Cardiovacular Risk Factors and Atherosclerosis in Patients with Systemic Scleroderma

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Abstract---- Purpose of the study. To evaluate the frequency of traditional cardiovascular risk factors, clinical and subclinical manifestations of atherosclerosis in patients with systemic scleroderma (SS). Material and methods. We examined 70 patients with a reliable diagnosis of SS (66 women and 4 men), cf. age 46 ± 10.8 years. The control group consisted of 50 "conditionally" healthy volunteers without systemic rheumatic diseases and Raynaud's syndrome, matched by sex and age. Material and methods. We examined 70 patients with a reliable diagnosis of SS (66 women and 4 men), cf. age 46 ± 10.8 years. Control group - 50 "conditionally" healthy volunteers without systemic rheumatic diseases and Raynaud's syndrome, matched by sex and age. Results. The prevalence of traditional cardiovascular risk factors and TFR% were comparable in patients with SS and in the control group. The frequency of menopause was higher in patients with SS ($p=0.005$). IHD was diagnosed more often in patients with SS (13% vs. 2%, $p<0.05$). The mean triglyceride level in SS patients was significantly higher than in the control group ($p<0.001$). There was a tendency to increase TIM max. and the frequency of thickening of the IMT complex in patients with SS compared with the control group. Conclusion. Among SS patients, there was a higher prevalence of clinical and subclinical manifestations of atherosclerosis compared with the control group, with no significant differences in the incidence of major cardiovascular risk factors.

Keywords--- Systemic Scleroderma, Atherosclerosis, Cardiovascular Risk Factors.

I. Introduction

Systemic scleroderma (SS) is an autoimmune connective tissue disease characterized by cutaneous and visceral fibrosis and generalized vascular pathology. An important link in the pathogenesis of SS is microcirculation disorders with activation and proliferation of endothelium and smooth muscle cells, vasospasm, aggregation of formed elements, stasis, deformation and reduction of the capillary network [1, 2, 15-20].

Endothelial dysfunction and hemorheological disorders characteristic of SS are considered as early predictors of atherosclerosis. The general pathogenetic mechanisms of these diseases suggest a high probability of atherosclerotic vascular lesions in patients with SS [3-6, 21-25].

It is known that along with a generalized lesion of small-caliber vessels, which is determined already at the early stages of the disease, changes in medium-sized vessels are also observed in SS [2, 5-12]. Peripheral arterial lesions according to angiography and ultrasound scanning of blood vessels in patients with SS were found with a significantly higher frequency when compared with the control group and was associated with a severe clinical course of the disease [11]. A number of studies in the study of medium-sized vessels in patients with SS demonstrated a predominant lesion of the ulnar arteries, which is a predictor of the development of digital necrosis [12-13]. A biopsy of the ulnar arteries revealed a narrowing of the lumen of the arteries, while there were no atherosclerotic plaques [8]. Angiography revealed stiff peripheral arteries in patients with SS [8]. Other researchers determined a decrease in the elasticity of the carotid arteries in patients with limited and, to a greater extent, diffuse form of SS [14]. According to the Scottish group for the study of systemic sclerosis (M.Ho, D.Veale, C.Eastmond), stenosis of the carotid arteries was observed in 64% of patients with SS at an average age of 57 (31-82) years and almost twice as often (35%) in control group. The frequency of atherosclerotic plaques and peripheral vascular disease was also higher among patients with SS, despite the absence of significant differences in the frequency of cardiovascular risk factors between the two groups [7, 14].

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 [9].

According to various studies, patients with SS are characterized by a high risk of mortality from cardiovascular diseases [18,19]. 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-SS 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 [19].

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 SS 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.

The aim of this study was to assess the frequency of traditional cardiovascular risk factors, clinical and subclinical manifestations of atherosclerosis in patients with SS.

II. Material and Methods

From 2015 to 2017, we examined 70 patients with a reliable diagnosis of SS (66 women and 4 men) admitted to the rheumatology, cardiorheumatology and rheumatology departments of the 1st clinic of the Tashkent Medical Academy. The average age of patients was 46 ± 10.8 years (from 20 to 64 years). Diffuse form of scleroderma was determined in 18 (25.7%), limited in 39 (55.7%), overlapping syndrome (SS/RA and SS/PM) in 13 (18.6%) patients. The duration of the disease ranged from 6 months to 38 years, with an average of 10 (4-15) years. The criteria for inclusion in the study were a reliable diagnosis of SS (ARA criteria) [20] and the age of patients from 17 to 65 years.

Clinical characteristics of patients with SS are presented in Table 1.

Therapy with glucocorticoids (GC) was received by 59 (84%) patients, D-penicillamine - 15 (21%), methotrexate - 6 (8.6%), plaquenil - 10 (14%), cyclophosphamide - 17 (24%) patients. All patients with SS were taking vascular drugs (antiplatelet agents, calcium antagonists).

Table 1: Clinical Characteristics of Patients with SS

Signs	**Patients with SS**	
S-m Reynaud	70	100
Digital ulcers	15	21
Hand contractures	49	70
Esophagitis	47	67
Pneumofibrosis (chest x-ray)	55	79
Restrictive violations (functional tests)	21	30
Pulmonary hypertension (ECHO-KG)	14	20
Diastolic dysfunction (ECHO-KG)	28	40
Violations of the rhythm of the heart (HM-ECG)	31	44
ANF (+)*	58	83

*ANF (antinuclear factor) was determined by indirect immunofluorescence

The control group consisted of 50 "conditionally" healthy volunteers (employees of the department of the Tashkent Medical Academy) who do not have systemic rheumatic diseases and Raynaud's syndrome, matched by sex (45 women and 5 men) and age (44.1 ± 7.4 years).

The study did not include patients and volunteers with clinical signs of infection, end-stage renal or hepatic insufficiency, uncontrolled diabetes mellitus.

To verify the diagnosis of SS and characteristics of organ pathology, all patients underwent instrumental studies, including chest X-ray, ECG, Echo-KG, Holter ECG monitoring (HM-ECG), functional pulmonary tests (spirometry, study of the diffusion capacity of the lungs).

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) [21], an increase in body mass index (BMI) (weight, kg/height, m2 ≥ 25 kg/m2) [22], 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], arterial hypertension (systolic blood pressure (SBP) ≥140 mm Hg, diastolic (DBP) ≥90 mm Hg or taking antihypertensive drugs), smoking, menopause, diabetes mellitus. Total coronary risk (TCR%) (10-year risk of cardiovascular events) was assessed using the Framingham scale.

To identify subclinical forms of atherosclerosis in patients with SS (n=60) and in the control group (n=45), 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 from two sides) and calculations average and maximum values of TIM. The presence of atherosclerosis was assessed by thickening of the intima-media complex (IMT from 0.9 to 1.2 mm) and the presence of atherosclerotic plaques (ATP) (local increase in IMT > 1.2 mm).

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 the statistical evaluation of the results, nonparametric 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 $p<0.05$.

III. Results

Comparison of traditional 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) (Table. 2).

TFR% in patients with SS was 3(1-27) %, which coincided with the average value of TFR% in the control group - 3(1-15)%.

Table 2: Traditional Cardiovascular Risk Factors in Patients with SS

Risk factors for atherosclerosis:	Patients with SS n=70 n(%)	Control group n=50 n(%)
Heredity according to CVD	22 (31%)	18 (36%)
BMI≥25 kg/m2	28 (40%)	22 (44%)
Dyslipidemia	53 (76%)	34 (72%)
Arterial hypertension	25 (36%)	12 (24%)
Smoking	5 (7%)	14 (28%)
Menopause	38 (57%)	11 (24%)
Diabetes	3 (4,3%)	-

*p<0,05

When analyzing the clinical manifestations of atherosclerosis, it turned out that coronary artery disease was determined more frequently among patients with SS. IHD was diagnosed in 9 (13%) patients with SS and only in 1 (2%) volunteer from the control group (p<0.05). MI (one case) was recorded only in the group of patients with SS, stroke - in one patient with SS and in 1 volunteer from the control group.

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) (Table 3).

Table 3: Mean Lipid Values in SS Patients and in the Control Group

Lipids: (mmol/l)	Patients with SS D, n=70	Control group, n=50
Cholesterol	5,5 (4,8-6,4)	5,6 (5,0-7,3)
Triglycerides	0,87 (0,63-1,76)*	0,55 (0,30-0,93)*
HDL	1,24 (0,99-1,68)	1,4 (1,21-1,62)

Me(LQ-UQ); * p<0,001

The mean and maximum IMT 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 4).

Table 4: The Thickness of the Intima-media Complex of the Carotid Arteries in Patients with SS and in the Control Group

TIM, mm	Patients with SS n=60	control group, n=45
TIM average	0,78 ±0,18	0,74 ± 0,08
TIM middle right	0,77 ± 0,18	0,74 ± 0,09
TI M 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*

M±SD, n (%), *p<0.05

A high positive correlation was established between IMT average and IMT 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 IMT 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 IMT, 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 IMT and cholesterol levels (r=0.31, t=2.44, p<0.05).

IV. Conclusion

A high prevalence of cardiovascular pathology and atherosclerotic vascular lesions in patients with SS in the absence of significant differences in the frequency of major cardiovascular risk factors was also observed in other studies [7, 11-12, 14-17]. It can be assumed that the factors involved in the pathogenesis of this disease are of paramount importance in the development of early atherosclerosis in patients with SS. This assumption is confirmed by a series of studies that show that anti-endothelial antibodies, dysfunction of the coagulation and fibrinolytic systems, an increase in the level of homocysteine, CRP, and intercellular adhesion molecules significantly increase the risk of atherosclerosis in SS. Thus, in patients with SS, along with scleroderma angiopathy, there are clinical and subclinical signs of atherosclerosis. These data indicate the advisability of prescribing drugs that have a protective effect on the vascular wall - statins and antioxidants - to patients with SS.

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