Disease characteristics of systemic sclerosis among Egyptian patients

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Introduction
Scleroderma, or systemic sclerosis (SSc), is a chronic connective tissue disease that has been classified as one of the autoimmune rheumatic diseases. The usual hallmarks of SSc are autoimmunity, inflammation, widespread small-vessel vasculopathy affecting multiple vascular beds, and progressive interstitial and vascular fibrosis in the skin and internal organs.
Aim of the work
The aim of the study was to determine the disease characteristics and frequency of different clinical manifestations among Egyptian patients.
Patients and methods
Seventy-five patients with SSc, all fulfilling the criteria of the American College of Rheumatology for classification of scleroderma, were selected for this study. They were being followed up in Cairo University Internal Medicine department. The patients' data were collected by a review of their medical records. We compared the frequency of symptoms in scleroderma patients with both diffuse cutaneous and limited cutaneous sclerosis (dcSSc and lcSSc).
Results
Fourteen patients out of 75 (18.7%) had dcSSc and 61/75 (81.3%) had lcSSc. We found that within the limited subtype 11/61 (18%) were male and 50/61 (82%) were female, with a male to female ratio of 1: 4.6. Within the diffuse subtype, 3/14 (21.4%) were male and 11/14 (78.6%) were female, with a male to female ratio of 1: 3.7. Raynaud's phenomenon was the first presenting manifestation (in 77.3%), followed by arthritis (in 12%) and skin tightness (in 9.3%).
Conclusion
SSc is more common in the female population than in the male population. lcSSc is more common than dcSSc.

Keywords:
diffuse cutaneous systemic sclerosis, limited cutaneous systemic sclerosis, systemic sclerosis

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Introduction

Scleroderma (from the Greek words '*skleros*', meaning hardness, and '*derma*', meaning skin; literally meaning hard skin) is a chronic multisystem autoimmune disease that is highly heterogeneous and has multiple overlapping and poorly defined clinical subsets [1].

The usual hallmarks of systemic sclerosis (SSc) are autoimmunity, inflammation, widespread small-vessel vasculopathy affecting multiple vascular beds, and progressive interstitial and vascular fibrosis in the skin as well as in internal organs, with lungs, heart, gastrointestinal tract, and kidneys being the main targets [2].

The disease has a female predilection with a female to male ratio of 3 : 1 and typically occurs in the third to fifth decades of life [3].

The group of diseases called scleroderma falls into two main classes: localized scleroderma and SSc. Both groups are further divided into diffuse cutaneous systemic sclerosis (dcSSc) and limited cutaneous systemic sclerosis (lcSSc) [4].

The clinical expression, severity, and progression are rather heterogeneous; the disease may progress very slowly with no or mild visceral injury, and sometimes it dramatically evolves with early severe organ damage [5].

The relative rarity and clinical heterogeneity of SSc have made formal epidemiological studies difficult. The estimated prevalence from population-based studies is between one and two per 10 000 population, with a higher estimated prevalence in North America. Reliable estimates of incidence are also elusive, but one in 100 000 per year is considered reasonably accurate. There appear to be two peaks of disease onset — the early 30s and the mid 50s — and, in common with most other autoimmune diseases, there is a female predominance [6].

These discrepancies may reflect true variation in disease occurrence among different populations or may be related to methodologic differences, such as the degree of scrutiny applied or the classification of disease.

The aim of this work was to determine the disease characteristics and the frequency of different clinical manifestations among Egyptian patients with SSc who presented to Kasr El Aini hospital.

Patients and methods

Seventy-five patients with SSc, all fulfilling the criteria of the American College of Rheumatology for classification of scleroderma (formerly, the American Rheumatism Association, ARA, 1980), were selected for the study [7]. They were being followed up in Cairo University Internal Medicine department. The patients' data were collected by medical record review.

Inclusion criteria

Patients were classified as having dcSSc or lcSSc as follows [4].

Diffuse cutaneous systemic sclerosis

Onset of Raynaud's within 1 year of onset of skin changes.

Truncal and acral skin involvement.

Presence of tendon friction rubs.

Early and significant incidence of interstitial lung disease (ILD), oliguric renal failure, diffuse gastrointestinal disease, and myocardial involvement.

Limited cutaneous systemic sclerosis

History of Raynaud's phenomenon for years (occasionally decades) before the onset of skin involvement.

Skin involvement limited to hands, face, feet, and forearms (acral).

A significant late incidence of pulmonary hypertension, with or without ILD, trigeminal neuralgia, skin calcifications, or telangiectasias.

Exclusion criteria

Cases of localized scleroderma (morphea and linear disease) were excluded from the study population.

Results

Out of the studied 75 patients, 14 (18.7%) were male and 61 (81.3%) were female, with a male to female ratio of 1: 4.3. The demographic data of all patients and the frequency of their initial presenting manifestations are shown in Tables 1 and 2.

Fourteen of 75 (18.7%) patients had dcSSc and 61/75 (81.3%) had lcSSc.

We found that within the limited subtype 11/61 (18%) were male and 50/61 (82%) were female, with a male to female ratio of 1: 4.6. Within the diffuse subtype, 3/14 (21.4%) were male and 11/14 (78.6%) were female, with a male to female ratio of 1: 3.7. The female population was found to be significantly more commonly affected as compared with the male population in both disease subsets ($P = 0.001$ in lcSSc and 0.007 in dcSSc).

No significant difference was observed between the limited and diffuse subtypes as regards demographic data. Also the comparison between male and female patients within each subset showed no significant difference apart from age, wherein within the diffuse subtype female patients were significantly older than male patients ($P = 0.034$), as shown in Table 3.

Table 1 Demographic data of all patients included in our study

Demographic features	Range	Mean	SD
Age (years)	17–70	36.17	13.9
Age at disease onset (years)	9–67	29.83	13.1
Disease duration (years)	0.3–20	6.35	4.7

Table 2 First presenting manifestations and their frequencies

Disease manifestation	No of patients ($N = 75$) (%)
Raynaud's phenomenon	58 (77.3)
Arthritis	9 (12)
Skin tightness	7 (9.3)
Muscle weakness	1 (1.3)

Table 3 Differences between male and female patients within each disease subset as regards their age, age at disease onset, and disease duration

Demographic features	dcSSc ($N = 14$)			lcSSc ($N = 61$)		
	Male	Female	*P*-value	Male	Female	*P*-value
Age in years (mean ± SD)	26.7 ± 2.3	46.6 ± 13.9	0.034	32.3 ± 15	35.3 ± 13	0.500
Age at disease onset (mean ± SD)	25.5 ± 0	37.5 ± 15.1	0.301	26.9 ± 15.5	29.1 ± 12	0.612
Disease duration in years (mean ± SD)	1.8 ± 1.3	9.1 ± 6.1	0.066	5.4 ± 4.3	6.2 ± 4.3	0.548

dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis.

Comparing the diffuse and limited subtypes as regards their initial presenting manifestations, a highly significant difference was found in the incidence of skin tightness between the two groups, being more common in the diffuse than in the limited subtype (P = 0.001). However, no significant difference could be found in other manifestations (Table 4).

Raynaud's phenomenon was the first presenting manifestation in 11/14 (78.6%) male patients, being the most common first disease manifestation in male patients, followed by arthritis in 2/14 patients (14.3%) and skin tightness in 1/14 patients (7.1%). The same order was seen in female patients, wherein Raynaud's phenomenon was the first disease manifestation in 47/61 patients (77%), followed by arthritis in 7/61 patients (11.5%) and skin tightness in 6/61 patients (9.8%). One female patient had myositis as her first disease manifestation (1.6%). No statistically significant difference was found between male and female patients regarding the first presenting manifestation (Table 5).

The frequencies of organ involvement among patients during the disease course are shown in Table 6. ILD, secondary pulmonary hypertension, proteinuria, and intestinal dysmotility were found to be significantly more common among patients with dcSSc than among patients with lcSSc (Table 6).

Manifestations of organ involvement occurred with varied frequencies between male and female patients, but this difference was not statistically significant (Table 7).

Table 4 Comparison between limited and diffuse groups as regards the frequency of the first presenting symptom

Presenting manifestation	Limited (N = 61) [n (%)]	Diffuse (N = 14) [n (%)]	P-value	Significance
Raynaud's phenomenon	49 (80.3)	9 (64.3)	0.347	NS
Arthritis	9 (14.8)	0 (0)	0.281	NS
Skin tightness	2 (3.3)	5 (35.7)	0.001	HS
Muscle weakness	1 (1.6)	0 (0)	0.418	NS

HS, highly significant; NS, nonsignificant.

Table 5 Comparison between male and female patients as regards the frequency of the first presenting symptom

Presenting symptom	Males (N = 14) [n (%)]	Females (N = 61) [n (%)]	P-value	Significance
Raynaud's	11 (78.6)	47 (77)	0.817	NS
Arthritis	2 (14.3)	7 (11.5)	0.869	NS
Skin tightness	1 (7.1)	6 (9.8)	0.843	NS
Myositis	0 (0)	1 (1.6)	0.418	NS

NS, nonsignificant.

Discussion

SSc is a connective tissue disease characterized by excessive collagen deposition in the dermis and internal organs, and by vascular hyper-reactivity and obliterative microvascular phenomena. SSc is responsible for diminished life expectancy, which is related to the extent of skin and visceral involvement, and is also responsible for tendon, joint, and vessel damage, leading to disability, handicap, and impaired health-related quality of life [8].

The lcSSc/dcSSc classification has been widely accepted and used in numerous clinical studies and therapeutic trials. It was shown that the extent of skin

Table 6 Comparison between limited and diffuse subtypes as regards the frequency of organ involvement

Disease manifestations	n (%)			P-value	Significance
	Total (N = 75)	Limited(N = 61)	Diffuse(N = 14)		
Skin tightness	75 (100)	61 (100)	14 (100)	—	—
Hypopigmentation	17 (22.7)	12 (19.7)	5 (35.7)	0.196	NS
Raynaud's	73 (97.3)	59 (96.7)	14 (100)	0.492	NS
Digital ischemia	56 (74.6)	45 (73.8)	11 (78.6)	0.974	NS
Myositis	15 (20)	11 (18)	4 (28.6)	0.374	NS
Arthritis	30 (40)	27 (44.3)	3 (21.4)	0.116	NS
Dysphagia	51 (68)	40 (65.6)	11 (78.6)	0.347	NS
Dysmotility	8 (10.7)	4 (6.6)	4 (28.6)	0.016	S
Esophageal reflux	29 (38.7)	22 (36.1)	7 (50)	0.344	NS
ILD	40 (53.3)	29 (47.5)	11 (78.6)	0.042	S
Pulmonary HTN	11 (14.7)	6 (9.8)	5 (35.7)	0.014	S
Primary	2 (2.6)	2 (3.3)	0 (0)	0.815	NS
Secondary	9 (12)	4 (6.6)	5 (35.7)	0.009	S
Pericardial eff.	4 (5.3)	2 (3.3)	2 (14.3)	0.098	NS
Proteinuria	5 (6.7)	2 (3.3)	3 (21.4)	0.042	S
Hypertension	6 (8)	4 (6.6)	2 (14.3)	0.310	NS

eff., effusion; HTN, hypertension; ILD, interstitial lung disease; NS, nonsignificant; S, significant.

Table 7 Comparison between male and female patients as regards the frequency of organ involvement

Disease manifestations	*n* (%)			*P*-value	Significance
	Total	Males (*N* = 14)	Females (*N* = 61)		
Skin tightness	75 (100)	14 (100)	61 (100)	—	—
Hypopigmentation	17 (22.7)	3 (21.4)	14 (23)	0.902	NS
Raynaud's	73 (97.3)	13 (92.9)	60 (98.4)	0.249	NS
Digital ischemia	56 (74.6)	11 (78.6)	45 (73.8)	0.974	NS
Myositis	15 (20)	3 (21.4)	12 (19.7)	0.882	NS
Arthritis	30 (40)	4 (28.6)	26 (42.6)	0.717	NS
Dysphagia	51 (68)	7 (50)	44 (72.1)	0.109	NS
Dysmotility	8 (10.7)	0 (0)	8 (13.1)	0.152	NS
Esophageal reflux	29 (38.7)	3 (21.4)	26 (42.6)	0.142	NS
ILD	40 (53.3)	6 (42.9)	34 (55.7)	0.565	NS
Pulmonary HTN	11 (14.7)	0 (0)	11 (18)	0.085	NS
Primary	2 (2.6)	0 (0)	2 (3.3)	0.815	NS
Secondary	9 (12)	0 (0)	9 (14.7)	0.281	NS
Pericardial eff.	4 (5.3)	0 (0)	4 (6.6)	0.325	NS
Proteinuria	5 (6.7)	0 (0)	5 (8.2)	0.298	NS
Hypertension	6 (8)	0 (0)	6 (9.8)	0.354	NS

eff., effusion; HTN, hypertension; ILD, interstitial lung disease; NS, nonsignificant.

involvement, as measured by longitudinal skin scoring according to Rodnan, regressed in dcSSc with time, although internal organ involvement progressed. Life expectancy has also been confirmed to be shorter in the diffuse form in several studies, in particular in women [9].

The aim of this work was to determine the prevalence and disease characteristics of systemic sclerosis among Egyptian patients who presented at Kasr El Aini hospitals.

Our study included 75 patients with SSc: 14 (18.7%) of them were male and 61 (81.3%) were female, with male to female ratio of 1: 4.3. This finding agrees with the results of Tager and Tikly [10] who found that SSc is more frequent in the female population, with a male to female ratio of 1: 4.6. Also, Pagalavan and Ong [11], who conducted a study in a Malaysian rheumatology center in 2007 and included Malays, Chinese, and Indian patients, found that SSc was — three to four times more common in women.

Compared with our results, a lower male to female ratio was reported in other studies, as in the study by Steen *et al.* [12], which included SSc patients in Allegheny County, Pennsylvania, and found that the male to female ratio was 1: 3. In addition, Englert *et al.* [13] studied 715 cases with SSc and found that the male to female ratio was 1: 2.3. Other studies on SSc patients found a female predominance but with a higher male to female ratio compared with our results, like the study by Kaliterna *et al.* [14], who found a male to female ratio of 1: 5.2. Alamanos *et al.* [15] found that, in Greece, SSc was more common in the female population with a male to female ratio of 1: 8.9. Walker *et al.* [16] found that the male to female ratio was 1: 6.7, and Lo Monaco *et al.* [17] conducted an epidemiological study on patients with SSc in northern Italy and found that the disease was more common in the female population but with a male to female ratio of 1: 9.7.

With regard to the frequency of disease subsets, 61 patients (81.3%) had limited scleroderma and the other 14 patients (18.7%) had diffuse scleroderma with a diffuse to limited ratio of 1: 4.3.

This finding is commensurate with many studies that reported that lcSSc is more common than dcSSc, but these studies reported a lower ratio between diffuse and limited subtypes: Alamanos *et al.* [15] reported a diffuse to limited ratio of 1: 3, Pagalavan and Ong. [11] found a diffuse to limited ratio of 1: 1.9, Walker *et al.* [16] conducted a study on 3656 patients with SSc from 30 different countries and found that the dcSSc to lcSSc ratio was 1: 1.6. Hunzelmann *et al.* [18] reported a diffuse to limited ratio of 1: 1.4, and Lo Monaco *et al.* [17] reported a diffuse to limited ratio of 1: 3.3. In contrast, Tager and Tikly [10] found that the diffuse SSc subset was more frequent than the limited subset. They reported a diffuse to limited ratio of 2.3: 1. The difference from our results may be related to racial factors, as they conducted their study on South African patients. Among Africans the majority of patients have dcSSc.

With regard to the proportion of male and female patients within disease subsets, we found that female patients were significantly more common than male patients within the lcSSc subtype ($P = 0.001$) and the dcSSc subtype ($P = 0.007$), wherein we observed that

within the limited subtype 11/61 (18%) were male and 50/61 (82%) were female, with a male to female ratio of 1: 4.6. Within the diffuse subtype, 3/14 (21.4%) were male and 11/14 (78.6%) were female, with a male to female ratio of 1: 3.7. Female patients were also found to be more common than male patients in both lcSSc and dcSSc by Hunzelmann *et al.* [18]. They found that the male to female ratio was 1: 3.2 in dcSSc and 1: 7.2 in lcSSc; however, Nguyen *et al.* [8] found that dcSSc was more frequent in male patients. This higher frequency of the dcSSc subset in the male population in the study by Nguyen and colleagues may be attributed to the fewer number of male patients included in our study (n = 14) compared with the other study (n = 62).

Studying the initial presenting manifestation, the most common first manifestation among our patients was found to be Raynaud's phenomenon in 58/75 (77.3%) patients. It was the first disease manifestation in 49/61 (80.3%) patients in the limited group and in 9/14 (64.3%) patients in the diffuse group.

This result is similar to those of Pagalavan and Ong [11] in whose study Raynaud's phenomenon was reported to be the most common initial complaint in ~70% of patients.

Tamaki *et al.* [19] conducted a study on 357 patients with SSc, and found that Raynaud's phenomenon was the initial symptom in 59% of patients. This frequency difference from our study can be explained by racial difference, higher number of patients (357 in the study by Tamaki and colleagues), and the fact that 75% of patients included in the study by Tamaki and colleagues had dcSSc.

Arthritis occurred in 30/75 (40%) patients in our study. Other studies reported higher frequencies of articular affection — for example, in the study by Pagalavan and Ong [11] arthralgia/arthritis was observed in 49.2% of patients and in the study by Tager and Tikly [10] arthralgia/arthritis was observed in 68% of the patients. The higher frequencies in these studies compared with our study may be attributed to the fact that these two studies reported all cases of articular involvement, whether arthralgia or arthritis, whereas we reported cases with arthritis only in our study. We observed that arthritis was more frequent within the limited subtype (44.3%) compared with the diffuse subtype (21.4%) but without significant difference (P = 0.116).

ILD was reported in 40 (53.3%) patients. This finding is similar to the results of Tager and Tikly [10], who found the frequency of pulmonary fibrosis among patients included in their study to be 56%. However, Tamaki *et al.* [19] reported a lower frequency of pulmonary fibrosis (45% of the patients included in their study) compared with our results. This may be explained by the larger sample size in the study by Tamaki and colleagues and also by racial difference. On the other hand, Pagalavan and Ong [11] reported a higher frequency of ILD, which was observed in 70.5% of the 61 SSc patients included in their study who were selected from different races: 45.9% of them were Malays, 39.3% were Chinese, and 14.8% were Indians. Phung *et al.* [20] reported ILD in 17.4% of patients included in their study. This lower frequency compared with our results could be explained by their larger sample size (184), shorter study duration (2 years), and racial difference (Australian). Our study found that ILD was significantly more common in the diffuse subtype (78.6%) than in the limited subtype (47.5%) (P = 0.042). This finding was similar to those of Walker *et al.* [16] and Hunzelmann *et al.* [18] (Interstitial pulmonary fibrosis (IPF) in dcSSc was 53.4 and 56.1%, and that in lcSSc was 34.7 and 20.8%, respectively).

Pulmonary hypertension (PHTN) occurred in 11/75 (14.7%) patients included in our study, showing a higher frequency within the diffuse subtype (35.7%), compared with the limited subtype (9.8%). The difference between the two groups was statistically significant (P = 0.014). Primary pulmonary arterial hypertension (PAH) (in the absence of ILD) was found in 2/75 (2.6%) patients, both of whom were from the limited subtype group (3.3%) (P = 0.815), whereas secondary PHTN (associated with ILD) was found in 9/75 (12%) patients. It was found to be significantly more common within dcSSc, in which it affected 5/14 patients (35.7%), than in lcSSc, in which it affected 4/61 patients (6.6%) (P = 0.009). This result met with that of Tager and Tikly [10], who found that pulmonary hypertension affected 13% of the patients included in their study. In 11% of them PHTN was secondary to IPF and was isolated PAH in 2%. Phung *et al.* [20] reported a higher frequency of PAH, wherein 24% of patients included in their study were diagnosed with possible PAH by echocardiography. This higher frequency can be attributed to the fact that the study by Phung and colleagueswas directed toward the diagnosis of PAH in SSc patients and therefore patients were referred to them because of the presence of symptoms suggestive of pulmonary hypertension (PH).

Pericardial effusion was found in 4 (5.3%) patients included in our study, with higher frequency in the dcSSc subtype (14.3%) compared with the lcSSc subtype (3.3%), but this difference did not reach statistical significance (P = 0.098). This is similar to the results of Tager and Tikly [10], who found that serositis was present in 7% of the patients included in their study.

The differences in frequencies of organ involvement between male and female patients included in our study were nonsignificant apart from ILD and PHTN, which were reported to be more frequent among female patients (55.7 and 18%, respectively) than among male patients (42.9 and 0%, respectively), but this difference was not statistically significant (P = 0.565 and 0.085). In contrast, Nguyen *et al.* [8] found that male patients exhibited ILD and echocardiography pulmonary artery pressure (PAP) more than 35 mmHg more often compared with female patients. This difference may be because of the larger number of male patients included in their study (62, compared with 14 in our study), and also due to racial difference.

Conclusion

SSc is more common in the female population than in the male population.

lcSSc is more common than dcSSc.

Raynaud's phenomenon is the most common first presenting disease manifestation.

dcSSc is more commonly associated with ILD, secondary pulmonary hypertension, proteinuria, and intestinal dysmotility compared with lcSSc.

Sex does not affect the frequency of organ involvement significantly.

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Conflicts of interest

There are no conflicts of interest.

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