Pulmonary Involvement in Patients with Systemic Sclerosis

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Abstract:

Background: Systemic sclerosis is a multisystem autoimmune disease of unknown etiology. The pulmonary system is involved in Systemic sclerosis and causes a significant increase in morbidity and mortality. This study aimed to assess the extent of pulmonary system involvement in patient with systemic sclerosis. **Methods:** This study was a case control study, done on thirty patients with systemic sclerosis and twenty age and sex matched as a control group**.** All patients included in the study were subjected to the following: Full history, evaluation of skin involvement using modified Rodnan skin thickness score. Investigations including: Pulmonary function test, radiological examination (plain chest X-ray and high-resolution computed tomograghy. **Results:** predominance of females among patients. 53.33% had limited scleroderma. Modified Rodnen Score ranged from 12 to 35 with mean of 21.03 ± 7.04. Regarding skin changes of systemic sclerosis patients, skin thickness (60%), hyper or hypopigmentation (100%), ischemic ulcers (30%) and subcutaneous calcinosis (20%). A higher frequency of ILD was observed among SSc patients included in this study. The most common patterns in the HRCT in the current study were ground-glass appearance, followed by, honeycombing. Pulmonary hypertension occurred in 30% patients There were highly statistically significant differences ($p<0.001$) between cases and the control group regarding PFTs and the severity of restrictive pattern. **Conclusion:** Pulmonary manifestations are very common in SSc in the form of ILD and PH. PFTs are cornerstone in the evaluation of dyspnea and for detection of pulmonary involvement in SSc patients.

Key words: Pulmonary involvement- systemic sclerosis- pulmonary function tests.

Introduction:

Systemic sclerosis (SSc) is a multisystem autoimmune disease of unknown etiology, characterized by endothelial dysfunction resulting in vasculopathy of small vessels, and dysfunction of fibroblasts with resultant excessive collagen production and fibrosis [(1)].

Fibrosis of internal organs can involve different body systems, including skin, pulmonary, cardiac, and gastrointestinal systems [(2)].

The pulmonary system is frequently involved in SSc and causes a significant increase in morbidity and mortality. Involvement can affect all parts of the respiratory tract including the blood vessels, lung parenchyma, airways, pleura, and respiratory muscles [(3)].

It is estimated that 80% of patients with SSc have some degree of pulmonary affection. This makes pulmonary system the second most commonly affected visceral system after the esophagus. Furthermore, pulmonary involvement predicts a poorer prognosis and is now considered the leading cause of death among patients with SSc [(4)].

Since lung fibrosis is an irreversible process, early diagnosis is mandatory to decrease morbidity and mortality. Assessment of ILD in SSc focuses on early detection, assessment of severity, and definition of progression and is best performed by regular PFTs [(2)].

This study aimed to assess the extent of pulmonary system involvement in patient with systemic sclerosis (SSc).

Subjects and Methods

This study was a case control study, done on thirty patients with systemic sclerosis (SSc), and twenty age and sex matched apparently healthy volunteers as a control group.

- **patients :-**

Thirty patients diagnosed as systemic sclerosis (SSc), the study group. These patients were recruited from the outpatients' clinic and inpatient department of the Rheumatology, Rehabilitation and Physical medicine of Benha university hospitals between March 2017 to January 2018.

- **Controls**

Twenty age and sex matched apparently healthy volunteers as a control group.

- **Methods :-**

Ethical consideration: Informed written consents were obtained from all subjects enrolled in this study.

All patients included in the study were subjected to the following:

1. Full history taking:

I.Personal history: Name, Age, Sex, Marital status, Residence, Occupation, Special habit of medical importance e.g. Smoking.

II.Complaint: obtained in patient's own words.

III.Present history:

Raynaud's phenomenon:

Description of the attack, precipitating factors, duration and frequency of the attack, site, digital ulcers, pitting scars.

Skin changes: Extent of skin thickening, hyperpigmentation and/ or hypopigmentation, ischemic ulcers, subcutaneous calcinosis (site, ulcers and discharge).

Chest symptoms: Progressive exertional dyspnea, tachypnea. Cough (dry or productive cough), hemoptysis. Cyanosis, chest pain (onset, course, duration, site, character, radiation, precipitating factors, relieving factors and associated symptoms).

Cardiac manifestations: Dyspnea, palpitation, lower limb edema.

II. Physical examination;

Examination of extremities:

Raynaud's phenomenon, clubbing, cyanosis, puffy hands and fingers, sclerodactly, digital or toe ulcers, pitting scars and loss of substance from the digital pad of fat, finger to palm distance in centimeters. digital or toe amputation and acroosteolysis, nail lesions (paronychia, ridges and furrows), and edema of lower extremities: its extent and if pitting or not, all were examined.

Examination of the skin:

1 - Assessment of skin thickening: a semi quantitative scoring system (The Modified Rodnan Skin Score – MRSS) was used to evaluate the degree of skin thickening by clinical palpation using a 0–3 scale (0=normal skin; 1=mild thickness; 2=moderate thickness; 3=severe thickness with inability to pinch the skin into a fold) for each of 17 surface anatomic areas of the body: face, anterior chest, abdomen, right and left separately for (fingers , forearms , upper arms, thighs, lower legs, dorsum of hands and feet). These individual values are added and the sum is defined as the total skin score (Maximum score = 51) [(5)].

2 – Hyperpigmentation, hypopigmentation and pruritis.

Cardiac examination:

a. Inspection: scars of previous operations, pulsations of different areas, site of the apex.

b. Palpation: pulsations &thrill (apex, pulmonary, epigastric and sternal).

c. Percussion: upper border (bare area of heart), left border, right border and waist of the heart.

d. Auscultation: first and second heart sounds, additional sounds, murmurs and pericardial rub.

Chest examination:

Inspection,. palpation, percussion and auscultation, were done.

III. Investigations:

Laboratory investigations:

Pulmonary function tests (Spirometry): All subjects underwent pulmonary function testing (spirometry) which were performed using computerized equipment. PFTs were performed using (Spiro Lap Spirometry) sensormedics system. Ambient temperature and pressure were entered with the patient data (age in years, weight in kilograms, height in centimeters, sex) so that all results were calculated as percent of predicted (% predicted) except for FEV1 /FVC %.

- **Spirometry :**

They include of flow volume loop and Maximal voluntary ventilation (MVV).

Technique:

(1) Flow volume loop [(6)] :

- **From flow volume loop the following data were collected :**

1-Vital capacity (VC) actual and percent of predicted.

2-Forced vital capacity (FVC) actual and percent of predicted.

3-Forced expiratory volume in the first second (FEV1) actual and percent of predicted.

4-FEV1/FVC %

5-Forced expiratory flow (25-75%).

6-Peak expiratory flow (PEF).

7-MVV.

(2) Maximal voluntary ventilation MVV. [(6)]:

1-The patient was instructed to begin with normal breathing.

2-The patient was instructed to begin breathing fast and deep.

3- The patient was instructed to continue deep rapid breathing until the end of the test . The test was ended automatically.

Patients with ILD show restrictive pulmonary functions with FVC less than 80% of predicted value. According to FVC patients can be classified in to:

1-mild (FVC 60-79% of predicted value)

2-moderate (FVC40-59% of predicted value)

3-severe (FVC less40% of predicted value) ([7]).

(3) The diffusion capacity of carbon monoxide (DLCO) ;

A reduction in the diffusion capacity of carbon monoxide (DLCO) (less than 70% of the predicted value) is the earliest detected abnormality in SSc patients with ILD including asymptomatic cases with normal chest radiograph. The decrease in DLCO correlates with the severity of ILD as detected by high-resolution computed tomography. Ventilatory pulmonary functions may reveal restrictive hypoventilation. The combination of normal lung volumes, reduced gas transfer and normal chest imaging suggests pulmonary vascular disease [(8)].

3) Radiological examination:-

I. Plain Chest X Ray

Postero-anterior (P.A.) and lateral views were done for assessment of patients with ILD and to also exclude other lung diseases.

II. High resolution computerized tomography scan (HRCT);

It is approach to patients with suspected diffuse infiltrative Lund disease **(DILD).**

HRCT scans were evaluated for the presence, distribution and extent of the following signs.

- **Ground glass attenuation was defined as** areas of increased attenuation without obscuring the underlying vessels and bronchi.
- **Reticular and reticulonodular opacities:**

Reticular opacities of high attenuation were defined as interlacing linearities together with faint scattered alveolar opacities 1-20 mm in diameter.

- **Honeycombing and bronchectatic changes;**

Honycombing cysts were defined as localized areas of small encysted air spaces representing lung parenchyma.

Bronchectatic changes represent dilated bronchi and distal bronchioles representing irreversible destruction of the bronchial tree.

- **Consolidation** represent patchy non segmental air space opacities with air bronchogram (open bronchus sign)

III. H- Doppler echocardiography:

Ethical considerations

Approval was taken from all cases and also from the Institutional Review Board (IRB) of Faculty of Medicine, Benha University.

Statistical analysis: The collected data were tabulated and analyzed using SPSS version 16 software (SpssInc, Chicago, ILL Company). Categorical data were presented as absolute and relative (%) frequencies. Chi-square test (X^2), or Fisher's exact test (FET) were used to analyze categorical variables. Student "t" test was used to analyze normally distributed variables among 2 independent groups. While non-parametric variables were analyzed using the Man Whitney U test. The accepted level of significance in this work was stated at 0.05 (P <0.05 was considered significant).

There was statistically highly significant difference (p<0.001) between cases with

Results

There was no statistically significant difference between Cases and Controls regarding age and sex. **(Table 1)**

Disease disorders ranged from 10 to 20 with mean of 15 ± .51 (years), Modified Rodnen Score ranged from 12 to 35 with mean of 21.03 ± 7.04. Regarding Type, Limited and Diffuse were found in 53.33%, and 46.67% respectively. **Table (2)**

Regarding Skin changes of systemic sclerosis patients, skin thickness (100%), hyper or hypopigmentation (100%), ischemic ulcers(30%) and subcutaneous calcinosis(20%). **Table (3)**

Regarding Plain X-ray, Interstitial fibrosis was present among 53.3%. Regarding HRCT, Normal was 46.6% and (Ground glass appearance and Honeycomb appearance were found in 33.33%, and 20% respectively. **Table (4)** Regarding Pul. HTN (mmhg) was 30% >25. **Table (5)**

There were highly statistically significant differences (p<0.001) between cases and the control group regarding PFTs and the severity of restrictive pattern. **Table (6)**

different severity in PFTs as regard FVC and FVE1 and a statistically significant

difference (p=0.04) as regard FVE1/FVC. **Table (7)**

Table (1): Comparison between Cases and Controls regarding demographic data**.**

			Cases (No.= 30)	Controls (No.= 20)	t.test	P. value
Age (Years)	**Rang**		40 - 60	40 - 60	**0**	**1**
	Mean ± SD		51 ± 5.89	51 ± 5.947		
Sex	**Female**	**No.**	18	12		
		%	60.0%	60.0%	X^2	**1**
	Male	**No.**	12	8	**.000**	
		%	40.0%	40.0%		

Table (2): Clinical data of systemic sclerosis patients

		Cases(No.= 30)	
Disease disorders (years)	**Rang**	10 - 20	
	Mean ± SD	15 ± .51	
Modified Rodnen Score	**Rang**	12 - 35	
	Mean ± SD	21.03 ± 7.04	
		No	%
Types	**Limited**	16	53.33%
	Diffuse	14	46.67%

Table (3): Skin changes of systemic sclerosis patients.

			Cases (No.= 30)
Skin Thickness	**-ve**	**No.**	0
		%	.0%
	+ve	**No.**	30
		%	100.0%
Hyper or hypopigmentation	**-ve**	**No.**	0
		%	.0%
	+ve	**No.**	30
		%	100.0%
Ischemic ulcers	**-ve**	**No.**	21
		%	70.0%
	+ve	**No.**	9
		%	30.0%
Subcutanous calcinosis	**-ve**	**No.**	24
		%	80.0%
	+ve	**No.**	6
		%	20.0%

Table (4): Chest radiological findings of systemic sclerosis patients

		No.	%
Plain X-ray	**Normal**	14	46.67%
	Interstitial fibrosis	16	53.33%
HRCT	**Normal**	14	46.67%
	Ground glass appearance	10	33.33%
	Honeycomb appearance	6	20%

Table (5): Pul. HTN of systemic sclerosis patients**.**

			Cases (No.= 30)
Pul. HTN (mmhg)	**<25**	**No.**	**21**
		%	**70.0%**
	30	**No.**	**3**
		%	**10.0%**
	45	**No.**	**3**
		%	**10.0%**
	50	**No.**	**3**
		%	**10.0%**

Table (6): Pulmonary function tests of the studied groups

			Cases(No.= 30)	Controls(No.= 20)	t.test	P. value
FVC %	**Rang**		18 – 85	75 - 106		
	Mean ± SD		61.33 ± 20.82	85.57 ± 8.43	**5.19**	**0.000**
FEV1	**Rang**		23 – 96	76 - 100		
	Mean ± SD		66.8 ± 19.04	87.93 ± 7.35	**5.67**	**0.000**
FEV1/ FVC	**Rang**		91 – 126	85 - 125		
	Mean ± SD		109.97 ± 10.13	110.8 ± 13.58	**0.05**	**0.96**
Diffusing	**Rang**		30 – 80	70 – 100	**39.13**	**.000**
Capacity of CO (DLco)	**Mean ± SD**		59.2 ± 9.4	85.1 ± 2.4		
	Normal	**No.**	14	17		
		%	46.67%	85%		
	Mild	**No.**	10	3		
Severity	**restrictive**	**%**	33.33%	15%	X^2	**.000**
	Moderate	**No.**	3	0	**31.95**	
	restrictive	**%**	10%	.0%		
	Severe	**No.**	3	0		
	restrictive	**%**	10%	.0%		

Table (7): Pulmonary function tests of the studied groups

		FVC				
		No	**Mean**	**SD**	**F. test**	**P. value**
Severity	**Normal**	14	82.29	2.29	185.18	<0.001**
	Mild restrictive	10	74.78	2.64		
	Moderate restrictive	3	54.71	3.86		
	Severe restrictive	3	29.71	8.01		
		FEV1			F. test	P. value
		No	Mean	SD		
Severity	**Normal**	14	87.57	8.42	24.20	<0.001**
	Mild restrictive	10	74.22	8.21		
	Moderate restrictive	3	60.14	4.06		
	Severe restrictive	3	43.14	16.88		
		FEV1/ FVC			F. test	P. value
		No	Mean	SD		
Severity	**Normal**	14	113.43	11.44	3	0.04*
	Mild restrictive	10	103.11	9.37		
	Moderate restrictive	3	116	7.79		
	Severe restrictive	3	109.29	7.72		

Discussion

The aim of the present work was to assess the extent of pulmonary system involvement in patient with systemic sclerosis (ssc).This study was a case control study, which done on thirty patients with systemic sclerosis (SSc), and twenty age and sex matched apparently healthy volunteers as a control group**.**

This study showed that, there was no statistically significant difference between Cases and Controls regarding age and sex.

This study showed that, a predominance of females among systemic sclerosis patients (60%).This finding agrees with the results of **Tager and Tikly, [(9)]** who found that SSc is more frequent in the female population. Also, **Pagalavan and Ong, [(10)]**, 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., [(11)]** and found that the male to female ratio was 1: 3. In addition, **Englert et al., [(12)]** 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., [(13)]**, who found a male to female ratio of 1: 5.2.

In this study, with regard to the frequency of disease subsets, 16 patients (53.33%) had limited scleroderma and the other 14 patients (46.67%) had diffuse scleroderma. This finding is agreement with many studies that reported that lcSSc is more common than dcSSc,: **Alamanos et al., [14]** reported a diffuse to limited ratio of 1: 3, and **Lo Monaco et al., [15]** reported a diffuse to limited ratio of 1: 3.3.

This study showed that, the Modified Rodnen Score ranged from 12 to 35 with mean of 21.03 ± 7.04.

Similar results presented by [16] who reported that mRSS was 21.2 ± 9.9 in 45 SSc patients. Also this is in agreement with, [17] who reported that mRSS was 15.5 ± 8.4 in 42 SSc patients.

In the present study, regarding Skin changes of systemic sclerosis patients, Skin Thickness (60%) , Hyper or hypopigmentation(100%), Ischemic ulcers(30%) and Subcutanous calcinosis(20%).This was consistent with the results of [9] who showed that, dyspnea was present among all systemic sclerosis patients and cough was present among 80%.

In the present study, 53.33% of patients had ILD. This finding is similar to the results of **Tager and Rikly, [9]**, who found the frequency of pulmonary fibrosis among patients included in their study to be 56%.

However, **Tamaki et al., [18]** 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.

An analysis carried out by the European Scleroderma Trials and Research group (EUSTAR) on a cohort of 3656 SSc patients, showed that ILD is present in 44% of cases with SSc [19].

In the present study, 53.33% of patients showed evidence of ILD by chest HRCT.

This was consistent with the results of **Solomon et al., [1]** who found that HRCT is the most sensitive and specific tool for detecting and describing any ILD present in SSc [20].

This study showed that, the most common patterns in the HRCT were ground-glass appearance, followed by, honeycombing, These were concurrent with studies done by **Cappelli et al., [19]**. However, the results of **Jezler et al., [21]** were different. bronchiolectasis was the most often described, followed by honeycombing, ground-glass opacity, septal thickening and consolidations. On HRCT, evidence of interstitial disease is seen in approximately 90% of patients, the main findings being a fine reticular pattern involving the

subpleural regions of the lower lobe. Other common findings include ground-glass opacities, honeycombing, and parenchymal micronodules. Bronchiectasis is an uncommon pulmonary manifestation of SSc [22].

Pulmonary hypertension (PHTN) occurred in 9/30 (30%) patients included in our study, showing a higher frequency. This result met with that of **Phung et al.,** [23] reported a higher frequency of PAH, wherein 24% of patients included in their study were diagnosed with possible PAH by echocardiography.

Pulmonary involvement has been reported in Egyptian SSc patients including PH in 26.7% and 75% had various degrees of ILD [24].

This study showed that, there were highly statistically significant differences ($p<0.001$) between cases and the control group regarding PFTs and the severity of restrictive pattern.

Similarly, the results of **Solomon et al.,** [1] revealed a reduction in FVC in 40–75% of SSc patients, with 15% of them showing a severe reduction. Moreover, **Scholand et al.,** [25] reported that PFTs are cornerstone tests in the evaluation of dyspnea, and allow determination of the clinical impact of ILD by accurately evaluating its severity. Furthermore, **Cappelli et al.,** [19] revealed a restrictive pattern, mainly due to parenchymal involvement, with reduced FEV_1 and FVC, and a normal or slightly increased FEV_1/FVC ratio.

Conclusion:

Pulmonary manifestations are very common in SSc in the form of ILD and PH. PFTs are cornerstone in the evaluation of dyspnea and for detection of pulmonary involvement in SSc patients.

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