patients with SS are characterized by a high risk of mortality from cardiovascular diseases [18,20]. In a cause-of-death analysis of 344 patients with SS in Denmark, it was shown that the group of patients with death caused by other, non-SSD conditions was twice as high as the group of patients whose direct cause of death was SS. At the same time, the main cause of death in the former was cardiovascular pathology [21-24].

Thus, the diagnosis of SS suggests the early development of vascular atherosclerosis, which is one of the main causes of death in patients. Research on the prevalence of atherosclerosis in patients with SSc is currently scarce, especially compared to the large number of studies on atherosclerosis in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and antiphospholipid syndrome (APS). The problem of the relationship between atherosclerosis and vascular damage in SS remains not fully understood [25].

The aim To determine the frequency of detection of atherosclerosis, to clarify the nature and main factors influencing atherosclerotic lesions of brachiocephalic arteries in patients with systemic scleroderma SS.

Material and methods We examined 40 patients with a reliable diagnosis of SS (36 women and 4 men) who were hospitalized in the departments of rheumatology and cardio-rheumatology of

the Tashkent Medical Academy from 2021 to 2022. The average age of patients was 47.5 ± 2.4 years (from 22 to 68 years). Diffuse form of scleroderma was determined in 20 (50%), limited in 20 (50%), overlapping syndrome (SS/RA and SS/PM) in 4 (10%) patients (1 pic.). The duration of the disease ranged from 1 to 35 years, with an average of 12 (5-16) years. The criteria for inclusion in the study were a reliable diagnosis of SS (ARA criteria) [20] and the age of patients from 18 to 68 years.



Picture 1. Clinical forms of observed SS patients (%)

The control group consisted of 20 "conditionally" healthy volunteers without systemic rheumatic diseases and Raynaud's syndrome, matched by sex (15 women and 5 men) and age (44.1±7.4 years).

To verify the diagnosis of SS and characterize organ pathology, all patients underwent instrumental studies, including chest X-ray, ECG, echocardiography, ECG Holter monitoring (HMECG), pulmonary function tests (spirometry, study of lung diffusion capacity).

In all patients of the main and control groups, classical risk factors for atherosclerosis were analyzed: a family history of cardiovascular diseases (CVD) in the next of kin (myocardial infarction (MI) or sudden death in men under 55 years of age, in women under 65 years of age) [27], an increase body mass index (BMI) (weight, kg/height, m2 ≥ 25 kg/m2) [282], dyslipidemia (abnormal levels of one or more classes of lipoproteins [total cholesterol (CH) levels> 5.0 mmol/l, high-density lipoprotein cholesterol (HDL cholesterol) < 1.0 mmol/l, triglycerides (TG) > 1.7 mmol/l] [23], arterial hypertension (systolic blood pressure (SBP) level ≥140 mm Hg, diastolic (DBP) ≥ 90 mm Hg or taking antihypertensive drugs) [29], smoking, menopause, diabetes mellitus [26]. Total coronary risk (TCR%) (10-year risk of developing cardiovascular events) was assessed using the Framingham scale.

To identify subclinical forms of atherosclerosis in patients with SS (n=40) and in the control group (n=20), an ultrasound scan of the carotid arteries was performed using a linear sensor with a radiation frequency of 7.5 MHz on a Voluson 730 Expert device (Austria) with measurement of the thickness of the intima complex - media (TIM) at three points (1 point - common carotid artery - 10 mm to the

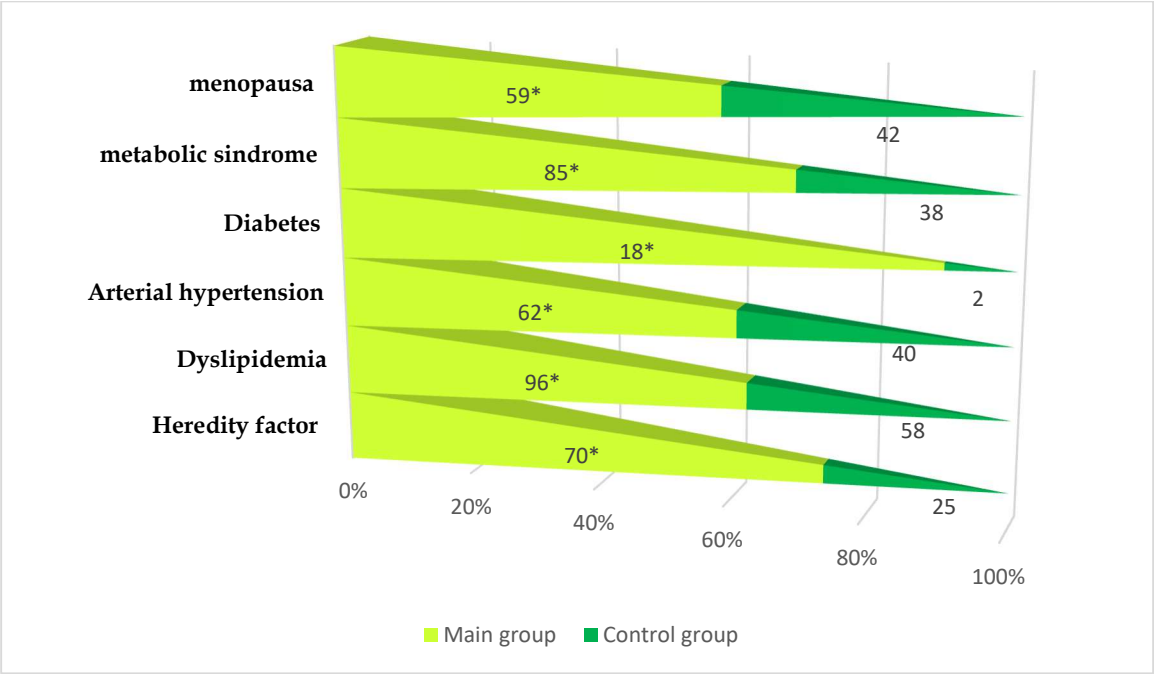
bulb; 2 point - 5-10 mm cranial from the beginning of the bulb; 3 point - internal carotid artery - 10 mm after bifurcation on both sides) and calculations average and maximum values of TIM. The presence of atherosclerosis was assessed by thickening of the intima-media complex (TIM from 0.9 to 1.2 mm) and the presence of atherosclerotic plaques (ATP) (local increase in IMT > 1.2 mm) [6]. The morphology of the carotid arteries, including IMT, as well as Doppler blood flow parameters were assessed using a Vivid 7 Dimension ultrasound machine (General Electric, USA) in accordance with the protocol of the American Society of Echocardiography. Both carotid arteries were evaluated, as a result, the highest value of IMT was taken into account, and the presence of atherosclerotic plaques was also taken into account.

Therapy with low doses of glucocorticoids was received by 20 (50%) patients, D-penicillamine — 10 (25%), methotrexate — 10 (25%), cyclophosphamide — 15 (37.5%). Some patients received combination therapy. Anamnestic indications for taking glucocorticoids at a dose of >10 mg in terms of prednisolone were the criterion for exclusion from the study. Also, the study did not include patients with severe concomitant cardiovascular pathology: indications of myocardial infarction, acute cerebrovascular accident, severe arterial hypertension, diabetes mellitus.

Indicators of lipid spectrum, glucose and uric acid, C-reactive protein (CRP) were determined on an empty stomach using an automatic analyzer Hitachi-902 (Japan).

Serum cytokine concentrations were assessed using xMAP (17-plex) technology on a BioPlex-200 analyzer (BioRad, USA). The concentration of IL-1β, IL-2, IL-4, IL-6 and TNF-α was assessed.Statistical processing of the results was carried out using the Statistica 6.0 software package (StatSoft, USA). Quantitative values are given as M±SD with correct distribution and as Me(LQ-UQ)-median with an interquartile range (25th - 75th percentile) with incorrect distribution of features. For statistical evaluation of the results, non-parametric methods were used: the Mann-Whitney test, the calculation of Fisher's exact test, and Spearman's correlation analysis. Differences were considered statistically significant at $p<0.05$.

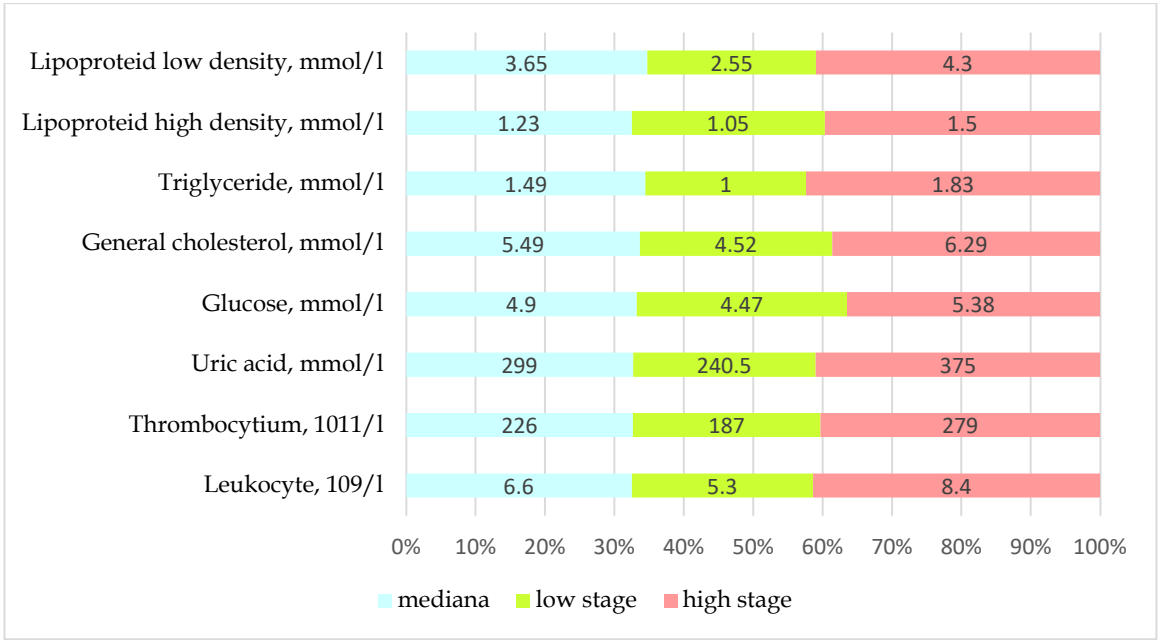
Results Comparison of cardiovascular risk factors in patients with SS and in the control group did not reveal significant differences, except that the frequency of smoking was significantly higher in the control group ($p=0.002$), and menopause was more common among patients with SS ($p=0.005$). When analyzing the clinical manifestations of atherosclerosis, it turned out that dyslipidemia was determined more frequently among patients with SS. It was diagnosed in 96% patients with SS and only in 58% volunteer from the control group ($p<0.001$). Metabolic syndrome was recorded in 85% of main group with SS, hereditary factor in 70% patient with SS and in 25 volunteer from the control group (pic.2).



Note-*p<0,001 statistically significant index than control group

Picture 2. Cardiovascular risk factors in patients with SS (%)

Comparison of blood lipid concentrations showed that the level of triglycerides in patients with SS was significantly higher than in the control group (p<0.001) The results of studies of the lipid spectrum, glycemia, uric acid content and as well as the degree of leukocyte and platelet are presented in picture 3.



Picture 3. Average lipid values in SS patients and in the control group

The mean and maximum TIM values of the carotid arteries, obtained by ultrasound scanning of these vessels, did not differ significantly in the groups of SS patients and controls. There was only a slight tendency to increase TIM max. (1.0 ± 0.36 and 0.88 ± 0.14) and the frequency of IMT thickening (42% and 38%, respectively) in patients with SS compared with the control group. Atherosclerotic plaques (IMT>1.2 mm) were determined in 10% of patients with SS and were absent in the control group (p<0.05) (Table 1).

Table 1

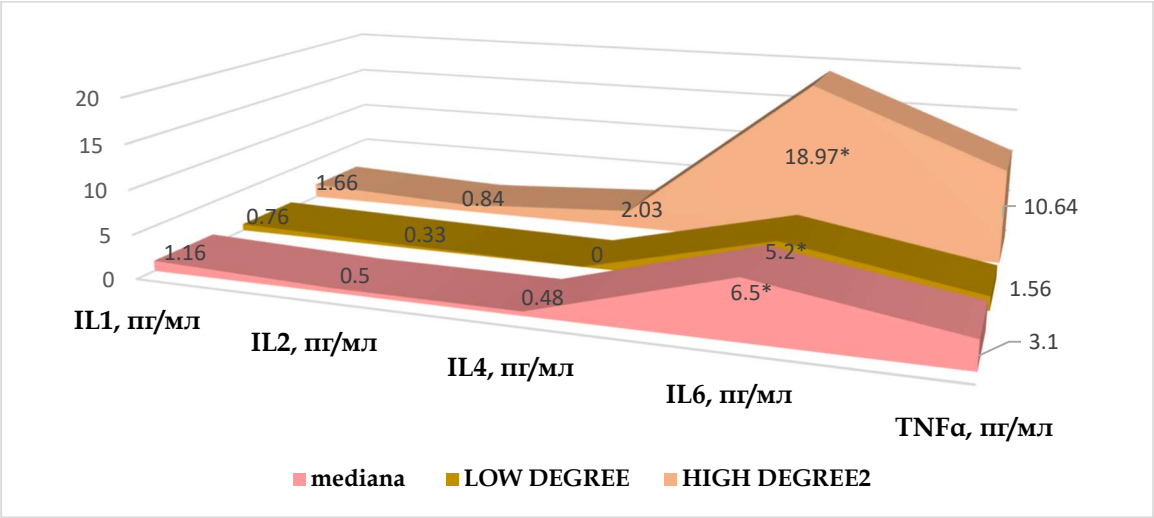
Thickness of the intima-media complex arteria in patients with SS and in the control group

Average, mm	Patients with SS n=40	Control group n=20
TIM average	0,78 ±0,18	0,74 ± 0,08
TIM middle right	0,77 ± 0,18	0,74 ± 0,09
TIM middle left	0,8 ± 0,2	0,75 ± 0,09
TIM maximum	1,0 ± 0,36	0,88 ± 0,14
TIM 0.9-1.2 (n,%)	25 (42%)	17 (38%)
TIM>1.2 (n,%)	6 (10%)*	0*

Note-*p<0,05 statistically significant index

A high positive correlation was established between TIM average and TIM max. with the age of patients with SS (respectively, r=0.64, t=6.28, p<0.001 and r=0.44, t=3.74, p<0.001). Mean TIM also correlated with disease duration (r=0.28, t=2.23, p<0.05).

In the group of patients with SS, positive correlations were found between TFR% and TIM, both mean (r=0.51, t=4.5, p=0.00003) and max. (r=0.41, t=3.4, p=0.001). In addition, they revealed a correlation between mean TIM and cholesterol levels (r=0.31, t=2.44, p<0.05).



Note - p<0,001 statistically significant increase of IL-6

Picture 4. Assessment of serum cytokine concentrations in SS patients (pg/ml).

Estimation of the concentration of cytokines in serum IL-1β, IL-2, IL-4, IL-6 and TNF-α is shown in the following figure. It clearly describes a statistically significant increase in interleukin-6 (pic. 4).

Table 2.

Relationship between risk factors, clinical and laboratory characteristics of the disease and TIM according to correlation analysis

Signs	Spearman's correlation coefficient	t (n=2)	p-degree
TIM and age*	0,45	3,085	0,04
TIM and glucose*	0,40	2,627	0,01
TIM and systolic BP	0,33	1,946	0,06
TIM and triglycerides	0,29	1,812	0,08
TIM and uric acid*	0,42	2,745	0,01
TIM and IL-6 *	0,25	2,865	0,001

Note-* statistically significant comparison

Correlation analysis revealed a positive relationship between TIM in the examined patients with SS and some risk factors (FR) for atherosclerosis: age, glycemia level, 10-year calculated Framingham risk index for cardiovascular events. There was a trend towards an association between TIM and systolic blood pressure (BP) and triglyceride levels, but not other assessed lipid parameters. A positive correlation was found between IL-6 levels and TIM.

Discussion We performed a search and assessment of the significance of factors affecting TIM in 40 patients with SS. At the same time, the structure of risk factors associated with an increase in TIM in the study generally corresponded to generally accepted ideas about their role in the pathogenesis of atherosclerotic lesions. The age of patients is one of the main non-modifiable factors for assessing cardiovascular risk, included both in the Framingham scale and in the more modern European scale of total cardiovascular risk SCORE (Systematic Coronary Risk Evaluation) [5].

Hyperuricemia, according to the Framingham study, was not classified as an independent risk factor for atherosclerosis (estimated by the frequency of cardiovascular events), since its effects depended on the presence of arterial hypertension [6]. Previously, it was shown that in patients with other diffuse connective tissue diseases, in particular systemic lupus erythematosus, accelerated progression of atherosclerosis is noted against the background of hyperuricemia [8]. However, such comparisons have not been previously made in patients with SS. It was possible to show a significant independent effect of the level of uric acid on TIM in patients with SS. At the same time, the mean values and median of uric acid in the examined group of patients were formally within the normal range and did not reach the saturation point.

Interleukin 6 is a classical inflammatory cytokine traditionally considered as an atherogenic factor [1]. Numerous studies have established its ability to suppress the expression of adhesion molecules by endotheliocytes, inhibit smooth muscle cells and macrophages. The data obtained are based on a positive relationship between the levels of IL-6 and TIM in patients with SS. One of the weaknesses of this study was the lack of consideration of the effect of immunosuppressive / cytotoxic

drugs on the course of the atherosclerotic process, which was associated with a high degree of heterogeneity of such therapy and the small size of the evaluated groups of patients.

Given that in all patients, despite the ongoing therapy, significant, uncontrolled activity of the autoimmune/immunoinflammatory process persisted, which served as the reason for this hospitalization, an attempt to assess the influence of inflammatory factors on the course of the atherosclerotic process, nevertheless, seemed justified.

Despite the fact that the frequency of dyslipidemia was almost the same in both groups, the average level of triglycerides in patients with SS was significantly higher than in the control group. Hypertriglyceridemia has been previously described in other systemic autoimmune diseases, in particular in SLE [31,32]. In these studies, an elevated triglyceride level in SLE patients was associated with high disease activity, which makes it possible to discuss the effect of the immunoinflammatory process on the development of dyslipidemia. According to our data, in the group of patients with SS, there was also a tendency towards an increase in the maximum TIM and the frequency of thickening of the intima-media complex of the carotid arteries when compared with the control group. At the same time, atherosclerotic plaques in the carotid arteries were detected in 10% of patients with SS and were absent in the control group, which indicates a more pronounced atherosclerotic vascular lesion against the background of SS.

The increase in TIM with age and with a longer duration of the disease, revealed in our study, indicates the predominant development of atherosclerosis in older patients. In addition, the dependence of IMT on TFR% and cholesterol levels in patients with SS was shown.

Summarizing the results obtained, it can be assumed that in patients with SS in the genesis of atherosclerosis, a significant proportion belongs to non-traditional risk factors of atherogenesis, primarily mediators of inflammation, as well as characteristic metabolic disorders and increased IL-6. This may indicate the existence of specific pathogenetic mechanisms of arterial wall damage in this cohort of patients and may qualify for re-evaluation of TIM in patients with SS.

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