Study of damage to the cardiovascular system in patients with systemic scleroderma

Nabiyeva A.X TTA magistr
Bekenova G.T Ilmiy Rahbar Dotsent

ABSTRACT

Subjects and methods. The investigation enrolled 125 patients with SS and 50 sex- and age-matched, apparently healthy individuals included in a control group. Standard electrocardiography was performed in all and EchoCG – in 121 patients. The Systematic Coronary Risk Evaluation (SCORE) scale was used to assess the risk of fatal CVD in 100 patients with SS and in 47 control individuals within 10 years.

Results and discussion. The frequency of TFRs in patients with SS was not significantly different from that in the control group, except for the occurrence of hypercholesterolemia and increased body mass index (BMI). In SS, BMI >25 kg/m^2 was observed significantly more often and the frequency of hypercholesterolemia was lower than in the controls ($p < 0.018$). Hypertension and diabetes mellitus were slightly more frequently encountered in SS patients than in the controls, but this difference was insignificant. Taking into account the Russian Society of Cardiology (RSC) guidelines, the cardiovascular risk (CVR) was assessed with the SCORE scale. A very high CVR was much more common in SS and a moderate CVR was much more frequently seen in the control group. There were no substantial differences in the frequency of low and high CVRs. SS is characterized by the increased frequency of high total CVD risk as compared to the controls. Hypertension, overweight, and over 50 years of age were associated with more obvious structural heart disease,

Conclusion. TRFs make a substantial contribution to the formation of a high CVR in patients with SS, promoting the development of atherosclerosis and its complications. Assessment of TGFs in SS patients will facilitate identifying patients at high risk for cardiovascular death and timely prescribing therapy. Hypertension is an important TGF that in SS is associated with considerable structural changes in the heart; therefore adequate blood pressure control is of importance in improving SS prognosis especially in patients older than 50 years.

Keywords: Systemic sclerosis; traditional risk factors for cardiovascular disease ;EKG ; echocardiography; SCORE scale.

Systemic scleroderma (SS) is a connective tissue disease characterized by systemic inflammation, widespread microcirculatory vasculopathy, and progressive skin fibrosis.and internal organs [1]. SJS varies in severity and progression most patients develop visceral complications, which are usually the cause of death [2] Primary heart disease that develops as a direct consequence of SJS, may be manifested by changes myocardium, pericardium and valvular apparatus. In patients SJS pathology of the heart can also be secondary to acute

scleroderma kidney and pulmonary arterial hypertension. Vasculopathy in SJS is characterized by a progressive restructuring of the microvasculature, which can contribute to the development of a variety of cardiovascular changes. Endothelial dysfunction and hemorheological disorders characteristic of SSc are also considered as risk factors for the early development of atherosclerosis (ASC). The common pathogenetic mechanisms of SJS and ASC suggest a high
likelihood of atherosclerotic vascular disease in patients with SJS [3, 4]. G.S. Ngian et al. [5] expressed
the assumption that AS in patients with SJS makes a certain contribution to macro- and microvascular damage to the myocardium. Patients with SSc have a fourfold an increase in mortality compared with the general population, with a third of the causes of mortality accounted for by cardiovascular diseases (CVD) [6]. In SSc, the leading cause of death unrelated to the underlying disease is CVD [7], which causes from 20 to30% of deaths [8]. ASC is a complex pathological process Part of which is infection, which is important for the entire evolution of atherosclerotic plaque (ATP) [9]. With autoimmune
inflammatory rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus
(SLE), primary antiphospholipid syndrome, systemic vasculitis, one of the main causes of disability and are cases of CVD associated with an increased risk of developing ASA. Compared to the general population,development of ASA in RA and SLE age and is often asymptomatically variable [10].

Apart from traditional risk factors (TFR), in systemic connective tissue diseases, additional risk factors are important: chronic inflammation, duration and activity of an autoimmune disease, immunosuppressive therapy. The role of chronic inflammation is indicated by the fact that inflammatory mediators such as
C-reactive protein, heat shock proteins, are also involved in the pathogenesis of ASC [3, 7, 11–15]. With rheumatic diseases, chronic inflammation can accelerate the formation of ATP, both through a direct effect on the wallsarteries, and indirectly, by influencing lipid profile.

Along with inflammation, antibodies produced in autoimmune diseases can also lead to changes in the blood lipid spectrum [9]. Other specific factors may also contribute to the development of premature ASA (decrease in the number and function of endothelial progenitor cells,accelerated apoptosis of endothelial cells, epigenetic changes) [16]. It has not yet been established whether ASC develops in patients
SJS earlier than in the population. A number of studies indicate an increase in the frequency of detection of ASA in SSD. It is known that both pronounced and subclinical manifestations of ASC are found in SJS with a high frequency. So, the defeat of the carotid arteries is noted in 40%, endothelial dysfunction - in 76.4% of patients.In SSc, the incidence of CVD and macrovascular disease is increased compared with the general population, and the combination SJS with ASA worsens the prognosis [17]. On examination 5860 of patients with SJS, it was shown that cardiovascular disorders were the cause of death in 26% of them, and among the causes of death not related to SJS itself, almost 1/3
(29%) of cases were due to CVD [18]. SJS is characterized by a high risk of mortality from vascular accidents [19].

In addition, patients with SSc have higher in-hospital mortality from cardiovascular complications (CVS) associated with ASA compared with patients with SLE and RA [20] The pathogenesis of ASC in SSc remains unclear. It is believed that TFRs contribute to its accelerated development [21].However, the results of studies in which TFR were evaluated in patients with SSc are contradictory and do not yet confirm
significant differences in the TGF profile compared to with control. Preliminary data show an increase in the frequency of arterial hypertension (AH), dyslipidemia and an increase in body mass index (BMI)
in patients with SJS, which may contribute to the formation functional and structural changes in the heart, worsening the prognosis of the

disease in general. At present, a comprehensive analysis of TFR is considered one of the promising approaches to improve prognosis in SSc. The aim of this study was to assess the frequency of CVD TFR in patients with SSc and to analyze their relationship with the clinical manifestations of SSc, as well as with structural changes in echocardiography data (EchoCG).

Material and methods

The study included 125 patients with SJS(113 women and 12 men) aged 22 to 71(average 50.68±11.9 years) and with a duration of illness from 1 year to 36 years (average 8.9±8.0 years). The diagnosis of SSc wasreliable and met the criteria of the American College of Rheumatology (ACR) 1980; and ACR/European League Against Rheumatism (EULAR) 2013 [22, 23].In 73% of cases, there was a limited form of SJS.Patients had a typical picture of SJS, including sclerodactyly (92%), gastrointestinal involvement (GIT; 92%), interstitial lung disease (ILD; 50%), signs of digital ischemia (43%), telangiectasia (43%), osteolysis (27%), soft tissue calcification (twenty%). The median skin score was 4 [2; eight]. The following TGFs were assessed: increase in BMI >25 kg/m2, hypercholesterolemia [total cholesterol (CH)>5.2 mmol/l], AH [level of systolic arterial pressure (BP)>140 mm Hg. Art. and diastolic blood pressure >90 mm rt. Art.], smoking, diabetes mellitus (DM). All patients received standard vascular therapy,according to indications - glucocorticoids, immunosuppressantsand statins. All patients with SSc underwent a standard electrocardiography (ECG) and 121 - echocardiography control the group consisted of 50 people (5 men and 45 women) aged 25 to 60 years (mean age 47.08±8.01 years)
from among the employees of the FGBNU NIIR them. V.A. Nasonova.The control and main groups were comparable in terms of gender and age. Assessing the risk of fatal CVD during10 years on the SCORE scale was carried out in 100 patients with SJSand 47 people from the control group. The rest (25 patients with SJS and 3 people from the control group) immediately were identified as being at very high cardiovascular risk (CVR) because they had diabetes and/or coronary heart disease (CHD), suffered a heart attack myocardial infarction (MI) or stroke. Data analysis was carried out using the statistical program Statistica 8.0.

Results

The frequency of TFR in patients with SJS did not differ significantly from that in the control group, with the exception of incidence of hypercholesterolemia and elevated BMI (Table 1). In SJS, an increase in BMI >25 kg/m2 was observed significantly more often, and the frequency of hypercholesterolemia was lower than in controls (p<0.018).AH and DM in SSc were slightly more common than
in control, but this difference is not significant. There were no smokers among patients with SJS and in the control group. When studying the relationship between TFR and clinical manifestations of SJS, it was noted that in the limited form of the disease, AH occurred significantly more often than with diffuse (34.1 and 5.9%, respectively; p=0.015). In patients with SJS older than 50 years, significantly more often than in younger patients,AH (36 and 12%, respectively; p=0.0029) and hypercholesterolemia (62.7 and 44%, respectively; p=0.0398) were detected.Taking into account the recommendations of the Russian Society of Cardiology (RCS), we assessed CVR on a scale SCORE. A very high risk was significantly more common in SSc, a moderate risk in the control group. There are no significant differences in the frequency of low and high risk observed. As can be seen from Table. 2, in SSc, the total risk of CVD
was high or very high on the SCORE scale in almost 1/3 of patients. At the time of the examination, 20% of patients already had proven signs of developed ASCand its complications, which significantly exceeded the corresponding indicator in the control group. In 14 (11%) patients there were signs of circulatory failure.It is known that in a number of diseases there is a certain relationship between CVR and changes in the structure and function.heart, e.g. with left ventricular remodeling
(LV). In SSc, structural changes in the heart compared to healthy individuals have not been

studied enough. In this study, 83% of patients with SJS had some or other changes in echocardiography (Table 3). It concerned the first sequence of changes in the aortic and mitral valves in the form of their compaction and calcification of the valves. LV diastolic dysfunction was observed in almost half sick. In 7% of patients, there was a significant decrease in the ejection fraction (EF) of the LV (<55%).When studying the profile of structural changes in patients with SJS, marked differences were revealed depending on the presence of individual TGFs. Yes, in males an increase in both atria was significantly more common than in women. At the same time, the frequency of the increase in the left atrial was respectively 23.5 and 7.7%(p=0.042), and the right - 20.8 and 7.2% (p=0.045) We also determined the frequency of individual

TFR in various structural changes in the heart. It has been shown that in patients with enlarged left atrium

the frequency of hypertension was significantly higher than in normal its size (30.3 and 8%, respectively; p=0.0016). In the subgroup of patients with enlarged right atrium, a significantly higher frequency of excess body weight and men were more than among patients,had normal sizes of the right auricle.

In patients with LV diastolic dysfunction, the frequency of AH and MI was significantly higher than without it (38.5 and 18.8%, respectively, p=0.0164; 7.7 and 0%, p=0.0191). Frequency LV hypertrophy was significantly higher in patients with elevated BMI. In the subgroup of patients with compaction

mitral valve frequency of hypertension was significantly higher (41.8%) than without it (15.2%; p=0.0010). In the presence of aortic valve sealing, the level of cholesterol and blood pressure was significantly higher than in its absence. Correlation the analysis showed a direct significant relationship between overweight (BMI >25 kg/m2) and hypertension (r=0.223773;p<0.05)

Conclusion

TFRs make a significant contribution to the formation high CVR in patients with SSc, contributing to the development of ASC and its complications. Evaluation of TGF in patients with SJS will allow

identify patients with a high risk of cardiovascular mortality and timely conduct therapy aimed at reducing it. AG is an important TFR that in SSc is associated with significant structural

changes in the heart, therefore, to improve the prognosis SJS is important for adequate control of hypertension, especially in people over 50 years of age.

Reference

1. Radic M, Kaliterna DM, Fabijanic D, Radic J. [Systemic sclerosis – pathogenesis, clinical manifestations and treatment]. *Lijec Vjesn.* 2010 May-Jun;132(5-6):162-8 (In Croat.).
2. Sherer Y, Shoenfeld Y. Mechanisms of disease: atherosclerosis in autoimmune diseases. *Nat Clin Pract Rheumatol.* 2006 Feb;2(2):99-106. doi: 10.1038/ncprheum0092
3. Nassenstein K, Breuckmann F, Huger M, et al. Detection of myocardial fibrosis in systemic sclerosis by contrast-enhanced magnetic resonance imaging. *Rofo*. 2008 Dec;180(12):1054-60.
4. doi: 10.1055/s-2008-1027864
5. Ngian GS, Sahhar J, Proudman SM, et al. Prevalence of coronary heart disease and cardiovascular risk factors in a national crosssectional cohort study of systemic sclerosis. *Ann Rheum Dis.*
6. 2012;71:1980-3. doi: 10.1136/annrheumdis-2011-201176
7. Bryan C, Howard Y, Brennan P, et al. Survival following the onset of scleroderma: results from a retrospective inception cohort study of the patients population. *Br J Rheumatol.* 1996;35:1122-6. doi: 10.1093/rheumatology/35.11.1122
8. Szekanecz Z, Koch AE. Vascular involvement in rheumatic diseases: vascular rheumatology. *Arthritis Res Ther.* 2008;10(5):224.
9. doi: 10.1186/ar2515

10. Belch JJ, McSwiggan S, Lau C. Macrovascular disease in systemic sclerosis: the tip of an iceberg? *Rheumatology*. 2008;47 Suppl
11. 5:v17. doi: 10.1093/rheumatology/ken280
12. Toms TE, Panoulas VF, Kitas GD. Dyslipidaemia in rheumatological autoimmune diseases. *Open Cardiovasc Med J*. 2011;5:64-75. doi: 10.2174/1874192401105010064
13. Sitia S, Atzeni F, Sarzi-Puttini P. Cardiovascular involvement insystemic autoimmune diseases. *Autoimmun Rev.* 2009 Feb;8(4):281-6. doi: 10.1016/j.autrev.2008.08.004
14. Szekanecz Z, Kerekes G, Der H, et al. Accelerated atherosclerosisin rheumatoid arthritis. *Ann NY Acad Sci.* 2007;1108:349-58. doi: 10.1196/annals.1422.036
15. Shoenfeld Y, Gerli R, Doria A, et al. Accelerated atherosclerosis inaytoimmune diseases. *Circulation*. 2005;112:3337-47.
16. doi: 10.1161/CIRCULATIONAHA.104.507996
17. Szucs G, Timar O, Szekanecz Z. Endothelial dysfunction precedesatherosclerosis in systemic sclerosis – relevance for prevention of vascular complications. *Rheumatology (Oxford).* 2007 May;46(5):759-62. doi: 10.1093/rheumatology/kel426
18. Szekanecz Z, Shoenfeld Y. Lupus and cardiovascular disease: thefacts. *Lupus*. 2006;15 Suppl:3-10. doi: 10.1177/0961203306071665
19. Soltesz P, Szekanecz Z, Kiss E, Shoenfeld Y. Cardiac manifestations in antiphospholipid syndrome. *Autoimmun Rev.* 2007;6:379-
20. 86. doi: 10.1016/j.autrev.2007.01.003
21. Hollan I, Meroni P, Ahearn J, et al. Cardiovascular disease inautoimmune rheumatic diseases. *Autoimmun Rev.* 2013 Aug;12(10):1004-15. doi: 10.1016/j.autrev.2013.03.013
22. Hettema ME, Bootsma H, Kallenbrg CGM. Macrovascular disease and atherosclerosis in systemic sclerosis. *Rheumatology*.
23. 2008;47:578-83. doi: 10.1093/rheumatology/ken078
24. Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors fordeath in systemic sclerosis: a study from the EULAR Scleroderma
25. Trials and Research (EUSTAR) database. *Ann Rheum Dis.* 2010
26. Oct;69(10):1809-15. doi: 10.1136/ard.2009.114264
27. Ioannidis JPA. Large scale evidence and replication: insights fromrheumatology and beyond. *Ann Rheum Dis.* 2005;64:345-6. doi: 10.1136/ard.2004.027979
28. Dave AJ, Fiorentino D, Lingala B, et al. Atherosclerotic cardiovascular disease in hospitalized patients with systemic sclerosis: higher mortality than patients with lupus and rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2014 Feb;66(2):323-7. doi: 10.1002/acr.22152
29. Sander GE, Giles TD. Cardiovascular complications of collagenvascular disease. *Curr Treat Opt Cardiovasc Med.* 2002 Apr;4(2):151-9. doi: 10.1007/s11936-002-0035-z
30. Masi AT, Rodnan GP, Medsger TA, et al. Preliminary criteria forthe classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum.*
31. 1980;23(5):581-90. doi: 10.1002/art.1780230510
32. Jordan S, Maurer B, Michel B, Distler O. Performance of the newEULAR/ACR classification criteria for systemic sclerosis in clinical practice. *Ann Rheum Dis.* 2013;72 Suppl 3:60.
33. doi: 10.1136/annrheumdis-2013-eular.239
34. Man A, Zhu Y, Zhang Y, et al. The risk of cardiovascular disease insystemic

sclerosis: a population-based cohort study. *Ann Rheum Dis.* 2013;72:188-93. doi: 10.1136/annrheumdis-2012-202007

35. Khurma V, Meyer C, Park GS, et al. A pilot study of subclinicalcoronary atherosclerosis in systemic sclerosis: coronary artery calcification in cases and controls. *Arthritis Rheum.* 2008;59:591-7. doi: 10.1002/art.23540
36. Mok MY, Lau CS, Chiu SS, et al. Systemic sclerosis is an independent risk factor for increased coronary artery calcium deposition. *Arthritis Rheum.* 2011;63:1387-95. doi: 10.1002/art.30283
37. Nordin A, Jensen-Urstad K, Bjornadal L, et al. Ischemic arterialevents and atherosclerosis in patients with systemic sclerosis: a population-based case-control study. *Arthritis Res Ther.*
38. 2013;15:R87. doi: 10.1186/ar4267
39. Хрипунова АА. Частота макрососудистых осложнений присистемной склеродермии и прогностическое значение в их развитии традиционных кардиоваскулярных факторов риска и иммуновоспалительных механизмов: Дисс. … канд. мед. наук. Ставрополь; 2012 [Khripunova AA. *Chastota makrososudistykh oslozhnenii pri sistemnoi sklerodermii i prognosticheskoe znachenie v ikh razvitii traditsionnykh kardiovaskulyarnykh faktorov riska i immunovospalitel'nykh mekhanizmov: Diss. … kand. med. nauk* [The frequency of macrovascular complications of systemic sclerosis and their prognostic significance in the development of traditional cardiovascular risk factors and immunoinflammatory mechanisms: Diss. ... Cand. Med. Sci.]. Stavropol'; 2012].
40. Патрикеева ДА. Клинико-диагностическое значение дисфункции почек как фактора риска кардиоваскулярной патологии у больных системной склеродермией: Дисс. … канд. мед. наук. Волгоград; 2015 [Patrikeeva DA. *Kliniko-diagnosticheskoe znachenie disfunktsii pochek kak faktora riska kardiovaskulyarnoi patologii u bol'nykh sistemnoi sklerodermiei: Diss. … kand. med. nauk* [Clinical and diagnostic value of renal dysfunction as a risk factor for cardiovascular disease in patients with systemic sclerosis: Diss. ... Cand. Med. Sci.]. Volgograd; 2015].
41. Lippi G, Caramaschi P, Montagnana M, et al. Lipoprotein and thelipid profile in patients with systemic sclerosis. *Clinica Climica Acta.* 2006;364(1-2):345-8. doi: 10.1016/j.cca.2005.07.015
42. Cerinic MM, Valentini G, Sorano GG, et al. Blood coagulation,fibrinolysis, and markers of endothelial dysfunction in systemic sclerosis. *Semin Arthritis Rheum.* 2003;32(5):285-95. doi: 10.1053/sarh.2002.50011
43. Borba EF, Borges CTL, Bonfa E. Lipoprotein profile in limitedsystemic sclerosis. *Rheumatol Int.* 2005;25:379-83. doi: 10.1007/s00296-004-0580-8
44. Tsifetaki N, Georgiadis AN, Alamanos Y, et al. Subclinical atherosclerosis in scleroderma patients. *Scand J Rheumatol.*
45. 2010;39(4):326-9. doi: 10.3109/03009741003605648
46. Schiopu E, Karen M, McMahon Maureen A, et al. Prevalence ofsubclinical atherosclerosis is increased in systemic sclerosis and is associated with serum proteins: a cross-sectional, controlled study of carotid ultrasound. *Rheumatology*. 2014;53:704-13. doi: 10.1093/rheumatology/ket411
47. Frerix M, Stegbauer J, Kreuter A, Weiner SM. Atherosclerotic plaques occur in absence of intima-media thickening in both systemic sclerosis and systemic lupus erythematosus: a duplex sonography study of carotid and femoral arteries and follow-up for cardiovascular events. *Arthritis Res Ther.* 2014 Feb 19;16(1):R54. doi: 10.1186/ar4489
48. Chu S-Y, Chen Y-J, Liu C-J, et al. Increased risk of acute myocardialinfarction in systemic sclerosis: a nationwide

population-based study. *Amer J Med.* 2013;126:982-8. doi: 10.1016/j.amjmed.2013.06.025

49. Шабанова СШ, Ананьева ЛП, Попкова ТВ и др. Традиционные кардиоваскулярные факторы риска и атеросклероз у больных системной склеродермией. Научно-практическая ревматология. 2007;45(4):24-30 [Shabanova SS, Ananjeva LP, Popkova TV, et al. Traditional cardiovascular risk factors and atherosclerosis in patients with systemic sclerosis. *Nauchno-Prakticheskaya Revmatologiya = Rheumatology Science and Practice.* 2007;45(4):24-
50. 30 (In Russ.)]. doi: 10.14412/1995-4484-2007-24-30
51. Tadic M, Cuspidi C, Pencic B, et al. Relationship between rightventricular remodeling and heart rate variability in arterial hypertension. *J Hypertens.* 2015 May;33(5):1090-7.
52. doi: 10.1097/HJH.0000000000000511
53. Foocharoen C, Pussadhamma B, Mahakkanukrauh A, et al.Asymptomatic cardiac involvement in Thai systemic sclerosis: prevalence and clinical correlations with non-cardiac manifestations (preliminary report). *Rheumatology (Oxford).* 2015 Sep;54(9):1616-21. doi: 10.1093/rheumatology/kev096
54. Rosato E, Gigante A, Gasperini ML, et al. Nutritional statusmeasured by body mass index is impaired and correlates with left ventricular mass in patients with systemic sclerosis. *Nutrition*. 2014 Feb;30(2):204-9. doi: 10.1016/j.nut.2013.07.025
55. Piccione MC, Bagnato G, Zito C, et al. Early identification ofvascular damage in patients with systemic sclerosis. *Angiology*. 2011 May;62(4):338-43. doi: 10.1177/0003319710387918