ACTA MEDICA SALINIANA

ORIGINAL PAPERS

ORGAN INVOLVEMENT IN SYSTEMIC SCLEROSIS

Irma Ovčina, Ljubinka Božić Majstorović, Jelena Mrđa

ISSN 0350-364X

DOI: 10.5457/850

Irma Ovčina
Ljubinka Božić Majstorović
Jelena Mrđa

ABSTRACT

Introduction: In systemic sclerosis, several organ systems can be affected, due to the basic pathophysiological mechanism at the endothelial level.
Aim: The aim of this research is to show the frequency of clinical manifestations as well as their correlation in our sample of patients.
Methods: Twenty-nine patients with systemic sclerosis were included in our study. A correlation was made between clinical manifestations, parameters and organic involvement.
Results: The number of patients who had esophageal involvement was 16 (55.2%), cardiac involvement 18 (62.1%), pulmonary 27 (93.1%) and renal 16 (55.2%). The occurrence of esophageal, cardiac and renal involvement was statistically significant in correlation with disease duration (p=0.017, p=0.014; p=0.032). The appearance of digital ulcerations (DU) was significantly correlated with esophageal and cardiac involvement, p=0.034 and p=0.01. Reduction of renal involvement, decrease in creatinine clearance and thinning of the renal parenchyma, occurred simultaneously with cardiac involvement in a statistically significant correlation, p= 0.014 and p=0.011. The reduction in ejection fraction and the occurrence of diastolic dysfunction also affected renal involvement, p= 0.009 and p=0.017.
Conclusion: We showed a correlation between the duration of the disease and organic involvement, as well as DU with cardiac and esophageal involvement. The connection between the cardiac and renal systems affects the overall course of the disease and the higher mortality of patients. Therefore, with early detection, adequate management and therapeutic modalities can be accessed in a timely manner in order to prevent further complications of the course of the disease.
Key words: cardiac involvement, renal involvement, Rodnan skin score, systemic sclerosis

Affiliations:

Received:
28.11.2024.

Accepted:

Corresponding author:
Irma Ovcina
irma.093@hotmail.com

Funding: none

Competing interests: none

INTRODUCTION

Systemic sclerosis (SS) is an autoimmune disease characterized by: dysregulation of the immune system, vasculopathy and fibrosis of skin and internal organs [1]. Several organ systems can be affected: skin, lungs, heart, musculoskeletal, kidneys and gastrointestinal tract [2]. Considering that the initial process is at the endothelial level, the numerous clinical presentations are not surprising. The aim of this research is to show the frequency of clinical manifestations as well as their correlation in our sample of patients.

MATERIAL AND METHODS

Our research included 29 patients with SS hospitalized at the University Clinical Center of the Republic of Srpska from January 2022 to December 2022. The informed consent was obtained from all participants in the study and the Ethic committee aproved our study. All patients are older than 18 years and have a diagnosis based on the American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) from 2013 [3]. Exclusion criteria were: overlap syndromes with other systemic connective tissue diseases, skin thickening caused by other conditions (morphea, myxedema, eosinophilic fasciitis, diabetes mellitus), skin ulcerations caused by nephrotic syndrome and congestive heart failure, and venous peripheral disease.

Clinical parameters

The severity of skin involvement was assessed by using the modified Rodnan skin score (mRSS). It includes an examination of 17 skin regions: face, chest, abdomen, upper arms, forearms, dorsum of hands, fingers, upper legs, lower legs, dorsum of feet and feet. Skin thickness is ranked from 0-3, with 0 indicating normal skin and 3 severe thickening of the skin. The maximum value is 51 [4]. Gastroenterological evaluation was performed using esophageal transit scintigraphy. As a pathological finding indicating SS is slowed transit [5]. The cardiological involvement was assesseb by using the echosonographic characteristics: tricuspid annular plane systolic excursion (TAPSE), left ventricle ejection fraction (LVEF) and pulmonary arterial systolic pressure (PASP) [6]. Pulmonary involvement was characterized by reduced lung diffusion capacity for carbon monoxide (DLCO). For reduced DLCO the value <75% was chosen. We also included forced expiratory volume (FVC) values [7]. Renal function was evaluated by using creatinine clearance and renal parenchymal thickness. [8, 9]. In addition to the laboratory findings, anti Scl 70 and anti centromeric (ACA) antibodies were performed.

Statistic analysis

Statistical analyzes were performed using SPSS version 22.0. Descriptive statistics were expressed as mean, standard deviation and median for quantitative parameters, while absolute numbers and percentages were used for qualitative parameters. Mann-Whitney U test and t test were used to detect differences between continuous variables, while chi square test was used for categorical variables. P values <0.05 were considered statistically significant.

RESULTS

The characteristics of the subjects are shown in table 1.

Table 1: Patients caracteristics and organ involvement

	Overall	Esophagus involvement N/mean P value	Heart involvement N/mean P value	Pulmonary Involvement N/mean P value	Renal involvement N/mean P value
Sex, F:M (%)	25:4 (86.21)	16 (55.17%)	16:2 (64%)	24 (82.76%)	15 (51.72%)
		0.187	0.597	0.198	0.191
Age (years), Mean±SD	56.93±10.57	57.0	58.67	56.41	59.18
		0.938	0.238	0.315	0.170
Duration (years), mean±SD	6.31±5.75	8	8.39	6.26	8.62
		0.017*	0.014*	0.650	0.032*
Raynaud phenomen, N(%)	27 (93.1)	14	16	25	15
		0.114	0.158	0.586	0.879
Ulceration, N(%)	13 (44.8)	10	12	11	9
		0.034*	0.01*	0.065	0.170
Arthritis, N(%)	6 (20.7)	5	4	5	4
		0.104	0.793	0.337	0.521
mRSS	21.41±9.67	24.4	16.42	21.7	24.13
		0.110	0.256	0.709	0.144
Anti Scl70, N(%)	14 (48.3)	8	7	14	8
		0.837	0.196	0.096	0.837
Anti Centromere, N(%)	12 (41.4)	8	10	10	8
		0.296	0.04*	0.05*	0.296

SD- standard deviation; mRSS-modified Rodnan skin score; *p< 0.05

A total of 29 patients were included. The average age was 56.93±10.57 years and most patients were female 25 (86.2%). The number of patients who had esophageal involvement was 16 (55.2%), cardiac involvement 18 (62.1%), pulmonary involvement 27 (93.1%) and renal involvement 16 (55.2%). Not a single patient was without involvement of at least one organ system. The mean age of patients with renal involvement was 59.18 years, which is the highest, followed by cardiac involvement at an mean of 58.67 years, esophageal involvement with an mean age of 57 years and lung involvement at 56.41 years. The mean duration of the disease was 6.31 years, and the duration is significantly correlated

with involvement of the esophagus, heart and kidneys (p=0.017, p=0.014 and p=0.032).

Raynaud phenomen (RP) is most prevalent in patients with pulmonary involvement 25 (86.21%), but without statistical significance. The occurrence of digital ulcerations (DU) was present in all categories, but it was statistically significant in cardiac and gastrointestinal involvement (p=0.034 and p=0.01). Arthritis was not significant associated with any systemic involvement. Modified RSS is the highest in patients with esophageal involvement, 24.4 and renal involvement, 24.13, but without statistical significance. ACA were mostly represented in pulmonary and cardiac involvement, 34.48%, which is statistically significant (p=0.04 and p=0.053). Anti Scl70 were not significantly elevated in individual organ involvement.

Esophageal involvement occurred in patients with all organ involvement in a statistically significant proportion. Table 2 shows the correlations of clinical parameters and organ involvement. Renal involvement occurred simultaneously with cardiac involvement in a statistically significant correlation, p= 0.014 and p=0.011 (for creatitine clearance and parenchymal thickness). Also, cardiac involvement is correlated with renal manifestations. The reduction of LVEF and the appearance of diastolic dysfunction are in a significant correlation with renal involvement, p= 0.009 and p=0.017.

Table 2: Correlation between cinical parameters and their occurence in heart, esophagus, pulmonary and kidney involvement

	Overall	Heart involvement N/mean P value	Esophagus involvement N/mean P value	Pulmonary involvement N/mean P value	Kidney involvement N/mean P value
Esophageal transit scintigraphy, N (%)	16 (55.17)	14 0.001*	16 <0.001*	15 0.879	12 0.017*
Creatinine clearance	90.69±37.92	79.82 0.014*	81.21 0.092	92.23 0.524	73.34 0.004*
Parenchymal thickness, N (%)	14 (48.28%)	12 0.011*	10 0.089	12 0.08	14 <0.001*
DLCO	60.32±16.84	63.32 0.438	61.92 0.846	58.32 0.010	62.12 0.948
FVC	87.24±16.22	87.94 0.912	89.75 0.308	85.51 0.030	86.43 0.650
PASP	24.14±8.81	26.16 0.173	25.25 0.812	23.89 0.399	25.31 0.503
TAPSE	22.21±2.18	21.44 0.012*	21.69 0.156	22.15 0.596	21.69 0.156
LVEF	53.97±7.72	50.27 0.001*	52.19 0.232	54.26 0.650	50.31 0.009*
Diastolic dysfunction, N (%)	16 (55.17%)	15 <0.001*	13 0.002*	14 0.114	12 0.017*

DLCO-diffusing capacity of the lungs for carbon monoxide; FVC-Forced vital capacity; PASP- Pulmonary arterial systolic pressure; LVEF- left ventricular ejection fraction; *p<0.05

DISCUSSION

In our study, 86.21% were predominantly female and the mean age of the patients was 56.93 years. Gender representation coincides with other studies, where it was 84% and 90%, respectively, and the mean age was 65 years, respectively 59 years [10-12]. Also, in a study where patients were divided into age groups, there were most patients in the 55-69 age group, which coincides with our results [13]. RP had 93.1%. It occurs in a large percentage in other researches, even up to 100% [13,14]. DU occurred in 44.8%, and arthritis in 20.7%. Both clinical manifestations occurred in a higher percentage among other researchers, 65.8-81.1% and 46.2-73.7% respectively [14,15]. The mean mRSS was 21.41, and in other studies the values were slightly lower, 17 respectively 9.9 [12,16]. Anti Scl70 occurred in 48.3% and ACA in 41.4%. The frequency of occurrence of antibodies is different in different researches [12,14,15].

The mean age of the patients was the highest in renal involvement 59.18 years, but without a statistically significant difference p= 0.17. The same age difference was obtained by a group of researchers where this difference was statistically significant [17]. Namely, with age, there is a decrease in perfusion and a decline in renal function, and the process itself is accelerated by the existence of this disease [18]. With the duration of the disease, the occurrence of esophageal, cardiac and renal involvement was statistically significant, p=0.017; p=0.014; p=0.032. The correlation between disease duration and organic manifestations was supported by another study [17]. There was no significant difference

in the occurrence of RP between organ systems. The appearance of DU was significantly correlated with esophageal and cardiac involvement, p=0.034 and p=0.01. A study by Khimdas et al also indicated an association between DU and esophageal involvement [19]. There were no difference in the value of mRSS between organ systems. Also, studies shown an association between mRSS and pulmonary involvement, which is not the case in our sample [20]. A possible reason is the significantly higher average mRSS compared to the other study (21.41 vs 9.9), as well as the high percentage of pulmonary involvement in our sample (93.1% vs 44.4%) [17]. In our sample, the occurrence of ACA in pulmonary and cardiac involvement was statistically significant. In other studies, there was no statistically significant difference [17].

Slowed esophageal transit is statistically significant, in expected esophageal involvement, and even with cardiac and renal involvement. Renal involvement was also associated with cardiac involvement. Also, a statistically significant association between LVEF and diastolic dysfunction and renal involvement was demonstrated. The simultaneous involvement of these two systems was also shown in a study where the simultaneous involvement was up to 52% and affects the higher mortality of these patients. The reason for the simultaneous occurrence is the presence of the same process of inflammation and fibrosis in all tissues, and prerenal kidney injury contributes to the progression of the disease [21].

CONCLUSION

Our sample shows a correlation between the duration of the disease and organic involvement, as well as DU with cardiac and esophageal involvement. The connection between the cardiac and renal systems affects the overall course of the disease and the higher mortality of patients. Therefore, with early detection, an adequate management can be accessed on time in order to prevent further complications in the disease course.

REFERENCES:

1. Denton CP, Khanna D. Systemic sclerosis. Lancet. 2017; 390:1685-99.
2. Clements PJ, Hurwitz EL, Wong WK, Seibold JR, Mayes M, White B et al. Skin thickness score as a predictor and correlate of outcome in systemic sclerosis. Arthritis Rheum. 2000; 43: 2445-54.
3. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Murray B, Tyndall A et al. Cassification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013; 72:1747–55.
4. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. Journal of Scleroderma and Related Disorders. 2017; 2(1):11-8.
5. Siraj QH, Buscombe JR, Kaye SA, Agnew JE, Black CM, Hilson AJW. Esophageal Scintigraphy in Systemic Sclerosis: A Simplified Imaging and Reporting Method. J Nucl Med Technol. 1996; 24:316-20.
6. Guazzi M, Bandera F, Pelissero G, Castelvecchio S, Menicanti L, Ghio S et al. Tricuspid Annular Plane Systolic Excursion and Pulmonary Arterial Systolic Pressure Relationship in Heart Failure: An Index of Right Ventricular Contractile Function and Prognosis. Am J Physiol Heart Circulatory Physiol. 2013. 305:1373–81.
7. Quanjer PH, Tammeling GJ, Cotes JE, Pederson OF, Peslin R, Yernault JC. Lung Volumes and Forced Ventilatory Flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl. 1993; 16:5–40.
8. Wang X, Vrtiska TJ, Avula RT, Walters LR, Chakkera HA, Kremers WK et al. Age, kidney function, and risk factors associate differently with cortical and medullary volumes of the kidney. Kidney Int. 2014; 85:677–85.
9. Takata T, Koda M, Sugihara T, Sugihara S, Okamoto T, Miyoshi K et al. Left renal cortical thickness measured by ultrasound can predict early progression of chronic kidney disease. Nephron. 2016; 132:25–32.
10. Westerling H, Bairkdar M, Gunnarsson K, Moshtaghi-Svensson J, Sysojev AO, Hesselstrand R et al. Incidence and prevalence of systemic sclerosis in Sweden, 2004–2015, a register-based study. Seminars in Arthritis and Rheumatism. 2022; 53:151978
11. Coi A, Barsotti S, Santoro M, Almerigogna F, Bargagli E, Caproni M et al. Epidemiology of systemic sclerosis: a multi-database population-based study in Tuscany (Italy). Orphanet J Rare Dis. 2021; 16: 90.
12. Ferreira Morales J, Guitierrez Tamayo AM, de Olaya EB, Rodriguez Padilla LM, Velasquez-Franco CJ, Mesa Navas MA. Úlceras digitales en esclerosis sistémica. Rev Colomb Reumatol. 2020;27:2–9.
13. Royle JG, Lanyon PC, Grainge MJ, Abhishek A, Pearce FA. The incidence, prevalence, and survival of systemic sclerosis in the UK Clinical Practice Research Datalink. Clin Rheumatol. 2018; 37:2103–11.
14. Asif S, Khan A, Faiq M, Din ZU, Zahoor S, Haroon M. Clinical and serological characteristics of systemic sclerosis: Experience of a tertiary care center in Pakistan. Arch Rheumatol 2021; 36(4):587-94
15. Janga HJ, Woob A, Kimb SY, Yongb SH, Parkb Y, Chungb K et al. Characteristics and risk factors of mortality in patients with systemic sclerosis-associated interstitial lung disease. ANNALS OF MEDICINE. 2023; 55 (1):663–71.
16. Matsuda KM, Yoshizaki A, Kuzumi A, Fukasawa T, Ebata S, Miura S et al. Skin thickness score as a surrogate marker of organ involvements in systemic sclerosis: a retrospective observational study. Arthritis Res Ther. 2019; 21: 129.
17. Cozzani E, Muracchioli A, Murdaca G, Beccali M, Caprioli S, Zentilin P et al. Correlation Between Skin

and Affected Organs in 52 Sclerodermic Patients Followed in a Diseases Management Team: Development of a Risk Prediction Model of Organ-Specific Complications. Front. Immunol. 2021; 12:588753.
18. Weinstein JR, Anderson S. The Aging Kidney: Physiological Changes. Adv Chronic Kidney Dis. 2010; 17:302–7
19. Khimdas S, Harding S, Bonner A, Zummer B, Baron M, Pope J, Canadian scleroderma research gropu. Association with digital ulcers in a large cohort of systemic sclerosis: Results from the canadian scleroderma research group registry. Arthritis Care & Research. 2011;63(1):142-149
20. Scheja A, Bartosik I, Wuttge DM, Hesselstrand R. Renal function is mostly preserved in patients with systemic sclerosis. Scand J Rheumatol. 2009; 38:295–8