Evaluation of the functional parameters in scleroderma cases with pulmonary involvement

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ÖZET

Skleroderma akciğer tutulumu olan hastalarda fonksiyonel parametrelerin değerlendirilmesi

Bu çalışmanın amacı skleroderma akciğer tutulumu olan hastalardaki fonksiyonel değişikliklerle tanısal testler arasındaki ilişkiyi irdelemek ve erken tanıda yardımcı olabilecek testleri saptamaktır. Bu prospektif çalışmaya 33 tane skleroderma akciğer tutulumu olan hasta dahil edildi. Solunum fonksiyon testleri yapılıp, ekokardiyografileri çekilen, arter kan gazları alınan hastalara altı dakika yürüme testi uygulandı. Yüksek rezolüsyonlu bilgisayarlı tomografileri çekilen hastalar; NYHA fonksiyonel sınıflandırması ve Borg dispne indeksine göre sınıflandırıldı. Hastalardan ayrıca SGRQ yaşam kalitesi anketini cevaplandırmaları istendi. Hastalarımızda en erken etkilenen fonksiyonel parametrenin %DLCO olduğu görüldü. %DLCO/%FVC oranının pulmoner arteryel hipertansiyonu noninvaziv olarak saptamadaki duyarlılığı düşük bulundu. SGRQ yaşam kalitesi anketinin ise tüm fonksiyonel parametreler ile korele olduğu saptandı. Skleroderma tanısı alan hastalar mutlaka pulmoner tutulum açısından değerlendirilmeli ve asemptomatik dahi olsalar bu açıdan takip edilmelidirler. Solunum fonksiyon testleri, ekokardiyografi, toraks yüksek rezolüsyonlu bilgisayarlı tomografi, altı dakika yürüme testi skleroderma akciğer tutulumunda tanı ve takipte kullanılan faydalı testlerdir. NYHA fonksiyonel sınıflandırması, Borg dispne indeksi ve MRC de erken tanıda yardımcıdır. SGRQ yaşam kalitesi anketi tanı ve takipte hastaların egzersiz kapasitesini belirlemede noninvaziv olarak kullanılabilecek faydalı bir testtir.

Anahtar Kelimeler: *DLCO, pulmoner hipertansiyon, 6 dakika yürüme testi, SGRQ.*

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SUMMARY

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To evaluate the relationship between functional changes in the scleroderma patients with pulmonary involvement and the diagnostic tests and to identify the tests that may be helpful in early diagnosis. In this prospective study, 33 scleroderma patients with pulmonary involvement were included. Pulmonary function tests, echocardiography, arterial blood gases, six minute walk tests, thorax high resolution computed tomography were performed and all patients were classified according to MRC dyspnea scores and NYHA(WHO) functional classification. Patients were also asked to conclude Saints Georges Respiratory Questionnaire (SGRQ). DLCO% found to be the earliest deteriorated parameter in our patients. Sensitivity of FVC%/DLCO% ratio, for detecting pulmonary arterial hypertension as a noninvasive method, was found low. SGRQ was found to be correlated with all functional parameters used in scleroderma follow up. Patients with scleroderma should be evaluated for pulmonary involvement and must be followed up ever if they were asymptomatic. Pulmonary function tests, echocardiography, thorax high resolution computed tomography, six minute walk tests are valuable tools that should be used in diagnosis and follow up. NYHA (WHO) functional classification, MRC and Borg dyspnea scores are also helpful for early diagnosis. SGRQ can also be helpful to evaluate the patients functional capacity in diagnosis and follow up as a non invasive parameter.

Key Words: *Carbon monoxide diffusion of the lungs (DLCO), pulmomary hypertension, 6MWD, scleroderma, St. George's respiratory questionnaire.*

Scleroderma is a chronic multisystemic disease of unknown origin, characterized by fibrosis on the connective tissue of skin and internal organs, vascular obliteration and increased synthesis of extracellular matrix (1-4). Pulmonary involvement is in the fourth place just after skin, peripheral vessels and esophagus. This involvement starts in the early stages of the disease but can be documented in late stages. It is progressive and affects mortality and morbidity (5). There are two kinds of pulmonary involvement: interstitial lung disease and pulmonary vascular involvement. More common occurrence is interstitial involvement. Due to its significance in prognosis of the disease, early diagnosis is very important. Close follow up of these patients with various functional tests is utmost importance. For this reason we evaluated the relationship between functional changes in cases with the diagnostic tests. With this, we aim to identify the tests that will be helpful in early diagnosis.

MATERIALS and METHODS

Patients who admitted to Clinical Immunology and Rheumatology Department or Respiratory Diseases Clinic of Ankara University School of Medicine between October 2005 and December 2007 were evaluated. The study was then explained to the patients who were diagnosed with scleroderma according to the criteria of American Rheumatology Association and also who were shown to have radiological pulmonary involvement. Among those patients, 33 were included to the study after taking informed consent. Detailed histories were taken; and after physical examination, dyspnea levels were identified according to the MRC dyspnea scale. Chest X-rays were obtained and evaluated for pulmonary involvement. All patients, regardless of the outcome of X-rays, undergone computerized tomography (CT), due to its sensitivity and its efficiency in identifying pulmonary involvement in patients with negative chest X-rays (2). Thorax CTs were performed as high resolution computerized tomography (HRCT) with 10 mm slices.

Pulmonary function tests (PFT) were performed under room air; in upright sitting position with Vmax 229 Sensor Mediks PFT machine and Carbon monoxide diffusion test for the lungs (DLCO) were done with single breath method. In one case, PFT and diffusion test could not be performed since PFT mouthpiece cannot be applied due to extreme fibrosis on mouth. Another patient did not cooperate with the tests. Radial artery blood samples were taken and blood gas analyses were done with COBAS B 121 machine. Patients were grouped according to MRC and WHO (NYHA) functional classification. Six minute walking test (6MWT) was performed to evaluate exercise capacities. Two patients; due to deep ulcerations and toe amputations; and 2 patients; due to severe fibrosis on knee joints could not perform the test. Twenty nine patients walked in a corridor with a known length for 6 minutes. Oxygen saturations were measured with finger saturation probes before and after the test. Degrees of shortness of breath were calculated according to Borg dyspnea index. The patients who had desaturations and who had 6 minute walking distance (6MWD) less than 380 meters were accepted to have poor functional status. The studies about PHT used 380 meters as a cut off value since it was found that the mortality is higher in the patients who had lower values than 380 m (6,7).

Pulmonary hypertension (PHT) was evaluated using echocardiography, a non-invasive screening method. All echocardiographic evaluations were performed with H.P. 5500 Sony Doppler Echo Machine. Ventricular dimensions and functions were assessed. Systolic pulmonary artery pressures were calculated using tricuspid insufficiency flow. Values of sPAP above 35 mmHg were considered as PHT (8).

Finally, patients were asked to complete SGRQ survey, which consists of 76 questions on quality of life. The aim of this survey was to define the symptoms and activities of the patients as well as the degree of disease. Statistical analysis was done with SPSS 14.0. Means, medians and standard deviations of each parameter was calculated separately. Spearman's rho correlation coefficient of parameters was calculated.

RESULTS

Among 33 patients that were included to the study, 28 were female (84.2%), 5 were male. 26 (78%) cases had diffuse scleroderma, whereas 7 (%21) cases had limited type. Average age was 52.7 ± 9.8, average disease duration was 11.24 years and average duration of Raynaud's phenomenon was 10 years. Majority of the patients complained about shortness of breath and purpling in fingers. Rales were present in more than half of the patients during physical examination (66%). Smoking ratio was low (18.2%). Majority of the patients fitted in functional class II of WHO (NYHA) functional classification and; dyspneas were evaluated according to MRC and majority was in MRC III class (Table 1). Arterial blood gas analysis revealed 39.4% to be normoxemic, and 51.5% to be mild hypoxemic. sPAP values of 23 patients were within normal ranges and in 10 cases the values were above 35 mmHg thus they were found to have PHT. Two cases had severe, 3 had moderate and 5 had mild PHT (Table 2). When respiratory functional parameters of the patients were observed; FEV_1%, FVC%, FEA 25-75% and FEV_1/FVC% were found to be within normal ranges but mean DLCO% were lower.

Table 1. Distribution of patients according to NYHA and MRC.

	NYHA		MRC	
	n	%	n	%
I	5	15.2	9	27.3
II	15	45.5	8	24.2
III	10	30.3	11	33.3
IV	3	9.1	5	15.2

Table 2. Distribution of patients according to sPAP values.

	n	%
sPAP < 35 mmHg	23	69.7
sPAP 36-45 mmHg	5	15.2
sPAP 46-55 mmHg	3	9.1
sPAP > 56 mmHg	2	6.1

Among all patients only 13 had restrictive defects. Out of 31 patients who undergone DLCO test, 27 had lower scores.

Among the patients who had a positive correlation between disease duration and duration of Raynaud's phenomenon, the DLCO% was observed to decrease as the duration increased (Figure 1). There was also a positive correlation between DLCO% and other PFT parameters. FVC%/DLCO% ratios were calculated and in 11 patients it was over 1.8. Only 3 of them had isolated PHT. DLCO% had a negative correlation with sPAP ($p< 0.05$) (Figure 2). Patients who had PHT have lower DLCO% (Figure 2) and SaO_2%; and higher SGRQ scores. They also had higher Borg and MRC dyspnea scores and had advanced NYHA functional classes. There was a inverse relationship between 6MWD and sPAP ($p= 0.001$); and also negative correlations between 6MWD and Borg ($p< 0.05$), MRC ($p< 0.0001$) and WHO (NYHA) functional parameters ($p< 0.005$).

There were negative correlations between SGRQ symptom, activity, involvement total scores and 6MWD (Figure 3); whereas there were a positive correlation between sPAP, NYHA, Borg and MRC. The correlation between SGRQa, SGRQi, SGRQt scores and SaO_2%, DLCO% were negative. The difference of sPAP values between diffuse and limited scleroderma patients was statistically significant. The values were higher in limited scleroderma cases.

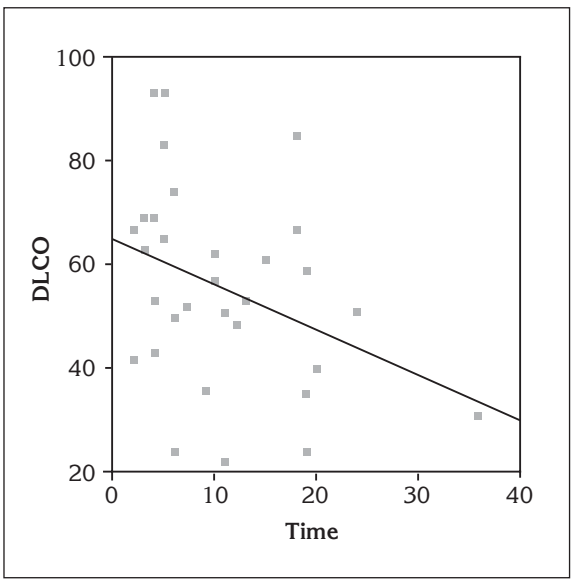

Figure 1. Correlation between DLCO% and disease duration ($p< 0.05$, $r= -400$).

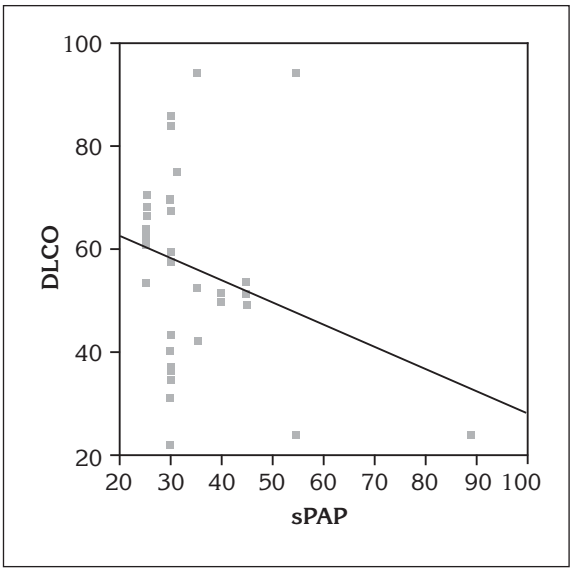

Figure 2. Correlation between DLCO% and sPAP ($p< 0.05$, $r= -400$).

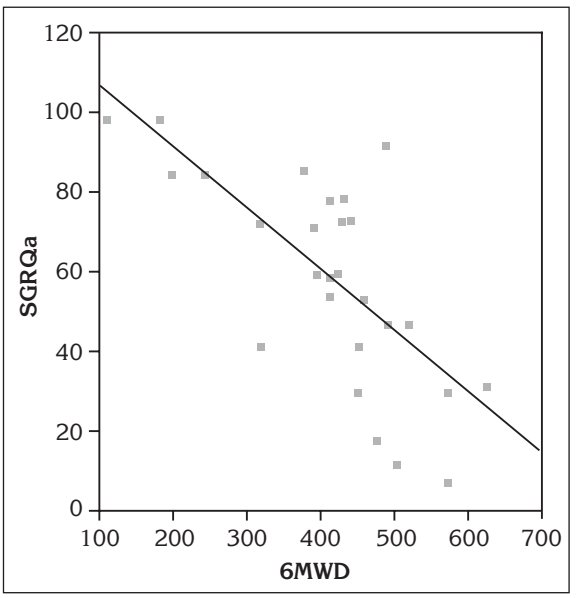

Figure 3. Correlation between SGRQa and 6MWD ($p< 0.0001$, $r = -685$).

DISCUSSION

Scleroderma is rarely encountered in population, and among connective tissue diseases; it's the most common cause of pulmonary involvement. The disease is categorized as diffuse or limited according to the degree of skin involve-

ment and literature says that limited form of the disease is more common in population. Seventy eight percent of our patients were diffuse and 21% were limited. Manoussakis et al. conducted a study with a similar distribution of disease as in our study (9). There is no data about the distribution pattern of the disease in Turkish population in the literature. Due to limited patient size of our study, it's not appropriate to generalize the ratios obtained. Further epidemiologic studies should be carried out on the subject.

Changes in the lungs start at the early stages of disease but certain time passes till it gets diagnosed. Disease at early stages usually missed with a plain chest X-ray, because of this, patients should be evaluated with HRCT. Harrison et al. showed pathological findings on HRCT in 44% of the cases suspected of pulmonary involvement with normal chest X-rays (2). In our study, we also had 15 (45%) cases who had normal chest X-rays, but all showed pathological changes in HRCT.

Although all patients had some findings in their HRCTs, restrictive defect was present in PFTs of 13 (36.3%) patients. This lead us to think the pulmonary involvement of the patients were at early stages. 81.1% (n= 27) of 31 patients that single breath carbon monoxide (CO) diffusion test could be performed had low DLCO%. This supported the knowledge on literature that DLCO% is the first functional parameter to change (2,4,10,11). Stupi, Steen and Medsger conducted studies on scleroderma patients and showed that a decrease in DLCO% starts 1-9 years prior to the diagnosis of the disease in 15-30% of the patients (12,13). Apart from this, DLCO% is also the earliest functional indicator of interstitial involvement. A decrease in DLCO% can be observed even in disease duration of 1 year or less.

Lewis et al. checked the relation between DLCO% and the other functional parameters; they found a positive correlation between DLCO% and FVC%. Scheja et al. reached the same conclusion (11). We also found a positive correlation between FVC% and DLCO% (p= 0.009). In the study conducted by Stupi et al. about pulmonary hypertension on patients with CREST syndrome; DLCO% was found to be significantly decreased (14). Mukerjee et al. found a weak correlation between sPAP and DLCO% (15). In our study DLCO% was significantly decreased in all patients with high sPAP values and this relation was found to be statistically significant ($p< 0.05$). This relation between DLCO%, s PAP and FVC% suggests that, single breath CO diffusion test could obtain information on early stages of pulmonary involvement of scleroderma. This data also supports the data in the literature that DLCO% is correlated with the severity of the disease in secondary PHT; and correlated with how widespread is the disease in case of secondary interstitial lung disease (16,17). As a result, we came into the conclusion to closely follow up the patients who have low DLCO% values for lung involvement.

FVC% and DLCO% decrease in same rate in interstitial lung disease seen in scleroderma but DLCO% decrease rate is more prominent in isolated PHT seen in scleroderma. Because of this, it would be more appropriate to use FVC% and DLCO% together. According to literature, the chance to develop interstitial disease is higher in patients when the ratio is below 1.4. Risk of developing isolated PHT dominates when the ratio goes over 1.8 (18). Launay et al. found higher ratios of FVC%/DLCO% in patients having PHT without interstitial lung disease (19). Stupi et al. had supporting results in their study (20). When we categorized the patients according to their FVC%/DLCO% ratios, 11 patients had values over 1.8. Isolated PHT was present in 3 patients out of 11 and all 3 were lScl. Hsu et al. compared MRI, echo and FVC%/DLCO% as non-invasive tests with catheter for detection of PHT. Sensitivity and specificity of FVC%/DLCO% ratio was found to be 71% and 72% respectively (21). Our study revealed 28% sensitivity and 66% specificity of FVC%/DLCO% ratio for purposes of detecting PHT. We interpreted this as a result of small size of patient population and the fact that majority of the patients were in the early stages of disease, thus did not develop PHT. Studies consisting large number of patients are needed to establish the reliability of FVC%/DLCO% ratio in non-invasive detection of PHT.

We observed that; as the DLCO% and FVC% decreased, PaO_2 and as a further result SaO_2% decreased ($p< 0.05$). As sPAP increased, patients' PaO_2 and SaO_2% values were found to decrease. Karabiyikoglu et al. showed a signifi-

cant negative correlation between mean PAP value obtained by right heart microcatheterisation method and SaO_2% and PaO_2 (22). Our study revealed a significant relation between the decrease in SaO_2% value and the increase in sPAP ($p< 0.02$). Since SaO_2% is the best indicator of survival in PHT (23); its decreased values in patients with increased sPAP could be explanatory for increased mortality.

PHT in scleroderma is detected in 5-50% of patients depending on the method used (24). In our study we chose Doppler echocardiography to detect PHT. sPAP > 35 mmHg is considered as PHT. In 3 patients who had isolated PHT, sPAP was found to be significantly higher. This was consistent with the knowledge in the literature. MRC and Borg dyspnea indexes are also correlated with sPAP and this result brings forth the necessity of further studies for lung involvement in patients with high dyspnea scores. Negative correlation between FVC% and NYHA, Borg and MRC further supports this. DLCO% is the first parameter affected in scleroderma and its strong correlation with NYHA functional score and MRC dyspnea index may help to show lung involvement and early diagnosis in scleroderma. Patients with high NYHA and MRC should be further studied and followed up.

6MWT is a valid test in determining exercise capacity in both PHT variant and interstitial lung disease variant (4,25). Negative correlation between 6MWD and dyspnea scores and functional classification leads that 6MWD is correlated with disease severity and it makes this test a valid tool for evaluating exercise capacity. Previous studies on PHT stated that patients who walked under 380 meters had higher mortality rates and 380 meters was defined as a cut-off (6,7). For all these reasons, we used that value as a cut-off as well.

We gave all the patients in the study the SGRQ quality of life questionnaire and found all 4 scores to be negatively correlated with FEV_1%, FEV_1 mL/sc, FVC% and FVCml. Although there were no statistically significant relation between 6MWD and DLCO%; SGRQa and DLCO% were correlated (Figure 4). We thought that SGRQa score can helpful in evaluating exercise capacity of patients at early stage, alongside 6MWT. Also, all parameters being directly proportional with

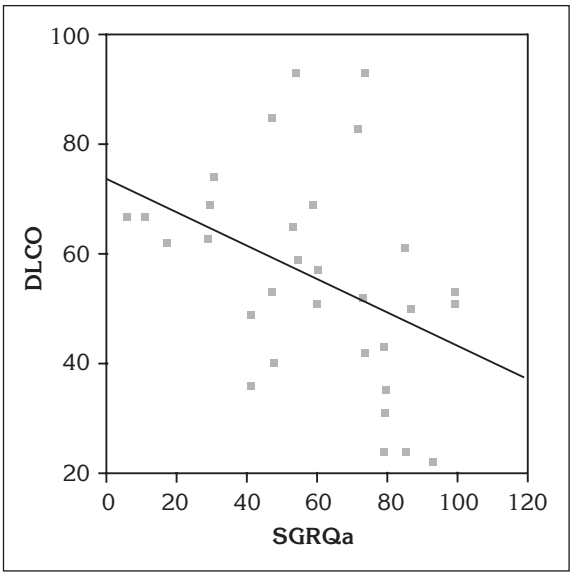

Figure 4. Correlation between DLCO and SGRQa (p= 0.005, r= -496).

sPAP, shows the importance of SGRQ in scleroderma patients with PHT. All 4 scores were inversely correlated with walking distance, but there were no significant relation with desaturations percentage. Strongest relation was found with SGRQa score ($p< 0.0001$, r= -685). Beretta et al. got similar results and reached the conclusion that SGRQ is an effective test for evaluating exercise capacity and can be used to determine daily activity status of patients who cannot perform 6MWT (26). Our results are supporting this idea.

To conclude; statistically significant relationships were found between PFT, sPAP and 6MWT which are used in diagnosis and follow up patients. Dyspnea scores and NYHA functional classification are also correlated with PFT, Echo and 6MWT in regard to reflect the status of the patients. SGRQ scores are found to be correlated with other follow up tests and this leads to the fact that they can be safely used to evaluate the quality of life of patients. FVC%/DLCO% ratio can be alerting for development of isolated pulmonary hypertension but the most sensitive non-invasive test to detect that is echocardiography. DCLO%, SGRQa, MRC and NYHA classification are all helpful in detecting pulmonary involvement. So it's suggested that patients with low DLCO% or high SGRQ a, MRC and NYHA should be closely followed up for pulmonary involvement.

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