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Serum interleukin-6 in systemic sclerosis and its correlation with disease parameters and cardiopulmonary involvement

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Abstract. *Objective:* To assess serum interleukin-6 (IL-6)level in patients with systemic sclerosis (SSc) and its correlations with European Scleroderma Study Group activity score (EUSTAR), Scleroderma Assessment Questionnaire (SAQ), disability index and cardiopulmonary involvement. *Methods:* Twenty SSc patients and 10 matched healthy controls were included. Serum IL-6 was measured in patients and controls. Disease activity, status,and disability were assessed.Cardiopulmonary involvement was evaluated by pulmonary function tests (PFTs), six minute walk test, echocardiography, and high resolution computed tomography (HRCT) of chest. *Results:* Serum level of IL-6 was significantly higher in patients with SSc (6.3± 1.4pg/ml) versus healthy controls (3.2± 0.4pg/ml) (P=0.002). IL-6 level showed positive correlations with disease duration (r=0.49, P=0.03), EUSTAR score (r=0.64, P=0.002), Index of Respiratory Status "IRS" (r=0.46, P=0.001), Index of Musculoskeletal Status "IMSS" (r=0.45, P=0.049), Index of Vascular Status "IVS" (r=0.39, P=0.04), mean and peak of pulmonary artery pressure (r=0.44 & 0.55, P=0.02 & 0.002 respectively). Negative correlations of IL-6 level with DLCO% (r=-0.49, P=0.006),six minute walk distance (6MWD) (r=-0.52, P= 0.003) and right ventricle fraction area change (r=-0.48, P=0.03) were found, while there were strong positive correlations with HRCT-ground glass score (r=0.77, P=0.0001) and HRCT–fibrosis score (r=0.62, P=0.003). *Conclusion:* IL-6 level is increased in patients with SSc and significantly correlates with EUSTAR score, IRS, DLCO, 6MWD, HRCT scores, and echocardiographic abnormalities of the right side of the heart. These results support the role of IL-6 in the disease activity and in the development of cardiopulmonary manifestations in SSc patients. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 321-330)*

Key words: systemic sclerosis, Interleukin-6, cardiopulmonary involvement

Introduction

Systemic sclerosis (SSc) is a generalized disorder of the connective tissue characterized by widespread microvascular and vascular lesions and by the increased deposition of matrix components in the skin and internal organs, particularly the gut, lung, heart, and kidney (1).

Pulmonaryinvolvement is second in frequency to oesophagus involvement. Interstitial lung disease (ILD) and pulmonary vascular disease, particularly pulmonary arterial hypertension (PAH), are the most commonly encountered types of lung involvement (2). Differentiation between ILD, PAH and other causes of dyspnea in patients with SSc, can be clinically difficult. However, the identification and staging of pulmonary manifestation is of paramount importance to the management of patients (3).

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The heart is a major organ involved in SSc. Cardiac involvement can generally be divided into direct myocardial effects and the indirect effect of other organ involvement (i.e. pulmonary hypertension, renal crisis) (4).

Although the pathogenesis of SSc remains unclear, a variety of cells contribute to the fibrosis process via mutual interactions and production of cytokines, including interleukin-6 (IL-6) (5). IL-6 is a cytokine with several potentially important roles in the pathogenesis of SSc. It is elevated in the serum of patients with SSc, especially those with diffuse skin involvement and early in the disease course (6).

Up-regulation of serum IL-6 in patients with SSc is associated with disease activity, severity, disability, worse outcome and reduced survival. Targeted IL-6 therapy in SSc has occurred in small case series that is underway (7).

The aim of the study was to assess serum IL-6 level in patients with SSc and to determine its correlations with European Scleroderma Study Group activity score (EUSTAR), Scleroderma Assessment Questionnaire (SAQ), disability index and cardiopulmonary involvement.

Patients and Methods

Study population

This prospective study was conducted on 20 SSc patients (17 females and 3 males) attending outpatient clinic of Rheumatology and Rehabilitation Department, Minia University Hospital. All patients fulfilled the criteria proposed by the American College of Rheumatology (8). Exclusion criteria included current smoking, recent symptoms or signs of lower respiratory infection at the time of the study and known histories of cardiopulmonary diseases. Ten age and sex matched apparently healthy subjects were participated as controls. The study protocol was approved by the local Ethic Committee of Faculty of Medicine and an informed consent was obtained from all patients.

Clinical assessment

A complete history was taken from each patient with attention to respiratory symptoms as dyspnea, cough, expectoration, chest pain, fatigue and dizziness. Disease activity was assessed using EUSTAR score (9). A total score of ≥3 for all parameters indicates disease activity. Scleroderma Assessment Questionnaire (SAQ) was used for measurement of disease status and level of impairment of different organ systems (10) "higher index value indicates more severe damage of particular organ system", and Health Assessment Questionnaire Disability Index (HAQ-DI) for assessment of disability in SSc patients (11).

Pulmonary function tests

Lung functions included spirometry and diffusion capacity were done using ZAN 300 system (Biomedica, Germany). The following parameters were measured: Forced vital capacity (FVC), Forced expiratory volume in the first second (FEV_1), ratio of FEV_1 to FVC (FEV_1/FVC), Forced expiratory flow between 25-75% of vital capacity (FEF_{25-75}%), and peak expiratory flow rate (PEF). Diffusing capacity of the lung for carbon monoxide (DLCO) corrected for hemoglobin concentration, total lung capacity (TLC), transfer coefficient (KCO) (which equals DLCO/ alveolar volume VA) were measured using the single breath technique. All parameters were calculated as percentages of values predicted from the patient's age, sex and height (12).

Pulmonary function tests were defined as "normal" when FVC and DLCO were ≥80% of predicted, restrictive if TLC was <80% and/or DLCO was <75% of predicted value. Obstructive defect was present if FVC ≥80% and FEV1/FVC ratio <70% of predicted and mixed defect if FVC and/or TLC <80% of predicted and FEV1/FVC <70% of predicted (13).

6-minute walk test (6MWT)

The 6MWT was performed according to the American Thoracic Society Guidelines (14). The test was conducted along an enclosed 30 m corridor. Patients and controls were asked to walk as far down the length of the corridor as they could at their own pace for 6 minute and 6 min walk distance (6MWD) was detected.

High Resolution CT

All patients underwent chest HRCT using CT examinations which were done on 16-slice machine

(GE bright speed, GE health care, USA). Images were taken through the chest with the following parameters: KV: 120, mA: 300, helical scan, slice thickness: 0.625, interval: 0.625, pitch: 0.562:1, detector configuration: 16x0.625, tilt: 0, reconstruction: lung window. Images were transferred to advanced workstation (AW volume share 2) with commercially available software that is capable of producing axial, coronal and sagittal reformats. Images were reconstructed with a high spatial frequency algorithm and photographed at window setting appropriate for viewing the lung parenchyma. Neither mediastinal window nor contrast was used. CT scans were revised by radiologist who was blinded to the clinical data of patients.

In order to quantify the lung involvement by ILD, Kazerooni HRCT Scoring system was used (15). Each lung lobe was scored for the extent (expressed as percent of the surface of the lobe) of ground glass (GG) opacity (HRCT-GG Score) and of reticular opacities or honey combing (HRCT-Fibrosis Score) on a scale of 0-5. The values of the score were as follows: 0 (absent), 1 (<5% of lobe), 2 (5-25%), 3 (25-50%), 4 (50-75%) and 5 (> 75%). Each lobe score was measured and the sum of all lobes was assigned into a fibrosis or a ground glass or both.

Echocardiographic examinations

Echocardiographic examinations were performed by the cardiologist who was blinded for clinical data, using an ultrasound system (Vivid 3, GE) equipped with GE 3S; sector array ultrasound probe (range 1.5-3.6 MHz). Conventional echocardiography was performed according to the American Society of Echocardiography recommendations (16-18).

LV systolic function was evaluated by estimating LV ejection fraction (EF) either by M mode and/or Simpson's biplane method, with values > or = 55% were considered normal (16). RV systolic function was estimated by 2D Fractional Area Change (FAC) & by Tricuspid Annular Plane Systolic Excursion (TAPSE). Right ventricle fraction area change (RV FAC) >35% & TAPSE >1.6 cm were considered normal (17). The LV and RV diastolic functions were evaluated by measuring early flow wave velocity (E), late flow wave velocity (A), E/A ratio, deceleration time (DT) of the mitral valve (MV) and tricuspid valve (TV) inflow velocities respectively. Also Tissue Doppler imaging (TDI) was used to assess ratio of the early diastolic flow velocity (E) to the annular velocity (e') at lateral MV and TV, then E/e' of MV andTV were calculated respectively (17, 18).

Grade I LV and RV diastolic dysfunction is considered if E/A ratio of MV and TV respectively were <0.8. Grade II LV diastolic dysfunction was considered if MV E/A = 0.8-1.5 & MV E/e'>8. Grade II RV diastolic dysfunction was considered if E/A of TV = 0.8- 2.1 and TV E/e'>6. Grade III LV diastolic dysfunction was estimated if MV E/A >2, MV DT <160, E/e'>13, while grade III RV diastolic dysfunction was considered if TV E/A>2, TV DT<120 (17, 18).

The pulmonary artery pressure (PAP) was evaluated by estimating the tricuspid regurgitation jet velocity (v), using Bernoulli's equation and was considered to be equal to the right ventricular systolic pressure in the absence of right ventricular outflow obstruction [PAP=RV systolic pressure=4v2 + RA pressure]. Pulmonary hypertension was considered if PAP >35 mmHg, when RA pressure is 0-5 mmHg. The mean PAP was evaluated from the pulmonary acceleration time (AT) using following equation [79-(0.45 × AT], providing that heart rate is between 60-100/m. Normal mean PAP is <25 mmHg (16).

Serum IL-6

Fasting blood samples were taken from patients and controls to measure IL-6 levels using an enzyme linked immunoassay(ELISA) kits supplied by (Biosource, Nivelles, Belgium). Collected serum was kept frozen at -70°C till the time of assay.

Statistical analysis

Data were analyzed by the SPSS version 16.0 statistical package.Categorical and quantitative variables were respectivelydescribed as numbers, percentage (%) and mean ± SD. Patients with SSc were compared with healthy controls by Student's *t*

test and by Chi-squared test (x^2). Correlation between variables was calculated byPearson correlation coefficient. P values <0.05 were consideredstatistically significant.

Results

Demographic and clinical data

Demographic and clinical data are shown in (Table 1). Five patients (25%) had dyspnea, 4 (20%) had cough, and 2 had chest pain. The mean of EUSTAR score was 3.6±1.9 indicating the presence of active disease and organ involvement in the group overall. The Index of Vascular Status was the highest index value in SAQ which indicates more severe damage of vascular system (Table 2). All indices of SAQ were positively correlated with EUSTAR score (r=0.61, P=0.005 for IVS, r=0.47, P=0.03 for IRS, r=0.62, P=0.004 for IGS, and r=0.47, P=0.04 for IMSS).

PFTs results

Table 3 shows that FVC%,FEV1%, DLCO%, TLC%, KCO% predicted and 6MWD were significantly lower among patients with SSc versus controls. On the other hand, FVC%/DLCO% and TLC%/DLCO% were significantly higher in patients than controls. PFTs results showed that,10 patients (50%) had restrictive pattern "3 of them had normal HRCT findings", 2 patients (10%) had obstructive function"one of them was ex-smoker", 4 patients (20%) had an isolated decrease of DLCO%

Table 1. Demographic and clinical data of the studied population

	Patients (n=20)	Controls (n=10)	P value
Age (y)			
Range	18-65	25-58	
Mean±SD	40.2±13.6	43.6±10.5	0.6
Sex			
Female, n (%)	17 (85%)	6 (60%)	
Male, n (%)	3 (15%)	4 (40%)	0.17
Disease duration (y)			
Range	2-18	--	
Mean±SD	7.4±4.2	--	
Disease subset			
Diffuse	13 (65%)	--	
Limited	7 (35%)	--	
Raynaud's phenomenon, n (%)	18 (90%)	--	
Digital pitting scars, n (%)	15 (75%)	--	
Telangiectasia, n (%)	2 (10%)	--	
Finger tip ulcer, n (%)	6 (30%)	--	
Friction rub, n (%)	1 (5%)	--	
Joint contracture, n (%)	11 (55%)	--	
Joint Swelling, n (%)	1 (5%)	--	
Muscle weakness, n (%)	4 (20%)	--	
Chest crackles, n (%)	2 (10%)	--	

Analysis was done by student t-test or chi-squared test

Table 2. Assessment of disease activity and disability in scleroderma patients

	Patients (n=20)
EUSTAR score	
Range	1.5-7
Mean± SD	3.6±1.9
IVS	
Range	0-2.8
Mean± SD	1.5±0.9
IRS	
Range	0-1.8
Mean± SD	0.4±0.5
IGS	
Range	0-2.4
Mean± SD	0.8±0.6
IMSS	
Range	0-2.3
Mean± SD	1±0.8
HAQ-DI	
Range	0-2
Mean± SD	0.8±0.6

EUSTAR=European Scleroderma Study Group activity score, IVS=Index of Vascular Status, IRS=Index of Respiratory Status, IGS=Index of Gastrointestinal status, IMSS=Index of Musculoskeletal Status, HAQ-DI=Health Assessment Questionnaire Disability Index

Table 3. Pulmonary function tests and 6MWD in scleroderma patients versus controls

	Patients (n=20)	Controls (n=10)	t	p
FVC %	68±21.9	90.6±3.5	-4.497	0.0001*
FEV1%	63.9±19	84±2.1	-3.306	0.003*
FEV1/FVC	81.5±12.7	76.7±3.1	1.94	0.06
DLCO%	46.2±19.7	87.3±4.2	-8.950	0.0001*
TLC%	73.2±19.6	90.5±3.1	-3.857	0.001*
KCO%	63.2±20.4	85.2±2.3	-4.774	0.0001*
FVC%/DLCO%	1.7±1.2	1±0.1	2.703	0.01*
TLC%/DLCO%	1.8±0.8	1±0.03	3.011	0.005*
6MWD (meters)	260.7±42.1	326.2±26.4	-12.291	0.01*

Analysis was done by student t-test. Data are represented as mean±SD. FVC=Forced vital capacity, FEV_1=Forced expiratory volume in the first second, FEV_1/FVC=ratio of FEV_1 to FVC, DLco%=percent predicted diffusing capacity of the lung for carbon monoxide, TLC=Total lung capacity, KCO=transfer coefficient 6MWD=6 minute walk distance.*P<0.05

and 4 patients (20%) had combined obstructive and restrictive disorders.

The most frequently abnormal PFTs in SSc patients is the decrease of DLCO (18 patients, 90%) either with or without a decrease of TLC.

Seven patients had FVC/DLCO ≥1.6 and 6 patients had TLC/ DLCO >2 which suggesting presence of both ILD and PAH.

The index of respiratory system was positively correlated with FVC%/DLCO% (r=0.58, P=0.008) and TLC%/DLCO% (r=0.60, P=0.005).

HRCT findings and scores

HRCT showed interstitial lung involvement in 17 patients (85%). Abnormal HRCT findings which observed in the patients were:ground glass appearance in 12 (60%) (Fig. 1), honey combing appearance in 7 (35%) (Fig. 2) and mixed findings in 17 patients (85%). The ground glass score ranged from 0 to 15 with a mean of 7.9±5.9 and the fibrosis score ranged from 0 to 12 with a mean of 6.8±4.5.

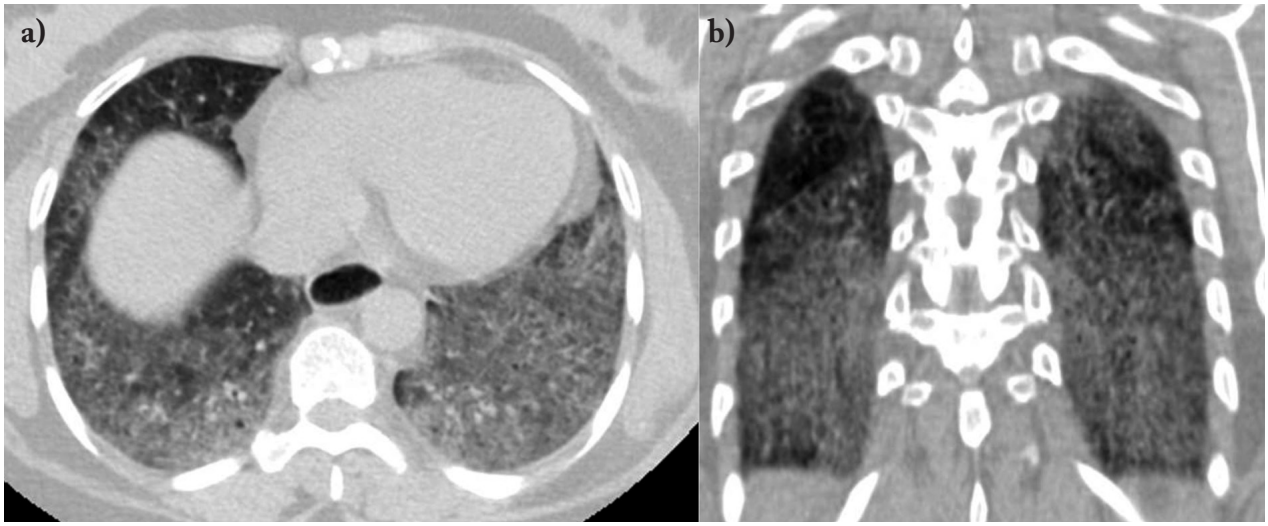

Fig. 1. Axial (a) and coronal (b) CT images show extensive ground glass opacities and interstitial thickening mainly seen at the posterior parts of both lungs

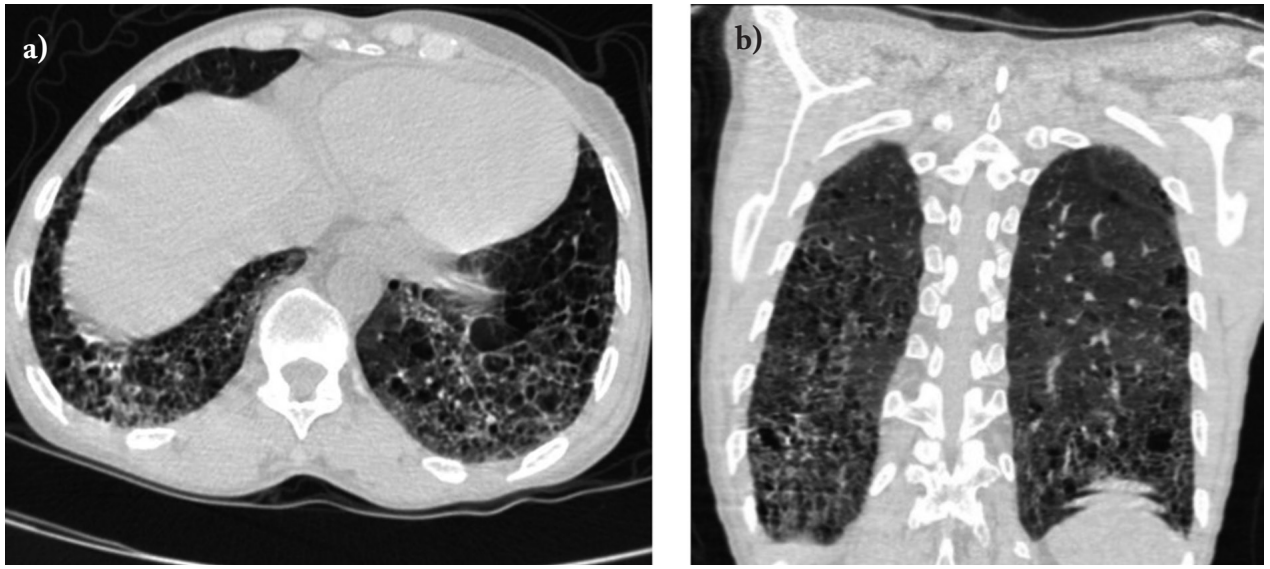

Fig. 2. Axial (a) and coronal (b) CT images show extensive interstitial thickening and multiple cystic changes giving the lung parenchyma a honeycomb appearance

Echo-Doppler data

Regarding frequency of cardiac involvement in patients with SSc; it was found that RV FAC & TAPSE were significantly lower in SSc patients than controls (p=0.0001 for both) (table 3), with 35% (7 patients) had RV systolic impairment when estimated by RVFAC, while TAPSE revealed 60% (12 patients) had RV systolic impairment.

Moreover; peak and mean PAP were significantly higher in SSc patients than control (p=0.0001 & 0.007 respectively) (Table 4), with 25% (5 patients) had pulmonary hypertension when estimated by peak PAP, while 30% (6 patients) had pulmonary hypertension when estimated by mean PAP.

Tissue Doppler findings revealed significantly higher E/e' ratio of mitral & tricuspid valve in SSC patients than control (p=0.0001 & p=0.009 respectively), with 50% (10 patients) had grade II LV diastolic dysfunction & 35% (7 patients) had grade II RV diastolic dysfunction.

No significant difference was found regarding LV systolic function estimated by EF, also the incidence of grade I LV & RV diastolic dysfunction between SSc patients & controls, and none of study population had grade III diastolic dysfunction.

The Index of respiratory system was positively correlated with peak and mean of PAP (r=0.69, P=0.006, r=0.64, P=0.002 respectively).

6-minute walk test (6MWT) results

Six minute walk distance was significantly lower in SSc patients than controls (P=0.001) (Table 3).As regards lung functions, 6MWD was positively correlated with FVC%, FEV1%, DLCO%, TLC%, KCO% (r=0.62, P=0.0001, r=0.59, P=0.001, r=0.90, P=0.0001, r=0.62, P=0.0001, r=0.70, P=0.0001 respectively), and negatively correlated with FVC%/DLCO% and TLC%/DLCO% (r=-0.49, P=0.006, r=-0.96, P=0.0001 respectively). Moreover, 6MWD was negatively correlated with HRCT–GG score, HRCT-fibrosis score,IRS (r=-0.45, P=0.047, r-=0.39, P=0.04, r-=0.40, P=0.03 respectively), peak and mean of PAP (r=-0.48, P=0.03, r=-0.58, P=0.008 respectively).

Relationship between EUSTAR score and cardiopulmonary involvement

EUSTAR score was negatively correlated with DLCO% (r=-0.49, P=0.03) and 6MWD (r=-0.47, P=0.04); while it was positively correlated with FVC%/DLCO% (r=0.43, P=0.04), TLC%/DLCO% (r=0.50, P=0.03), HRCT-GG score (r=0.46, P=0.04), HRCT-Fibrosis score (r=0.58, P=0.007), peak PAP (r=0.59, P=0.007) and mean PAP (r=0.49, P=0.03).

Table 4. ECHO-Doppler data in patients with scleroderma versus controls

	Patients (n=20)	Controls (n=10)	t	p
Grade I LV diastolic dysfunction	2 (10%)	1 (10%)	0.120	0.7
E/e' MV by tissue Doppler	8.8±2.6	4.6±0.9	6.596	0.0001*
Grade II LV diastolic dysfunction	10 (50%)	0	7.500	0.006*
Grade I RV diastolic dysfunction	7 (35%)	1 (10%)	2.131	0.1
E/e' TV by tissue Doppler	5.7±1.9	4.4±0.7	2.799	0.009*
Grade II RV diastolic dysfunction	7 (35%)	0	4.565	0.03*
RV FAC (%)	41.1±8.4	50.7±4.6	27.613	0.0001*
Peak PAP (mmHg)	32.9±6.1	24.8±4.1	4.314	0.0001*
Mean PAP (mmHg)	22.2±8.9	15.9±2.4	2.959	0.007*
LV ejection fraction (%)	66.6±7.9	72±9.5	15.470	0.15
TAPSE (cm)	1.4±0.5	1.7±0.2	26.100	0.03*

Analysis was done by student t-test & chi square test. Data are represented as mean ± SD or number & percentage. LV= left ventricle, RV= right ventricle, MV= mitral valve, TV= tricuspid valve, E/A=ratio of early flow wave velocity and late flow wave velocity, RV FAC= Right ventricle fraction area change, PAP=pulmonary artery pressure, TAPSE=Tricuspid Annular Plane Systolic Excursion, E/e`=ratio of the early diastolic flow velocity to the annular velocity at lateral mitral valve and tricuspid valve. *P<0.05

Serum IL-6 assay and its relationship with other variables

Serum levels of IL-6 were significantly higher in patients with SSc (6.3±1.4 pg/ml) compared to healthy controls (3.2±0.4 pg/ml) (P=0.002) (Fig. 3).

A- *Relationship of IL-6 with disease duration, EUSTAR score, SAQ and disability index*

There was a moderate positive correlation between serum levels of IL-6 and disease duration (r=0.49, P=0.03). Serum levels of IL-6 were strongly positively correlated with EUSTAR score (r=0.64, P=0.002), while they moderately positively correlated with IRS (r=0.46, P=0.001), and IMSS (r=0.45, P=0.049). Moreover, serum levels of IL-6 were weakly positively correlated with IVS (r=0.39, P=0.04), but there was no correlation with both of IGS and HAQ –DI.

B- *Relationship between IL-6 and cardiopulmonary involvement*

Serum IL-6 levels were negatively correlated with DLCO% (r=-0.49, P=0.006) and 6 MWD (r=-0.52, P=0.003),while they were strongly positively correlated with both of HRCT–GG score (r=0.77, P=0.0001) and HRCT–fibrosis score (r=0.62, P=0.003) (Fig. 4).In addition to interstitial lung disease, positive correlations of serum IL-6 levels with mean PAP (r=0.44, P=0.02), and peak PAP (r=0.55, P=0.002) were also noted. Moreover, there was negative correlation between serum IL-6 levels and right ventricle fraction area change (r=-0.48, P=0.03).

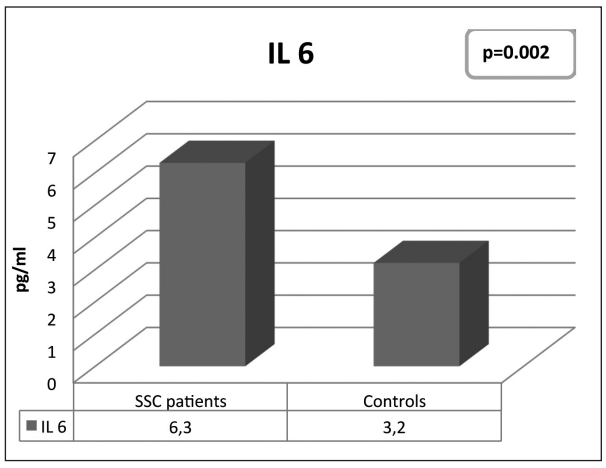

Fig. 3. Serum levels of IL-6 in patients with SSc versus controls

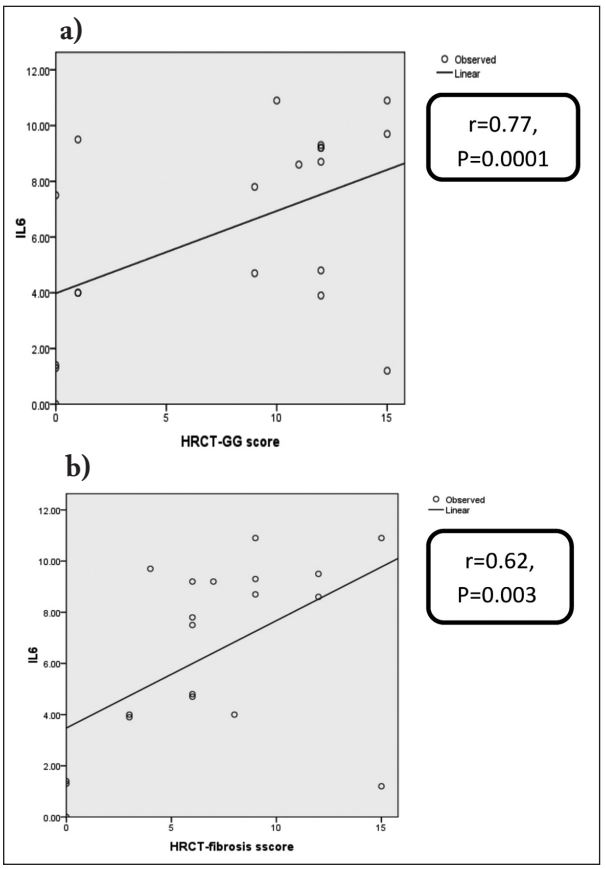

Fig. 4. Correlations between serum levels of IL-6 and HRCT scores (a, HRCT-GG score; and b, HRCT-fibrosis score) in SS-cpatients

Discussion

IL-6 is a multifunctional cytokine which is implicated in the pathogenesis of multiple chronic inflammatory diseases. Many investigations indicate that IL-6 may be involved in the pathogenesis of SSc. IL-6 levels were found to be increased in serum of SSc patients; the values were higher in diffuse versus limited subset of the disease (19) and in patients with alveolitis in comparison with patients without lung involvement (20).

We assessed the serum level of IL-6 in SSc patients and studied its relationships with EUSTAR score, SAQ, disability index and cardiopulmonary involvement (assessed by PFTs, 6MWT, ECHO, and HRCT abnormalities). Similar to previous reports, we demonstrate significantly higher levels of serum IL-6 in patients with SSc compared to controls (21, 22). The observed strong positive cor-

relation between IL-6 and EUSTARscore (r=0.64, P=0.002) suggests that IL-6 might contribute to the active stage of the disease, as postulated by Bosello et al. (23) and Jurisic et al. (24).

In the present study, serum levels of IL-6 showed moderately positive correlation with disease duration (r=0.49, P=0.03) which was reported by Jurisic et al. (24). Moreover, serum levels of IL-6 were moderately positively correlated with IRS (r=0.46, P=0.001), and IMS (r=0.45, P=0.049), while they weakly positively correlated with IVS (r=0.39, P=0.04), and these correlations were not reported previously.

Pulmonary function tests for our patients revealed restrictive pattern in 10 patients (50%) and 3 of them had normal HRCT and this restrictive function could be the result of sever skin and subcutaneous chest wall involvement. Meanwhile only 2 patients (10%) had obstructive pulmonary functions as airway disease is rare in SSc when compared to other collagen vascular disease which could be attributed to a history of smoking (25).The most frequent abnormal PFT in our patients is the decrease of DLCO (90%) either with or without a decrease of TLC. A reduced DLCO usually reflects restrictive and/or pulmonary vascular disease and correlates with the extent of lung disease on HRCT (26).

Reduced FVC and DLCO provide important prognostic information in SSc-ILD (26). Yet, our results confirm significant positive correlations between the 6MWD and FVC%, DLCO%, FEV1%, TLC%, and KCO%.

Our results revealed no correlation between serum level of IL-6 and FVC, or TLC and this coincides with Yousif et al. (27) results as they explained this finding to that these parameters are usually affected later than declined DLCO which is the early PFT abnormality encountered in patients with ILD.

HRCT pattern seen in SSc is generally nonspecific interstitial pneumonia (NSIP) with a greater proportion of ground glass opacities and a lower degree of coarse reticulation. However, a usual interstitial pneumonia (UIP) pattern can also be seen. Honeycomb cysts can be seen in up to a third of patients with SSc-ILD and are more common in patients with limited cutaneous SSc (28). In the present study, we found that 85% of the studied patients had ILD (detected by HRCT) with 60% of them had a ground glass pattern and 35% had reticular and or honeycombing findings.

In the present study, serum levels of IL-6 were strongly positively correlated with HRCT-GG and fibrosis scores, this was also supported by the correlation of IL-6 with functional lung impairment and exercise capacity as expressed by the DLCO reduction and 6MWD. This matches the results of De Santis et al. (20) study who used the same HRCT scoring system as described by Kazerooni et al. (15). They demonstrated significantly positive correlation between HRCT score and IL-6 plasma level (r=0.36, P=0.001) suggesting that patients with a greater extent of lung affection on HRCT had a more aggressive disease.

The reported rates of pulmonary arterial hypertension in scleroderma patients have been wide ranging (5 to 50%), depending on the methodology used and the cut-off value of PAP considered for diagnosis. Doppler echocardiography is a helpful means of assessing PAP (29). In the current study, 25-30% of SSc patients had pulmonary hypertension with restrictive pulmonary function, and a significant negative correlation was found between peak and mean of PAP, and 6MWD as reported by Villalba et al. (30). Serum levels of IL-6 were moderately positively correlated with mean PAP (r=0.44, P=0.02) and peak PAP (r=0.55, P=0.002) which reported by Gourh et al. (21).

Because ILD and PAH are both associated with restrictive defects, the FVC/DLCO ratio should be calculated. A proportionate reduction in FVC and DLCO, yielding an FVC/DLCO ratio of less than 1.6, suggests ILD rather than PAH. While if FVC/DLCO ≥1.6 and or TLC/DLCO ≥2 suggest a mixture of ILD and pulmonary vascular involvement (31). The present study identified 7 patients (35%) with FVC/DLCO ≥1.6 and 6 patients with TLC/DLCO >2 which suggesting presence of both ILD and PAH, and ECHO can proved increased PAP >35 mmHg in five of them (25%). In agreement with our results Launay et al. (32) reported the prevalence of both PAH and ILD and it varies from 15% to 22% in patients with SSc.

Whether in idiopathic pulmonary arterial hypertension "IPAH" or SSc-related pulmonary arterial hypertension "SSc-PAH", cardiac (particularly RV) function is the single most important determinant of survival and should be the focus of more investigation. Overbeek and colleagues (33) compared the relationship between mean RV pressure and stroke

volume in a limited number of patients with SSc-PAH and IPAH. Although both groups had similar right atrial pressure and cardiac index, patients with SSc-PAH demonstrated lower stroke volumes for any given mean RV pressure, suggesting significantly impaired RV contractility.

In the current study, there was a significant difference of RV systolic function parameters (RV FAC & TAPSE) in SSc patients vs controls (41.1vs 50.7, P=0.001 and 1.4 vs 1.7, P=0.03 respectively). On the other hand, there was no significant difference according to LVEF between SSc patients and controls (66.6 vs 72, P=0.15). Considering RV and LV inflow velocities, it was found that E/e' of MV and TV were significantly higher in patients than controls (8.8 vs 4.6, P=0.0001 and 5.7 vs 4.4, P=0.009 respectively). This is in agreement with the results of Jurisic et al. (24) who found that LVEF had no difference between patients and controls (68 vs 65, P=0.24) and E/e' was significantly higher (4.3 vs 3.38, P=0.008) in SSc patients.

Values of the IRS were higher in patients with lung fibrosis, restrictive lung dysfunction and/or decreased lung diffusing capacity, than in patients with normal pulmonary function (34). In the present study, IRS was positively correlated with FVC%/DLCO%, TLC%/DLCO%, peak and mean of PAP. These results documents usefulness of IRS in assessment of cardiopulmonary involvement in SSc patients.

In conclusion; serum IL-6 is higher in SSc patients than healthy controls. A positive correlation of serum IL-6 with EUSTAR score and index of respiratory system and their association with DLCO, 6MWD, HRCT scores, and echocardiographic abnormalities of right side of the heart support the role of IL-6 in the disease activity and in the development of cardiopulmonary manifestations in SSc patients. Further studies using large series may lead to more significant results.

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