J Musculoskelet Neuronal Interact 2023; 23(4):489-497

Journal of Musculoskeletal and Neuronal Interactions JMNI

Original Article

Determinants of Six-Minute Walk Test Performance in Women with Systemic Sclerosis

Nazenin Hande Sezgin[1], Serap Acar[1], Sema Savci[1], Buse Ozcan Kahraman[1], Aylin Tanrıverdi[1], Aydan Köken Avşar[2], Ahmet Merih Birlik[2]

[1]School of Physical Therapy and Rehabilitation, Dokuz Eylul University, Izmir, Turkey;
[2]Faculty of Medicine, Department of Rheumatology, Dokuz Eylul University, Izmir, Turkey

Abstract

Objectives: The aim of this study was to investigate the determinants of six-minute walk test (6MWT) distance in women with systemic sclerosis. **Methods**: In this cross-sectional study, 36 women with systemic sclerosis were assessed using the Medsger Systemic Sclerosis Severity Scale (MSS), modified Rodnan Skin Score (mRSS), Health Assessment Questionnaire (HAQ), University of California Scleroderma Clinical Study Consortium Gastrointestinal Tract Scale, quadriceps strength measurement, Milliken Activities of Daily Living Scale (MAS), and International Physical Activity Questionnaire. The 6MWT was performed to assess the participants' functional capacity and examine factors affecting functional capacity. **Results**: 6MWT distance was moderately associated with disease severity, with 14 participants walking less than 80% of the predicted distance. 6MWT distance was also significantly correlated with spirometry values and MSS, mRSS, HAQ, and MAS scores ($p<0.05$). In linear regression analysis, MSS and MAS scores were identified as independent predictors of 6MWD and accounted for 42.5% of variance ($R^2 = 0.425$). **Conclusion**: Disease severity and activities of daily living are independently associated with functional capacity in women with scleroderma, with MSS and MAS scores accounting for 42.5% of variance in 6MWT distance in the linear regression model.

Keywords: Activities of Daily Living, Disease Severity, Functional Capacity, Pulmonary Effect, Systemic Sclerosis

Introduction

Systemic sclerosis (scleroderma) is a chronic inflammatory connective tissue disease affecting the visceral organs including the kidney, lungs, and heart, but also causing vascular and skin involvement[1]. The articular manifestations of scleroderma also cause musculoskeletal system disorders and impaired motor functions. Muscle, bone, and joint involvement in scleroderma can interfere with activities of daily living (ADL) and negatively affect functional capacity[2]. Therefore, functional capacity is limited in patients with scleroderma, especially those with cardiopulmonary and musculoskeletal symptoms[3]. Previous studies have demonstrated reductions in functional capacity and peak oxygen consumption in individuals with scleroderma[4]. Pulmonary systemic involvement, reduced muscle strength in the lower extremities, and pain act in concert to reduce functional and aerobic capacity in individuals with scleroderma[5]. These common symptoms initiate a vicious cycle that causes further decrease in physical functioning and health-related quality of life, leading to rapid deterioration of physical condition and reduced functional capacity[6].

The six-minute walk test (6MWT) is among the methods used to evaluate exercise capacity in individuals with scleroderma. The outcome measures of this test are distance covered and percentage of predicted distance. In this simple, noninvasive, reproducible clinical exercise test, distance walked is recorded to determine the individuals' exercise capacity. This exercise test is used to assess both scleroderma progression and its effects on pulmonary function[7]. Baseline 6MWT distance (6MWD) values of scleroderma patients

The authors have no conflict of interest.

Corresponding author: Serap Acar, PT, PhD, Assoc. Prof. Mithatpaşa Street No: 1606 İnciraltı Health Campus Balçova, İzmir, Turkey
E-mail: acarserap2@gmail.com
ORCID: 0000-0001-8226-1543

Edited by: G. Lyritis
Accepted 31 October 2023

without pulmonary arterial hypertension (PAH) have not yet been analyzed. However, 6MWD may guide the establishment of realistic treatment targets for individuals with scleroderma at risk of developing PAH[8].

Scleroderma is characterized by extrapulmonary manifestations such as skin fibrosis, musculoskeletal and cardiac involvement, and anemia. The modified Rodnan Skin Score (mRSS) is a semiquantitative clinical assessment tool that evaluates the severity and extent of skin involvement in scleroderma patients, and a score of ≥20 is considered an indicator of skin sclerosis, severe internal organ involvement, and mortality[9]. The presence of any of these conditions or multiple organ involvement may limit 6MWD[10]. Therefore, the aim of this study was to investigate the determinants of 6MWD in women with scleroderma. We hypothesized that there is a relationship between 6MWT and clinical and functional parameters in scleroderma patients without PAH.

Materials and Methods

Patients

The study participants were 18–75 years of age and had been diagnosed with scleroderma according to the 2013 criteria of the American Rheumatology Association/European Rheumatology Association. Participants were recruited from the scleroderma outpatient clinic of the rheumatology department of Dokuz Eylul University. The participants were enrolled in the study between June 2018 and June 2019 and evaluated in the Dokuz Eylul University School of Physical Therapy and Rehabilitation.

A G-Power analysis was used to determine the sample size. For 80% power, error margin of 0.05, and effect size of 0.257 according to the 6MWD variable, the minimum number of patients required was calculated as 36[11]. Women aged 18–75 years who were diagnosed with scleroderma, visited the rheumatology outpatient clinic, and had a hemoglobin level higher than 10 g/dL were included in the study. Those with a left ventricular ejection fraction less than 50%, PAH, cardiac arrhythmia, neurologic or cognitive impairment, acute or chronic kidney disease, active inflammatory arthritis, malignancy, pregnancy, active ischemic skin ulcers, or history of orthopedic or related surgery were excluded from the study.

The participants' demographic and clinical characteristics were recorded. Disease severity and prognosis were evaluated with the Medsger Systemic Sclerosis Severity Scale (MSS), and skin thickness was assessed with the mRSS. Pulmonary function was assessed as static and dynamic lung capacities. Functional capacity was assessed by 6MWT. Quadriceps muscle strength was assessed with a handheld dynamometer and disability level was assessed using the Health Assessment Questionnaire (HAQ). Gastrointestinal tract involvement was assessed with the University of California Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0 instrument (UCLA SCTC GIT 2). The Milliken Activities of Daily Living Scale (MAS) was used to evaluate upper extremity function in ADL. Physical activity level was assessed with the International Physical Activity Questionnaire (IPAQ).

Evaluation Protocol

Disease Severity Assessment

Disease severity and prognosis were evaluated with the MSS, which consists of 9 questions scored between 0 and 4 points. A total score higher than 3 indicates severe disease[12].

Skin Involvement Assessment

The mRSS is a reliable tool to evaluate cutaneous involvement in sclerosis by assessing skin thickness. It is based on 17 different regions, including the face, neck, thorax, abdomen, shoulders, hands, legs, and feet, each scored from 0 to 3 (0 = normal, 1 = mild thickness, 2 = moderate thickness, 3 = severe thickness). The scores are then summed (total score of 0–51), with a higher total score indicating greater skin involvement[13].

Pulmonary Assessment

Pulmonary function testing was performed to assess pulmonary involvement[14]. Static and dynamic lung capacities were evaluated using the SensorMedics model 6200 BodyBox spirometer (Viasys Healthcare Inc., USA). Forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, total lung capacity (TLC), and diffusing capacity for carbon monoxide (DLCO) values previously recorded by the physician were obtained from the individuals' medical records.

PAH was diagnosed by right heart catheterization according to the criteria in the 2015 European Society of Cardiology/European Respiratory Society Guidelines[15].

To determine the severity of interstitial lung disease (ILD), the following scores were used in high-resolution computed tomography assessment; 0 = no interstitial changes; 1 = thickened septal lines, subpleural lines, parenchymal bands, and subpleural cysts; and 2 = honeycombing. In the modified ILD scoring from 0 to 3, microcystic honeycombing is scored as 2, and a score of 3 is assigned if more than 25% of the honeycombing area was macrocystic. Scores from 6 sections in different parts of the lung were summed to yield a total score between 0 and 18, with higher scores indicating more severe lung involvement[16].

Functional Capacity

Functional capacity was assessed with the 6MWT, performed as recommended by the American Rheumatology Association[17]. The 6MWT is simple to apply and has high reproducibility in clinical settings. It is also useful for monitoring disease progression and treatment results and is commonly used for patients with scleroderma. During the 6MWT, participants walked as fast as they could along a 30-m corridor marked at 3-m intervals for 6 minutes. The

Table 1. Demographic Characteristics and Evaluation Results.

N=36	Median (IQR)	Range
Age (years)	55.00 (50.00-63.00)	32-72
Height (cm)	157.50 (155.00-162.75)	145-170
Weight (kg)	64.50 (58.50-75.75)	48-93
BMI (kg/m^2)	25.51 (24.05-29.03)	19.47-38.04
MSS	4.00 (3.00-6.00)	1-9
mRSS	4.50 (0-10.25)	0-21
FEV_1 (L)	1.94 (1.74-2.24)	1.06-2.68
FEV_1 (% predicted)	86.80 (75.37-99.20)	44.70-120.20
FVC (L)	2.44 (2.13-2.80)	1.20-3.24
FVC (% predicted)	93.20 (78.00-100.70)	40.90-115.40
FEV_1 /FVC (%)	82.60 (78.98-86.82)	67.61-91.46
TLC (L)	4.34 (3.70-4.75)	2.47-5.99
TLC (%predicted)	91.00 (76.55-99.90)	48.00-135.00
DLCO (L)	5.84 (4.64-6.66)	2.77-9.60
DLCO (% predicted)	70.00 (63.00-87.00)	36.00-126.00
Dominant quadriceps strength (kg)	17.33 (15.04-20.11)	11.50-25.60
Dominant quadriceps strength (% predicted)	60.14 (49.68-72.75)	33.63-88.34
HAQ	0.25 (0.00- 0.56)	0-1
UCLA SCTC GIT-2	0.23 (0.08-0.41)	0-1.25
MAS	640.50 (586.75-658.50)	432-675
IPAQ	321.75 (145.50-664.12)	0-1466
6MWD (m)	430.00 (401.25-471.25)	322.50-525.00
6 MWD (%predicted)	84.99 (73.99-92.51)	60.48-99.88

BMI: body mass index, FEV_1: forced expiratory volume in the first second, FVC: forced vital capacity, TLC: total lung capacity, DLCO: diffusing capacity for carbon monoxide, MSS: Medsger Systemic Sclerosis Severity Scale, HAQ: Health Assessment Questionnaire, mRSS: modified Rodnan Skin Score, UCLA SCTC GIT 2: University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0, MAS: Milliken Activities of Daily Living Scale, IPAQ: International Physical Activity Questionnaire, 6MWD: Six Minute Walk Distance, IQR: interquartile range.

normative 6MWD values of the individuals were determined using the equation developed by Jay et al.[18].

Muscle Strength

Quadriceps muscle strength was assessed with a handheld dynamometer (Lafayette, IN, USA). This simple and noninvasive method is reliable for evaluating quadriceps muscle strength in individuals with chronic pulmonary disease. The measurement was made in the sitting position, with the popliteal region in contact with the floor and with the leg supported. The procedure was repeated 3 times on both the right and left side. The mean values were recorded in kilograms[19]. The normative quadriceps muscle strength values of the individuals were determined with the equation developed by Andrews and Bohannon et al.[20].

Disability Level

Disability level was assessed using the HAQ, which was developed by Fries et al. in 1980 to evaluate physical disability in individuals with rheumatoid arthritis. The HAQ consists of 20 items in 8 subscales: dressing, rising, eating, walking, hygiene, reaching, gripping, and common ADLs. Each item is scored from 0 to 3 points, with the highest score in each subscale used as its score and the average of the subscale scores used to obtain a total score ranging from 0 to 3. Higher scores indicate greater disability[21].

Gastrointestinal System Assessment

Gastrointestinal system assessment was done using the UCLA SCTC GIT 2.0, which is a questionnaire specific to systemic sclerosis that assesses quality of life related to health and gastrointestinal symptoms. The questionnaire consists of 34 items in 7 scales (e.g., reflux, constipation, distention). Higher score reflects more severe gastrointestinal symptoms[22].

Activities of Daily Living

The MAS was used to assess upper extremity activity limitation in the performance of ADLs. This instrument

consists of 47 items that evaluate gross and fine motor function in areas such as dining, cooking, dressing, object manipulation, and cleaning. The instrument evaluates both ability and need for each ADL. After multiplying these values, the scores for each item are summed for ability level. In the combined scoring procedure, each item is scored up to 15 points for a maximum score of 705 points. Higher score reflects better functioning. The Turkish version of this questionnaire was validated by Akel et al.[23].

Physical Activity Level

Physical activity level was assessed using the IPAQ, which consists of 7 questions regarding time spent walking, sitting, and engaging in light, moderate, and vigorous activity[24]. These times are then multiplied by each activity's metabolic equivalent (MET) values. This questionnaire has been validated for use in Turkish populations[25].

Statistical Analysis

Data obtained from the present study were analyzed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY). Descriptive statistics for numerical variables were expressed as median and interquartile range or minimum and maximum values. The normality of the data was assessed using distribution histograms, probability graphs, and Shapiro–Wilk test. Pearson and Spearman correlation analyses were used for normally and non-normally distributed data, respectively. Correlation coefficients lower than 0.25 were interpreted as very weak correlation; 0.25–0.50 as weak correlation; 0.50–0.75 as moderate correlation, and higher than 0.75 as good to excellent correlation[26]. 6MWD as an indicator of functional capacity was evaluated in a linear regression model including statistically significant dependent and independent variables using the Enter Method. The statistical significance level for all tests was $p<0.05$.

Results

The 36 women who participated in the study had a median age of 55 (range: 32–72) years (Table 1). Of these patients, 17 (47.2%) had limited cutaneous systemic sclerosis (lcSSc), 17 (47.2%) had diffuse cutaneous systemic sclerosis (dcSSc), and 2 (5.55%) had systemic sclerosis sine scleroderma. The median MSS and MAS scores were 4 and 640.5, respectively. Median HAQ score was 0.25. In the pulmonary function test, FEV_1/FVC, FVC, and DLCO parameters were within normal range. Median dominant quadriceps muscle strength was 17.33 kg and the median 6MWD was 430 m. 6MWD was below 80% of predicted in 14 patients (Table 1).

When patients' main clinical and laboratory characteristics were analyzed, disease subset was classified as lcSSc and dcSSc. According to this classification, the patients' disease distribution was 56.1% lcSSc and 43.9% dcSSc. Serological specificity was categorized according to antibody profile. No

Table 2. Patients' Main Clinical and Laboratory Characteristics.

	n (%)
Disease subset lcSSc/dcSSc	23 (56.1) / 18 (43.9)
Serological specificities	
Negative	10 (24.4)
Anti-centromere negative/positive	14 (34.1) / 17 (41.5)
Anti-Scl70 negative/positive	16 (39) / 15 (36.6)
Comorbidities	
ILD	11 (26.8)
ILD score (mean ± SD)(range)	3.63 ± 3.84 (0 – 16)
PAH	4 (9.8)
Medical treatment	
Corticosteroid negative/positive	17 (41.5) / 24 (58.5)
Immunosuppressive negative/positive	19 (46.3) / 22 (53.7)
Patient follow up duration (years) (mean ± SD)(range)	10.70 ± 4.49 (5 – 18)

lcSSc: limited systemic sclerosis, dcSSc: diffuse systemic sclerosis, ILD: interstitial lung disease, SD: standard deviation.

Table 3. Correlations Between Variables.

N=36	6MWD	
	r	P
MSS	**-0.545**	**0.002***
mRSS	**-0.528**	**0.003***
FEV_1 (L)	**0.393**	**0.032***
FEV_1 (% predicted)	0.224	0.235
FVC (L)	**0.504**	**0.005***
FVC (% predicted)	0.357	0.053
FEV_1/FVC (%)	**-0.453**	**0.012***
TLC (L)	**0.413**	**0.026***
TLC (% predicted)	0.300	0.114
DLCO (L)	0.280	0.157
DLCO (% predicted)	**0.399**	**0.044***
Right quadriceps strength (kg)	0.046	0.796
HAQ	**-0.392**	**0.018***
UCLA SCTC GIT 2	-0.104	0.546
MAS	**0.472**	**0.004***
IPAQ	0.234	0.170

*FEV_1: forced expiratory volume in the first second, FVC: forced vital capacity, TLC: total lung capacity, DLCO: diffusing capacity for carbon monoxide, MSS: Medsger Systemic Sclerosis Severity Scale, HAQ: Health Assessment Questionnaire, mRSS: modified Rodnan Skin Score, UCLA SCTC GIT 2: University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0, IPAQ: International Physical Activity Questionnaire, MAS: Milliken Activities of Daily Living Scale, 6MWD: Six-Minute Walk Distance, r: Spearman's rho, *p<0.05.*

Table 4. Linear Regression Model Assessing the Associations Between 6MWD and Systemic Sclerosis Characteristics.

6MWD					
	B	SE	Beta	t	P
Constant	-175.895	229.966	-	-0.765	0.452
MAS	0.903	0.382	0.623	2.363	**0.026***
MSS	-8.883	4.093	-0.313	-2.170	**0.040***
HAQ	5.787	3.499	0.404	1.654	0.111
FVC (L)	30.134	18.401	0.274	1.638	0.114

F(4,35)= 6.364 multiple R: 0.710 multiple R^2: 0.425 SE: standard error.
*MAS: Milliken Activities of Daily Living Scale, MSS: Medsger Systemic Sclerosis Severity Scale, HAQ: Health Assessment Questionnaire, FVC: forced vital capacity. *p<0.001.*

autoantibodies associated with scleroderma were detected in 24.4% of the patients. Anti-centromere antibodies were negative in 34.1% of patients and positive in 41.5% of patients and anti-Scl70 antibodies were negative in 39% and positive in 36.6% of the patients (Table 2). The presence of PAH, ILD, and ILD score were assessed as disease-related comorbidities. PAH was present in 9.8% and ILD in 26.8% of the patients. The mean ILD score was 3.63 (range: 0-16). Corticosteroid and immunosuppressive treatment were received by 58.5% and 53.7% of the patients, respectively. Patient follow-up time ranged from 5 to 18 years with mean of 10.70 years (Table 2).

Correlation analysis revealed moderate correlations between 6MWD and FEV_1 (L) (r=0.393, p=0.032), DLCO% (r=0.399, p=0.044), FVC (L) (r=0.504, p=0.005), FEV_1/FVC% (r=-0.453, p=0.012), and TLC (L) (r=0.413, p=0.026) values and HAQ (r=-0.392, p=0.018), MSS (r=-0.545, p=0.002), mRSS (r=-0.528, p=0.003) and MAS (r=0.472, p=0.004) scores (Table 3).

A linear regression model was used to further analyze the variables correlated with 6MWD. The regression model included FVC and MSS, HAQ, and MAS scores and accounted for 42.5% of the variance in 6MWD (F[4,25]=6.364, p=0.001, R^2=0.425). The results showed that MAS (p=0.026) and MSS (p=0.040) scores were independent factors associated with 6MWD, with each unit increase in MAS score corresponding to a 1-m increase and each unit increase in MSS score to a 9-m decrease in 6MWD (Table 4).

Discussion

In this study, we detected correlations between 6MWD and disease severity, level of disability, skin thickness, pulmonary function, and ADL performance in women with scleroderma. In the linear regression analysis, disease severity and ADL performance emerged as independent factors associated with 6MWD.

Disability in individuals with scleroderma occurs as a result of various aspects of the disease, especially skin fibrosis[27], which is a distinguishing feature for individuals with scleroderma[28]. In the European Scleroderma Trials and Research (EUSTAR) cohort, Wu et al. demonstrated reduced pulmonary function and increased mortality in individuals with dcSSc, including progressive skin fibrosis in individuals with scleroderma[29]. The mRSS is associated with skin involvement and was used as an indicator of our participants' risk of disease progression in the lungs. The median mRSS score was reported to be 23 in individuals with dcSSc and 9.5 in those with lcSSc[30]. In our participants, the median mRSS was 4.5, indicating mild skin involvement, and participants with an increased mRSS had lower 6MWD. Pugnet et al. also reported a relationship between mRSS and 6MWD in their group of 56 scleroderma patients, but this relationship was not significant in the regression analysis, as in our study[31].

Pulmonary function tests are commonly used to investigate pulmonary involvement in scleroderma[13]. In a study by Kesikburun et al., pulmonary involvement was significantly correlated with respiratory muscle strength, function level, quality of life, and fatigue[32]. In our participants, respiratory function was consistently maintained within the normal range according to spirometry measurements. However, higher FEV_1, DLCO, FVC, and TLC values were associated with better 6MWD. Deuschle et al. showed that DLCO is a good marker in scleroderma and that 6MWD and pulmonary function test results were moderately correlated[33]. A meta-analysis demonstrated that in patients with mild pulmonary involvement, improved exercise capacity was found to be associated with a lower risk of ILD and had no negative impact on scleroderma progression[34]. In another study, small airway involvement was shown to be a common condition in scleroderma and explained bronchial involvement in scleroderma-associated ILD. This was reported to have a significant effect on individuals' ADL performance and perceptions of illness[35].

In the present study, the 6MWT was used to assess functional capacity in women with scleroderma. Sanges et al. reported an average 6MWD of 438.3 m in their study of 298 scleroderma patients[9]. Gadre et al. stated that the mean 6MWD in 55 scleroderma patients with PAH was 285.83 m, while scleroderma patients without PAH walked 418.78 m[36].

In the above mentioned study by Deuschle et al., scleroderma patients with PAH, FVC <80%, and class III–IV dyspnea severity according to New York Heart Association (NYHA) classification had 6MWD of 465–480 m[33]. In our participants without PAH, 6MWD was moderately associated with disease severity, with 14 participants walking less than 80% of the predicted distance according to normative values, similar to the literature. In another randomized controlled study conducted with 22 women with scleroderma and a control group, the patients' baseline 6MWD was found to be 518 m, which increased to 532 m after 6 months of exercise intervention. The authors concluded that the improvement in functional capacity is associated with an increase in quality of life and a decrease in the level of disability[6].

As scleroderma progresses, muscle atrophy and joint contractures worsen[37], while increasing changes in the small blood vessels of the musculoskeletal system may cause insufficient oxygenation and result in reduced exercise performance[38]. In accordance with the literature, the participants in our study had lower dominant quadriceps muscle strength than predicted values. In the study by Lima et al. including 20 scleroderma patients and 20 controls, it was found that quadriceps muscle strength was lower compared to the control group and was associated with 6MWD[3]. Justo et al. also observed that women with scleroderma had lower quadriceps muscle strength than the control group, and imbalance between quadriceps and hamstring muscle strength led to insufficient functional capacity[39]. In another study, a significant relationship between muscle strength and lung function was detected in scleroderma, with a significant improvement in hand grip and quadriceps muscle strength after physiotherapy, leading to improved physical performance[40].

The HAQ is a physical assessment questionnaire that evaluates the level of mobility, self-care, daily activities, and functional disability in individuals with scleroderma. The validity, reliability, and sensitivity of the questionnaire to health situations have been demonstrated previously[41]. According to Bruce et al., a score of 0–1 indicates mild to moderate disability, 1–2 moderate to high disability, and >2 severe disability. In patients with osteoarthritis and rheumatoid arthritis, HAQ scores have been reported as 0.8–1.2[42]. Clements et al. reported a mean HAQ score of 1.04 in individuals with scleroderma as well as significant correlation between HAQ disability index and clinical and laboratory assessments of hand dysfunction, inflammation, skin, joint, and muscle involvement[43]. The HAQ scores of our participants indicated a moderate to high level of disability. Impens et al. reported a decrease in 6MWD with increased disability, even at lower disability levels[44]. We also observed a relationship between 6MWD and HAQ score in the present study, with walk distance decreasing as disability level increased.

Nearly all (~90%) individuals with scleroderma have esophageal reflux, swelling, distention, constipation, diarrhea, and fecal incontinence attributable to the vasculopathy, fibrosis, and loss of function associated with the disease[45]. Azevedo et al. showed that gastrointestinal involvement is the main cause of malnutrition in individuals with scleroderma and that scleroderma patients with nutritional problems engaged in less physical activity[46]. The median UCLA SCTC GIT 2 score in our participants indicated mild severity. There was no significantly correlation between 6MWD and UCLA SCTC GIT 2 score because our patients were in relatively good physical condition despite the presence of gastrointestinal problems. However, our study was the first to evaluate the potential relationship between UCLA SCTC GIT 2 score and 6MWD. Further studies are needed to clarify whether gastrointestinal involvement has an adverse impact on functional capacity.

The ability to perform ADLs may be compromised in individuals with scleroderma, as the increased deposition of collagen results in increased skin thickness and may cause reduced muscle strength[47]. Nonato et al. performed Glittre Activities of Daily Living Test in individuals with scleroderma and found that they had longer task completion time than healthy controls. In addition, they found that peripheral saturation values correlated with pulmonary function parameters throughout the test[2]. In the present study, the MAS score indicated mild impairment in ADL performance. The major finding of our study was the significant increase in 6MWD with higher MAS scores. The multiple regression analysis also revealed that MAS score is an independent indicator for functional capacity as assessed with the 6MWT, as each unit increase in MAS score was found to be associated with a 1-m increase in 6MWD. The linear regression model accounted for 42.5% of the variance in 6MWD. Sandqvist et al. reported a significant relationship between hand function and ADL performance in women with scleroderma and recommended assistive devices to improve those mobilization activities[48]. Given the systemic involvement of scleroderma, upper extremity strength is likely to be affected, thereby compromising the patient's ability to perform ADLs. To the best of our knowledge, our study is the first to evaluate the relationship between functional capacity assessed with 6MWT and ADLs involving the upper extremities.

Chronic systemic inflammation may restrict physical activity, and the resulting sedentary behavior may increase inflammation in individuals with scleroderma[49]. Liem et al. also reported a decrease in physical activity level in individuals with scleroderma. Among our participants, 75% were sedentary according to their physical activity level evaluated using the IPAQ. The decrease in physical activity was consistent with mild involvement in individuals with scleroderma. However, there was no statistical relationship between 6MWD and IPAQ score. According to regression analysis, IPAQ was not significantly correlated with 6MWD in scleroderma[50]. Physical activity includes exercise as well as other activities; exercise is a subcategory of physical activity that involves planned, structured, repetitive, and purposeful activity[50]. As a result of the impact of SSc on patients' overall health status, the exercise capacity of SSc patients was found to be limited as well[51]. The lack of a significant relationship is likely because the majority of our

patients had a sedentary lifestyle.

In scleroderma, cardiopulmonary system involvement can result in reduced exercise tolerance. Pulmonary involvement such as lung fibrosis and PAH, as well as premature cardiovascular disease are more common in SSc patients. Although physical activity level is affected in SSc patients, the clinical assessment of exercise capacity in SSc has not been studied previously. Thus, the novelty of this study is demonstrating the leading factors related to limited exercise capacity in SSc patients[49].

MSS score is an indicator of multiple organ and systemic involvement and disease activity in scleroderma, and thus aids in the diagnosis and treatment of the disease[11]. The MSS scores of our participants were consistent with mild disease severity and accounted for 42.5% of the variance in 6MWD. Linear regression analysis demonstrated that each unit increase in MSS score was associated with a 9-m decrease in 6MWD. Sanges et al. also reported a significant relationship between 6MWD and MSS score and suggested that disease activity may affect walking distance[9].

Limitations

The present study had several limitations. Firstly, our participants had mild to moderate disease severity. Although the number of participants included in the study was sufficient according to the power analysis of the sample size, the inclusion of participants with different disease severities and subtypes may provide more information. Secondly, the present study did not include any men due to the female predominance in this disease. Thirdly, low IPAQ scores may be considered a limitation of this study because when compared to the exercise capacity results, the IPAQ scores were insufficient for interpretation of the data analysis. This may be the result of a similar low level of physical activity in the SSc patients.

Conclusions

Our study identified MSS and MAS scores as independent variables significantly associated with distance walked in the 6MWT. Therefore, the 6MWT is an appropriate tool to evaluate the functional capacity of patients with scleroderma in terms of disease severity and ability to perform ADLs.

Ethics approval

The Noninvasive Research Ethics Committee of Dokuz Eylul University approved the data collection and research protocol for this study (protocol number 2018/15-02). The study was conducted in accordance with the Declaration of Helsinki.

Authors' contributions

All of the authors declare their participation in the design, execution, and analysis of the study. They have prepared the manuscript, approved the final version, and accept responsibility for its integrity.

Consent to participate

All patients provided written informed consent upon enrollment to the study.

References

1. Giunta A, Tirri E, Maione S, Cangianiello S, Mele A, De Luca A, et al. Right ventricular diastolic abnormalities in systemic sclerosis. Relation to left ventricular involvement and pulmonary hypertension. Ann Rheum Dis 2000;59(2):94–8.
2. Nonato CP, Azevedo BLPA, Oliveira JGM, Gardel DG, de Souza DCN, Lopes AJ. The Glittre Activities of Daily Living Test in women with scleroderma and its relation to hand function and physical capacity. Clin Biomech 2020;73:71–7. A
3. Lima TRL, Guimarães FS, Carvalho MN, Sousa TLM, Menezes SLS, Lopes AJ. Lower limb muscle strength is associated with functional performance and quality of life in patients with systemic sclerosis. Brazilian J Phys Ther 2015;19(2):129–36.
4. De Oliveira NC, Sabbag LMDS, Ueno LM, De Souza RBC, Borges CL, Pinto ALDS, et al. Reduced exercise capacity in systemic sclerosis patients without pulmonary involvement. Scand J Rheumatol 2007;36(6):458–61.
5. Pettersson H, Åkerström A, Nordin A, Svenungsson E, Alexanderson H, Boström C. Self-reported physical capacity and activity in patients with systemic sclerosis and matched controls. Scand J Rheumatol 2017;46(6):490–5.
6. Filippetti M, Cazzoletti L, Zamboni F, Ferrari P, Caimmi C, Smania N, et al. Effect of a tailored home-based exercise program in patients with systemic sclerosis: A randomized controlled trial. Scand J Med Sci Sport 2020;30(9):1675–84.
7. Battaglia S, Bellia M, Serafino-Agrusa L, Giardina A, Messina M, Cannizzaro F, et al. Physical capacity in performing daily activities is reduced in scleroderma patients with early lung involvement. Clin Respir J 2017;11(1):36–42.
8. Vandecasteele E, De Pauw M, De Keyser F, Decuman S, Deschepper E, Piette Y, et al. Six-minute walk test in systemic sclerosis: A systematic review and meta-analysis. Int J Cardiol 2016;212:265–73.
9. Steen,D.Virgina,A.ThomasJM.Severeorganinvolvement in systemic sclerosis with diffuse scleroderma. Am Collage Rheumatol 2000;43(11):2437–44.
10. Sanges S, Giovannelli J, Sobanski V, Morell-Dubois S, Maillard H, Lambert M, et al. Factors associated with the 6-minute walk distance in patients with systemic sclerosis. Arthritis Res Ther 2017;19(1):1–11.
11. Garin MC, Highland KB, Silver RM, Strange C. Limitations to the 6-minute walk test in interstitial lung disease and pulmonary hypertension in scleroderma. J Rheumatol 2009;36(2):330–6.
12. Medsger TA Jr, Bombardieri S, Czirjak L, Scorza R, Della

Rossa A, Bencivelli W. Assessment of disease severity and prognosis. Clin Exp Rheumatol 2003;21(3 Suppl 29):S42-S46.
13. Clements PH. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. J Rheumatol 1995;22.7:1281–5.
14. Antoniou KM, Margaritopoulos GA, Goh NS, Karagiannis K, Desai SR, Nicholson AG, et al. Combined pulmonary fibrosis and emphysema in scleroderma-related lung disease has a major confounding effect on lung physiology and screening for pulmonary hypertension. Arthritis Rheumatol 2016;68(4):1004–12.
15. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2016;37(1):67–119.
16. Morelli S, Ferri C, Polettini E, Bellini C, Gualdi GF, Pittoni V, et al. Plasma endothelin-1 levels, pulmonary hypertension, and lung fibrosis in patients with systemic sclerosis. Am J Med 1995;99(3):255–60.
17. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7.
18. Jay SJ, Enright P. Reference equations for the six-minute walk in healthy adults [1] (multiple letters). Am J Respir Crit Care Med 2000;161(4 I):1396.
19. O'Shea SD, Taylor NF, Paratz JD. Measuring muscle strength for people with chronic obstructive pulmonary disease: retest reliability of hand-held dynamometry. Arch Phys Med Rehabil 2007;88(1):32–6.
20. Andrews AW, Thomas MW, Bohannon RW. Normative values for isometric muscle force measurements obtained with hand-held dynamometers. Phys Ther 1996;76(3):248–59.
21. Fries JF, Spitz P, Kraines RG, Holman HR. Measurment of patient outcome in arthritis. Arthritis Rheum 1980;23(2):137–45.
22. Khanna D, Furst DE, Maranian P, Seibold JR, Impens A, Mayes MD, et al. Minimally important differences of the UCLA scleroderma clinical trial consortium gastrointestinal tract instrument. J Rheumatol 2011;38(9):1920–4.
23. Akel BS, Öksüz Ç, Karahan S, Düger T, Kayihan H. Reliability and validity of milliken activities of daily living scale (MAS) in measuring activity limitations of a turkish population. Scand J Occup Ther 2012;19(4):315–21.
24. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-Country reliability and validity. Med Sci Sports Exerc 2003;35(8):1381–95.
25. Saglam M, Arikan H, Savci S, Inal-Ince D, Bosnak-Guclu M, Karabulut E, et al. International physical activity questionnaire: Reliability and validity of the Turkish version. Percept Mot Skills 2010;111(1):278–84.
26. Dawson, B., Trapp RG. Basic and clinical biostatistics. Lange Medical Books/McGraw-Hill, New York.; 2004.
27. Khanna D, Furst DE, Clements PJ, Al E. Standardization of the modified rodnan skin score for use in clinical trials of systemic sclerosis 2017;2(1):11–8.
28. LeRoy EC, Medsger J. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001;28(7):1573–6.
29. Wu W, Jordan S, Graf N, De Oliveira Pena J, Curram J, Allanore Y, et al. Progressive skin fibrosis is associated with a decline in lung function and worse survival in patients with diffuse cutaneous systemic sclerosis in the european scleroderma trials and research (eustar) cohort. Ann Rheum Dis 2019;78(5):648–56.
30. Wirz EG, Jaeger VK, Allanore Y, Riemekasten G, Hachulla E, Distler O, et al. Incidence and predictors of cutaneous manifestations during the early course of systemic sclerosis: A 10-year longitudinal study from the EUSTAR database. Ann Rheum Dis 2016;75(7):1285–92.
31. Pugnet G, Marjanovic Z, Deligny C, Boussardon K, Benzidia I, Puyade M, et al. Reproducibility and utility of the 6-minute walk test in systemic sclerosis. J Rheumatol 2018;45(9):1273–80.
32. Kesıkburun B, Köseoğlu BF, Şahın A, Turgay M, Doğan A, Öken ÖA. The effects of respiratory muscle weakness and pulmonary involvement on functional status, fatigue and health related quality of life in patients with systemic sclerosis. Arch Rheumatol 2015;30(2):116–23.
33. Deuschle K, Weinert K, Becker MO, Backhaus M, Huscher D, Riemekasten G. Six-minute walk distance as a marker for disability and complaints in patients with systemic sclerosis. Clin Exp Rheumatol 2011;29(2 Suppl 65):S53-S59.
34. Vandecasteele E, De Pauw M, De Keyser F, Decuman S, Deschepper E, Piette Y, et al. Six-minute walk test in systemic sclerosis: A systematic review and meta-analysis. Int J Cardiol 2016;212:265–73.
35. de Alegria SG, Litrento PF, de Oliveira Farias I, Mafort TT, Lopes AJ. Can home rehabilitation impact impulse oscillometry and lung ultrasound findings in patients with scleroderma-associated interstitial lung disease? A pilot study. BMC Res Notes 2022;15(1):1–6.
36. Gadre A, Ghattas C, Han X, Wang X, Minai O, Highland KB. Six-minute walk test as a predictor of diagnosis, disease severity, and clinical outcomes in scleroderma-associated pulmonary hypertension: the DIBOSA study. Lung 2017;195(5):529–36.
37. Ranque B, Bérezné A, Le-Guern V, Pagnoux C, Allanore Y, Launay D, et al. Myopathies related to systemic sclerosis: A case-control study of associated clinical and immunological features. Scand J Rheumatol 2010;39(6):498–505.
38. Mimura Y, Ihn H, Jinnin M, Asano Y, Yamane K, Tamaki K. Clinical and laboratory features of scleroderma patients developing skeletal myopathy. Clin Rheumatol 2005;24(2):99–102.
39. Justo AC, Guimarães FS, Ferreira AS, Soares MS, Bunn PS, Lopes AJ. Muscle function in women with systemic sclerosis: Association with fatigue and general physical function. Clin Biomech (Bristol, Avon) 2017;47:33-39.

40. Alhowikan AM. Impact of supervised exercise training on systemic sclerosis with multiple organ involvement: A case report. J Pak Med Assoc 2022;72(5):972–4.
41. Racine M, Hudson M, Baron M, Nielson WR, Pope J, Markland J, et al. The impact of pain and itch on functioning and health-related quality of life in systemic sclerosis: An exploratory study. J Pain Symptom Manage 2016;52(1):43–53.
42. Bruce B, Fries JF. The stanford health assessment questionnaire: dimensions and practical applications. Health Qual Life Outcomes 2003;6:1–6.
43. Clements PJ, Wong WK, Hurwitz EL, Furst DE, Mayes M, White B, et al. Correlates of the disability index of the health assessment questionnaire: A measure of functional impairment in systemic sclerosis. Arthritis Rheum 1999;42(11):2372–80.
44. Impens AJ, Wangkaew S, Seibold JR. The 6-minute walk test in scleroderma - how measuring everything measures nothing. Rheumatology (Oxford) 2008;47 Suppl 5:v68-v69.
45. Randone SB, Guiducci S, Cerinic MM. Musculoskeletal involvement in systemic sclerosis. Best Pract Res Clin Rheumatol 2008;22(2):339–50.
46. Azevedo VF, de Souza Müller C, Rinaldi L, Bredt MC, Giovanni K, Pereira MAC, et al. Nutritional evaluation and physical functional ability in scleroderma patients. Acta Reumatol Port 2009;34(2):228–34.
47. Casale R, Buonocore M, Matucci-Cerinic M. Systemic sclerosis (Scleroderma): An integrated challenge in rehabilitation. Arch Phys Med Rehabil 1997;78(7):767–73.
48. Sandqvist G, Eklund M, Åkesson A, Nordenskiöld U. Daily activities and hand function in women with scleroderma. Scand J Rheumatol 2004;33(2):102–7.
49. de Oliveira NC, Portes LA, Pettersson H, Alexanderson H, Boström C. Aerobic and resistance exercise in systemic sclerosis: State of the art. Musculoskeletal Care 2017;15(4):316–23.
50. Liem SIE, Meessen JMTA, Wolterbeek R, Ajmone Marsan N, Ninaber MK, Vliet Vlieland TPM, et al. Physical activity in patients with systemic sclerosis. Rheumatol Int 2018;38(3):443–53.
51. Cuomo G, Santoriello C, Polverino F, Ruocco L, Valentini G, Polverino M (2010) Impaired exercise performance in systemic sclerosis and its clinical correlations. Scand J Rheumatol 39(4):330–335.