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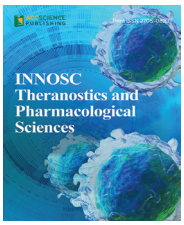

RESEARCH ARTICLE

Cardiovascular Evaluation in Patients with Systemic Sclerosis in the Turkish Population

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Abstract:

Cardiac involvement in systemic sclerosis (SSc) can lead to high morbidity and mortality. Therefore, early diagnosis and treatment are required. The aim of this study was to investigate the clinical, laboratory, and echocardiographic features of SSc, evaluate the proportion of patients with cardiovascular disease, and compare them with other population-based studies in the Turkish population. This study included 150 patients who were previously diagnosed and treated in the rheumatology clinic. Their age, sex, clinical signs and symptoms, laboratory and echocardiography findings, and concomitant diseases were evaluated. The results showed that the disease duration was <1 year and, at most, 11 years, with only one patient having elevated pulmonary artery pressure. In addition, patients with SSc in our region had similar demographic, clinical, laboratory, and echocardiographic features with those in other countries. This study demonstrated that hypertension is positively correlated with disease duration and the incidence of pulmonary hypertension is very low in patients with SSc.

Keywords: Systemic sclerosis, Cardiovascular disease, Scleroderma, Pulmonary hypertension, Hypertension

1. Introduction

Systemic sclerosis (SSc) is a chronic multisystemic autoimmune inflammatory disease characterized by fibrosis, vasculopathy, and extracellular matrix synthesis and accumulation in the skin and internal organs. Among its clinical manifestations, skin hardening and thickening are the most crucial determinants of skin fibrosis. This chronic multisystemic disease is characterized by changes in the skin, circulatory system, synovium, and musculoskeletal system due to connective tissue accumulation and fibrosis in the internal organs, especially the gastrointestinal system, heart, lungs, and kidneys [1]. SSc is generally seen in women between ages 30 and 55. Although it is accompanied by severe complications, it has a low incidence.

The exact prevalence of SSc in Turkey is unknown. In view of regional differences across the world, it is essential to evaluate patients with SSc in different regions. Differences in incidence are due to the diversity of genetic and ethnic composition, climatic conditions, and environmental exposures [2].

The presentation of SSc is complex and varies to a certain extent. Therefore, the classification criteria for SSc, published by the American College of Rheumatology (ACR) in 1980, have rendered a more straightforward approach to the diagnosis and treatment of the disease [3,4]. By focusing

on different clinical features as initial symptoms in its diagnosis, such as the presence of Raynaud phenomenon, the nail bed capillary pattern, proximal or distal cutaneous changes, and the presence of autoantibodies [5], SSc can be divided into two types: SSc with limited skin involvement and diffuse skin involvement. By referring to the European League Against Rheumatism (EULAR) records, Minier *et al*. stated that puffy fingers are the main findings in the initial assessment of SSc [6].

Hypertension (HT), diabetes mellitus (DM), and renal diseases are the major systemic vascular diseases in which differences can be observed in the disease progression, presentation, and prognosis. The previous studies have shown that the development of HT can be predicted in patients over 45 with high inflammatory markers and skin involvement [7]. HT causes vascular changes similar to those observed in SSc [8]. Perivascular inflammatory infiltrates, impaired angiogenesis, and endothelial apoptosis are all observed in the early stages of the disease. Data from animal models have shown that prolonged, uncontrolled overexpression of vascular endothelial growth factor may have paradoxical effects on the formation of new vessels, leading to capillary changes similar to those observed in SSc. In addition to impaired angiogenesis, defective vasculogenesis may contribute to the vascular symptoms in SSc [9]. Cardiovascular diseases are frequently observed in patients with rheumatoid joint diseases and individuals with SSc [10].

Although the relationship between SSc and pulmonary arterial hypertension (PAH) is known, idiopathic PAH and PAH associated with SSc (SSc-PAH) are histologically different [11]. SSc-PAH is the most common form of PAH associated with connective tissue disease. SSc-PAH is essential to all cases of PAH [12]. Approximately 12%–15% of patients with SSc are estimated to have a lifetime risk of developing PAH. Despite treatment with pulmonary vasodilators, patients with SSc-PAH have a high mortality rate [13].

Although the etiopathogenesis of scleroderma-like conditions in DM is associated with non-enzymatic glycation of collagen, it has not been established. High blood glucose levels can stimulate the proliferation of fibroblasts and the production of other extracellular matrix components, causing skin hardening. Scleroderma-like syndrome, especially diabetic sclerodactyly as the most common skin manifestation of type 1 DM, strongly correlates with the duration of the disease. In many cases, it may be challenging to distinguish the histopathological changes in diabetic scleroderma-like syndrome from those in the course of SSc [14].

Cardiac involvement in SSc may lead to high morbidity and mortality. Therefore, early diagnosis and treatment are required. For instance, the 10-year mortality of patients with cardiac involvement in SSc is around 20%. Both primary and secondary cardiac involvement may be present in SSc. While primary involvement occurs due to the direct effect of inflammation on cardiac tissue, secondary involvement is secondary to pulmonary hypertension.

SSc may cause myocardial fibrosis and right and left ventricular systolic and diastolic dysfunction, as well as pericardial and endocardial damages. Echocardiography is a contributory non-invasive test used to evaluate cardiac involvement. Through echocardiography, the left and right ventricular functions can be assessed, and pulmonary hypertension can be detected with high sensitivity [15].

In this study, we aimed to investigate the clinical, laboratory, and echocardiographic features of SSc patients in our center, evaluate the proportion of patients with cardiovascular disease ratio, and compare them with other population-based studies in the Turkish population.

2. Methods

2.1. Study participants

In this study, 150 patients who were previously diagnosed and treated in the rheumatology clinic were included in the study. Their age, sex, clinical signs and symptoms, laboratory and echocardiography findings, and concomitant diseases were evaluated. The determinants of the study were signs of excessive fibrosis (skin lesion and pulmonary fibrosis), vasculopathy (hypertension and proteinuria), and inflammation (arthritis and elevated C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], or rheumatoid factor [RF]). This study was approved by the Local Ethics Committee.

2.2. Observations

The diagnosis of SSc was based on the SSc criteria by EULAR and ACR [17]. Raynaud's phenomenon was defined clinically discoloration of the skin of the fingers in response to exposure to cold or emotional stress) and through nailfold videocapillaroscopy.

In echocardiography, the left and right ventricular dimensions and functions, wall thickness, systolic pulmonary artery pressure, and tricuspid gradient were evaluated. PAH was confirmed by the right heart catheterization with pulmonary artery pressure >40 mmHg.

Skin lesion was defined as any observation of focal swelling, stiffness, or atrophy, regardless of location. Arthritis was considered as swelling and tenderness in one or more joints. Chest radiography or computed tomography (CT) was used to evaluate the presence of pulmonary fibrosis. Local standards and the European Society of Cardiology (ESC) guidelines were used to diagnose and treat arterial hypertension. In cases of dysphagia accompanied by changes in gastroscopy or barium swallow, gastrointestinal involvement was considered. Proteinuria was detected in 24-h urine samples by microelectrophoresis, and spot urine was examined for cylindruria. Standard measurement methods were used for CRP (>10 mg/L) and RF (>14 IU/mL), and an ESR of 25 mm/h was determined as the limit value. Anemia was considered when hemoglobin (Hgb) levels were < 13 g/dL and 12 g/dL in men and women, respectively. Low-density lipoprotein of more than 160 mg/dL was accepted as the limit value for the diagnosis of hyperlipidemia.

We also evaluated the patient's history for coronary artery disease and antidiabetic and antihypertensive treatment.

2.3. Statistical analysis

The data obtained were evaluated using SPSS 22.0. Mean values and frequencies were used for statistical analysis. In general, descriptive statistics were used. Statistical significance was accepted as $P < 0.05$.

3. Results and Discussion

In our study, the mean age of the patients was 47.75, with the youngest being 19, and the oldest 78. The disease duration was <1 year and, at most, 11 years; the mean disease duration was 5.41 years. Hypertension was detected in 34.7% of patients (**Table 1**). RF values were low in 52.7% and high in 47.3% of patients (**Table 2**). We found the mean ejection fraction (EF) to be 60.21% through echocardiographic evaluation and the systolic pulmonary artery pressure to be 31 mmHg (**Table 3**). Hypertension was found to be positively correlated with disease duration ($r = 0.278$; $P = 0.001$) (**Table 4**).

The mean age of the patients in our study was similar to other community-based studies [5]. In addition, the proportion of female patients in our study at 87.3% was similar to EULAR records at 87.8%. The frequency of SSc-associated pulmonary hypertension in our study was 6%, whereas that in the previous prospective study was between 7.8% and 12% [16]. The proportion of patients with EF < 55% was 3.4% in our study and 5.4% in the EULAR-based study [17]. Comparing with the mean pulmonary artery pressure (31 mmHg) observed in our study, the mean pulmonary artery pressure in a similar study was observed to be 33.3 mmHg [18]. In the same study [18], the left ventricle end diastolic diameter, interventricular septum, posterior wall thickness, and EF values were similar with those observed in our study.

Table 1. Assessment in systemic sclerosis

Disease	Negative	Positive
Hypertension	98 (65.3%)	52 (34.7%)
Diabetes mellitus	142 (94.7%)	8 (5.3%)
Coronary artery disease	124 (82.7%)	26 (17.3%)
Hyperlipidemia	132 (88%)	18 (12%)
Anemia	124 (82.7%)	26 (17.3%)
Proteinuria	106 (70.7%)	44 (29.3%)
Cylindruria	139 (92.7%)	11 (7.3%)
Pulmonary hypertension	149 (99.3%)	1 (0.7%)

Table 2. Inflammatory markers in systemic sclerosis

Markers	Negative	Positive
CRP	141 (94%)	9 (6%)
ESR	116 (77.3%)	34 (22.7%)
RF	79 (52.7%)	71 (47.3%)

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; RF: Rheumatoid factor

Table 3. Evaluation results in systemic sclerosis

Parameters	Number	Minimum	Maximum	Mean	Standard deviation
Age	150	19	78	47.75	13.337
Disease duration (years)	150	0	11	5.41	2.774
Ejection fraction (%)	150	35	72	60.21	4.912
Left ventricular end-diastolic diameter (mm)	150	34	57	42.87	3.764
Right ventricle diameter (mm)	150	2	40	20.92	3.220
Pulmonary artery pressure (mmHg)	150	17	111	31.07	11.816
Tricuspic regurgitation velocity (m/sn)	150	12	96	25.82	10.647

Table 4. Relationship between hypertension and duration of systemic sclerosis

Variables	Hypertension	Disease duration
Hypertension		
Correlation	1	0.278**
Sig. (2-tailed)		0.001
Number	150	150
Disease duration		
Correlation	0.278**	1
Sig. (2-tailed)	0.001	
Number	150	150

Statistical significance at $p<0.05$

Similar to our study, the decrease in myocardial contractility was lower than predicted in many studies, which is contentious given the presence of myocardial depression in SSc [19-21].

In most of our patients, the ESR and CRP levels were low. A study has reported that high ESR values are strongly associated with pulmonary hypertension in such patients [22]. High CRP levels were observed in 6% of our patients, whereas one-fourth of patients in a study of inflammatory indicators had high CRP levels [23]. In another study, high CRP levels were observed in 48% of patients, rising to 80% in patients with finger ulcers [24]. Low ESR and CRP levels were attributed to the disease activities. Compared with a regional study in Central Ukraine [5], anemia and CRP results were lower, while ESR was higher; however, cylindruria and proteinuria values were similar.

Hyperlipidemia was observed in 12% of patients who participated in our study. Similar to the previous studies, we found that impaired lipid profile is associated with increased macrovascular diseases in patients with SSc [25,26].

Unlike previous studies [14], we could not detect a significant relationship between DM and SSc. This can be explained by the low number of DM patients and the short duration of DM.

HT was observed in 34.7% of patients who participated in our study. We found a significant relationship between age and HT in SSc. In addition, there was also a significant correlation between HT and disease duration. HT at the onset of SSc was found to be associated with skin lesion, arthritis, pulmonary fibrosis, abnormal platelet and ESR levels, and a higher incidence of cylindruria. Moreover, the incidence of gastrointestinal complications was observed to be higher in hypertensive patients. The absence of HT was associated with a higher incidence of anemia. In hypertensive patients, the mean pulmonary artery pressure was slightly higher, and the mean glomerular filtration rate was significantly lower; these results were similar with those observed in the Central Ukraine population [5].

The limitations of our study were the small geographical area constituting the patients included in our study, the omission of evaluating the age of onset of SSc and the initial symptoms, and the inability to perform diastolic evaluation on all patients.

4. Conclusions

As seen in our study, patients with SSc in our region had similar demographic, clinical, laboratory, and echocardiographic features with those in other countries. The results are comparable with those in the UK registry, Pittsburg Scleroderma Databank, PHAROS registry, CRRG registry, and Brazilian registry (GEPRO). Our study was based on the fact that there may be regional differences especially

in scleroderma patients. The study provides an overview of cardiovascular disease risk factors in scleroderma patients in the Turkish population. Our study is a pioneer for more complex studies to be done in the scleroderma patient group.

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None.

Conflict of interest

The authors declare no conflicts of interests.

Author contribution

Conceptualization: Suleyman Serdar Koca
Formal analysis: Mehdi Karasu
Investigation: Mehdi Karasu, Ozkan Karaca
Writing – original draft: Tarik Kivrak
Writing – review & editing: Tarik Kivrak

Ethics approval and consent to participate

This study was approved by the Local Ethics Committee (218714).

Consent for publication

Consent for publication was obtained from all the participants.

Availability of data

The data can be obtained following request from the corresponding author.

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