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Evaluation of six-minute walk test in juvenile systemic sclerosis

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Abstract

The objective is to evaluate the walking distance and oxygen desaturation during the six-minute walk test and to establish correlations between the test results and other clinical findings so to assess the reliability of the test for evaluation of children with juvenile systemic sclerosis (jSSc). A total of 25 jSSc, 27 juvenile systemic lupus erythematosus (jSLE), and 30 healthy controls were included. The test is conducted according to the guidelines recommended by the American Thoracic Society, standardized in 2002. Median values of walking distances were 470 (415–580) m in jSSc; 518 (376–618) m in jSLE; and 562 (493.5–618) m in healthy controls. jSSc patients walked significantly less distance comparing to controls ($p < 0.001$). jSSc patients with lung involvement walked less than those without lung involvement [463.2 (418–565) m vs. 491.5 (415–580) m], but without a significant difference ($p = 0.82$). The frequency of lower extremity pain during and after the test was significantly higher in the jSSc cohort compared to both control groups ($p = 0.001$). Patients with myalgia were found to walk less than those without myalgia [446.5 (415–538) m vs. 493.5 (428–580) m] ($p = 0.04$). Patients with jSSc have limited walking distances. Despite the decreased walking distance among jSSc patients with ILD and/or PAH, the limited number of patients makes the results inappropriate for interpretation. Low extremity pain influences the walking capacity of jSSc patients.

Keywords Pediatric systemic sclerosis · Six-minute walk test · Pulmonary arterial hypertension · Interstitial lung disease

Introduction

Juvenile systemic sclerosis (jSSc) is a rare autoimmune disease characterized by heterogeneous evolution and outcome with the potential for multisystemic involvement; including the gastrointestinal, cardiac, renal, and pulmonary systems [1]. Pulmonary vascular disease and interstitial lung fibrosis, ranging from 30 to 70%, are the leading causes of morbidity and mortality in jSSc [2, 3]. The effect of these serious complications on the progressive and insidious course of the disease brings up the importance of assessing pulmonary disease severity.

The six-minute walk test (6MWT), which is easy to perform and cost effective, has been proposed as the best indicator of functional capacity among all submaximal exercise tests [4]. It is a self-paced test, which correlates with the daily physical activity, used for evaluating prognosis and response to therapy in patients with cardiopulmonary diseases. The practicability of the test has led to consideration of its possible utility in systemic sclerosis-related pulmonary arterial hypertension (PAH) and interstitial lung diseases (ILD) [5]. While the results of studies on the availability of the test in adults are contradictory, there are limited data concerning the usefulness of 6MWT in children with jSSc.

The objectives of this study were to evaluate the six-minute walk distance (6MWD) and oxygen desaturation during the 6MWT and to establish correlations between the test results and other clinical findings so to assess the reliability of the test for evaluation of children with jSSc.

Methods

Juvenile systemic sclerosis patients

Totally of 25 patients, who were regularly followed up at Cerrahpasa Medical Faculty, Pediatric Rheumatology

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Department with diagnosis of jSSc were included in the study. All the target patients met the Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for jSSc [6].

Demographic characteristics including age, gender, and smoking habits were recorded for all patients. Medical history and disease characteristics, laboratory examinations (auto-antibody profiles), and treatment modalities (calcium channel blockers, disease-modifying drugs, endothelin receptor antagonists, corticosteroids, and immunosuppressive agents) were obtained from the patients' documents. Duration of Raynaud's phenomenon and disease duration (time since diagnosis jSSc was confirmed by a physician) was examined. A standard clinical examination was performed with conventional assessment of possible lung, heart, kidney, skin, and muscle involvement, and disease activity scoring and severity. Echocardiography, pulmonary function tests [forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DL_{CO})], chest high-resolution computerized tomography (HRCT) examinations which were regularly performed as part of their routine screening were evaluated. Lung functioning was assessed by measuring percentage (%) of predicted DLCO (DLCO < 60% has been considered as reduced). Diagnosis of ILD was determined based on the presence of interstitial fibrosis or ground glass opacities on HRCT as reported by the radiologist. The extent and severity of skin involvement were measured by means of the modified Rodnan Skin Score (mRSS) and ranged from 0 (normal) to 3 (most severe) on 17 different body parts combining to a total maximum score of 51 [7]. Juvenile Systemic Sclerosis Severity Score (J4S) was calculated for nine different organ systems (general, peripheral vascular, skin, joints and tendons, muscle, gastrointestinal, lung, heart, and kidney) each scored on a scale of 0–4 [8]. Information on current therapy and compliance was evaluated.

Control group

Control group consisted of 30 healthy controls and 27 juvenile systemic lupus erythematosus (jSLE) patients.

Healthy group consists of healthy children of the hospital staff. All healthy group subjects were medication-free. We used the jSLE patients as a disease control due to similar nature of the disease pathogenesis, since both represent the connective tissue disorder. In addition, our jSLE cohort is the most extensive connective tissue disorder cohort at our department. Demographic characteristics including age at the time of the study and gender were recorded for both control groups. The same physical examinations were performed to exclude coincidental disease.

Patient selection

Clear inclusion and exclusion criteria were constructed to obtain reliable results. Subjects had no orthopedic disorder or history of any other chronic disease influencing their exercise capacity such as cystic fibrosis, congenital heart disease, immunodeficiency syndromes, chronic pulmonary disease, or uncontrolled asthma. Subjects were not involved in any competitive sport and they were lifetime non-smokers. Subjects having resting tachycardia or uncontrolled hypertension (95th percentile by age) were excluded from the study. The patients with resting SpO_2 of $\leq$90% in room air were not included in the study. Approval was obtained for the study from the Ethics Committee of the Cerrahpasa Medical School (approved: 08/02/2018-53142). Informed consent was obtained both from parents and the subjects.

The six-minute walk test

The test is conducted according to the guidelines recommended by the American Thoracic Society (ATS), standardized in 2002 [9]. The primary measurement was the total distance (m) walked. Secondary measures included fatigue and dyspnea, measured before and after test with a modified Borg scale.

A light meal was acceptable before the test, but the subject was told to avoid vigorous exercise within 2 h of beginning the test. In brief, exact age and sex were noted. Body weight and height were measured with a calibrated weighing scale and stadiometer using standard anthropometric methods and the body mass index (BMI, in kg/m^2) was calculated by dividing the weight (kg) by the square of the body height in meters. No "warm-up" period before the test was allowed and the subject sat at rest in a chair, located near the starting position. Thereafter, the blood pressure (mmHg), heart rate, and SpO_2 (%) were measured after a resting period in sitting position for at least 10 min. The corridor was 30 m in length. A starting line, which marks the beginning and end of each 60 m lap, was marked on the floor using brightly colored tape. Small cones were used to mark the turnaround points. The length of the corridor was marked every 3 m.

The subject was then instructed to walk up and down a measured corridor, covering as much ground as possible in 6 min without running. The test was self-paced and the patient was allowed to rest if desired, although the clock continued to run. The 6MWT was performed by the same investigator. The wording of encouragement during the testing was standardized ("keep going", "you are doing fine", and "everything is going well") and given

by the same person at set times during the test. Each time the participant returns to the starting line, the investigator recorded the lap, so all completed laps were noted down with tick marks on the worksheet. When 6 min was up, the subject was asked to stop, and the spot was marked by placing a piece of tape on the floor. The number of meters in the final partial lap was measured using this piece of tape and marked distance guides on the floor. Finally, the additional distance covered from the final partial lap was added to the distance of completed laps (60 m × number of laps) to figure out the total walking distance of the subject.

All the subjects were asked if anything kept them from walking further. The Borg Scale which is a well-validated scoring system on a 0–10-point scale was used to determine the patient self-reported fatigue and dyspnea levels. Pulse and oxygen saturation were measured and recorded at the end of the test immediately using a handheld pulse oximeter placed on the index finger of the patient's right hand or ear lobe probe when no good pulse signal was obtained by the finger probe. Oxygen desaturation was defined as a decrease in peripheral SpO_2 from baseline 4% and a severe desaturation as $SpO_2 \leq 88\%$ at the end of the test. Blood pressure was measured directly after the test and recorded. The results of the groups were evaluated after completion of the study.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics for Windows 21.0 software (Released 2012, IBM Corp., Armonk, NY, USA). First, we performed the Shapiro–Wilk test to evaluate the distribution of the variables. For demonstration of the numerical data, we used mean ± SD in case of normal distribution and median (minimum–maximum) values for data without normal distribution. Quantitative data analysis was performed using independent student *T* test for two independent study groups and paired sample *T* test for two dependent groups with normal distribution. To analyze data without normal distribution between two groups, we used Mann–Whitney *U* test for independent groups and Wilcoxon test for two dependent groups. In the case of comparison of three study groups, we used one-way ANOVA for variables with normal distribution and Kruskal–Wallis test for variables without normal distribution. For categorical variables, we used Chi-squared test. Spearman's correlation test was used to determine any correlation between continuous variables. A significance level of 0.05 was assumed for the statistical tests.

Results

Demographic data

A total of 82 children; 25 jSSc (22 female, 3 male) 27 jSLE (21 female, 6 male) and 30 healthy children (16 female, 14 male) performed 6MWT. Demographic and disease characteristics of the study groups are shown in Table 1. There was no difference between groups in terms of age or BMI distribution ($p > 0.05$). However, there was a significant difference in gender distribution when comparing jSSc and jSLE to healthy children ($\chi^2 = 8.797$, $p = 0.01$).

Table 1 Demographic characteristics of patients with juvenile systemic sclerosis, juvenile systemic lupus erythematosus, and healthy children

Total (*n*:82)	jSSc (*n*:25)	jSLE (*n*:27)	Healthy children (*n*:30)	*p* value
Female/male ratio				$p = 0.01$
n (%)	22 (88)/3 (12)	21 (77.8)/6 (22.2)	16 (53.3)/14 (46.7)	
Body mass index				$p = 0.06$
Mean ± SD	18.75 ± 2.99	20.43 ± 3.05	19.94 ± 1.69	
Median (min–max)	18.5 (14–26.5)	21 (15–25)	20 (17–25)	
Age at the time of the study (years)				$p = 0.06$
Mean ± SD	16.44 ± 3.19	16.74 ± 3.59	15.57 ± 1.50	
Median (min–max)	16 (9–21)	17 (6–23)	16 (12–18)	
Age at disease onset (years)			–	$p = 0.1$
Mean ± SD	10.3 ± 2.9	11.8 ± 3.5		
Median (min–max)	11 (2–15)	11 (5–18)		
Age at diagnosis (years)			–	$p = 0.5$
Mean ± SD	11.9 ± 2.7	12.6 ± 3.3		
Median (min–max)	12 (8–17)	12 (6–18)		
Disease duration (months)			–	$p = 0.05$
Mean ± SD	74.0 ± 46.5	47.2 ± 38.0		
Median (min–max)	72 (6–228)	28 (1–117)		

jSSc juvenile systemic sclerosis, *jSLE* juvenile systemic lupus erythematosus

Six-minute test results

Six-minute walking test results were examined, as shown in Table 2. Median values of walking distances were 470 (415–580) m in jSSc; 518 (376–618) m in jSLE and 562 (493.5–618) m in healthy controls. Patients with jSSc walked significantly less distance than the control groups ($p < 0.001$). Only one patient diagnosed with jSLE, needed to stop before 6 min due to fatigue.

Heart rate recovery and the magnitude of desaturation after performing the 6MWT were compared between groups. Heart rates increased in all study groups without a significant difference ($p = 0.06$).

None of the subjects needed supplemental oxygen during the test. In jSSc cohort, the median values of SpO_2 (%) detected before and after the test were 98 (95–99) and 98 (92–99), respectively. A significant difference was obtained in comparison of two variables (z:2.49, $p = 0.013$). However, no significant difference was obtained when we compared SpO_2 variation in control groups; z: 0.75, $p = 0.44$ for jSLE and z: 0.57, $p = 0.56$ for healthy controls.

Twenty-two participants (26.8%) described low extremity pain as myalgia; 12 (54.6%) of them were jSSc and 8 (36.4%) of them were jSLE, while 2 (9.1%) were healthy controls. The frequency of lower extremity pain during and after the test was significantly higher in the jSSc cohort compared to both control groups: ($n = 12$, 48%) ($p = 0.001$).

Six-minute walk distance in jSSc patients based on their clinical characteristics

The baseline characteristics of patients are shown comparatively in Table 3. In our jSSc cohort, 12 (48%) patients had lung involvement. Patients with lung involvement [median distance 463.2 (418–565) m] walked less than those without lung involvement [median distance 491.5 (415–580) m]. However, there was no statistically significant difference ($p = 0.82$). Although 7 (28%) patients with DLco $\leq 60\%$ [median distance 446.5 (429–565) m] walked less than those with DLco $\geq 60\%$ [median distance 492.5 (415–580) m], no significant difference was detected ($p = 0.43$). Eight (32%) patients with FVC $< 80\%$ [median distance 446.5 (418–565) m] walked less than those with FVC $\geq 80\%$ [median distance 493.5 (415–580) m] without a statistically significant difference ($p = 0.16$). Mean disease activity scores (J4S) of jSSc patients was 6.7 ± 4.5. There was no correlation between walking distances and activity scores ($p = 0.8$). Mean mRSS of jSSc patients was 18.4 ± 12.3. No significant correlation was found between patients walking distances and mRSS ($p = 0.15$).

Ten out of 25 (40%) jSSc patients had limited range of motion (ROM) in lower extremities. The median walking distance for patients with limited ROM in lower extremities was 498.2 (418–565) m, while it was 456.5 (415–580) m in those without limited ROM ($p = 0.5$). Consequently, we have not found significant difference when we compared patients with and without limited ROM according to walking distance. On the other hand, jSSc patients with myalgia ($n = 12$, 48%) were found to walk less [median distance

Table 2 Comparing six-minute walk test results between study groups

Total (n:82)	jSSc (n:25)	jSLE (n:27)	Healthy children (n:30)	p value
6MWD (m)				$p \leq 0.001$
Mean ± SD	480.18 ± 47.22	513.66 ± 51.70	553.21 ± 41.65	
Median (min–max)	470 (415–580)	518 (376–618)	562 (493.5–618)	
Prewalk SpO_2 (%)				$p = 0.08$
Mean ± SD	98.0 ± 0.9	98.4 ± 0.6	98.0 ± 0.6	
Median (min–max)	98 (95–99)	98 (97–99)	98.0 (97–99)	
Postwalk SpO_2 (%)				$p = 0.04$
Mean ± SD	97.5 ± 1.6	98.3 ± 0.7	97.9 ± 0.5	
Median (min–max)	98 (92–99)	98 (96–99)	98.0 (97–99)	
Prewalk heart rate				$p = 0.5$
Mean ± SD	90.4 ± 12.1	95.0 ± 15	93.2 ± 5.18	
Median (min–max)	92 (66–106)	95 (68–120)	92 (82–104)	
Postwalk heart rate recovery				$p = 0.06$
Mean ± SD	105 ± 15	111 ± 17	104 ± 6.7	
Median (min–max)	109 (65–127)	110 (74–141)	103 (91–118)	

jSSc juvenile systemic sclerosis, *jSLE* juvenile systemic lupus erythematosus, *6MWD* six-minute walk distance, *SpO_2* oxygen saturation by pulse oximetry

Table 3 Baseline characteristics of patients with juvenile systemic sclerosis and juvenile systemic lupus erythematosus

	jSSc (*n*:25)	jSLE (*n*:27)
Clinical characteristics		
Type of disease	LSSc: 6 (24) DSSc:19 (76)	
Raynaud phenomenon (disease onset), *n* (%)	25 (100)	4 (14.8)
Digital ulcer, *n* (%)	16 (64)	–
Nailfold capillary changes, *n* (%)	18 (72)	–
Gastrointestinal involvement, *n* (%)	6 (24)	0
Renal involvement, *n* (%)	2 (8)	3 (11)
Cardiac involvement, *n* (%)	3 (12)	0
Lung involvement, *n* (%)	12 (48)	0
PAH, *n* (%)	2 (8)	0
DLCO < 60%, *n* (%)	7 (28)	–
FVC < 80%, *n* (%)	8 (32)	–
Pulmonary fibrosis, *n* (%)	6 (24)	–
Musculoskeletal involvement, *n* (%)	10 (40)	13 (48)
Limited ROM, *n* (%)	10 (40)	–
Myositis, *n* (%)	0	0
Avascular necrosis, *n* (%)	–	0
Neurologic involvement, *n* (%)	1 (4)	3 (11)
Laboratory characteristics		
Anemia, *n* (%)	6 (24)	4 (14.8)
ANA positivity, *n* (%)	23 (92)	23 (85.2)
AntiScl70 positivity, *n* (%)	7 (28)	–
Disease activity		
mRSS, (mean ± SD)	18.4 ± 12.3	–
J4S, (mean ± SD)	6.72 ± 4.5	–
SLEDAI-2k, (mean ± SD)	–	4.9 ± 3.1
Medication history		
CCB, *n* (%) Months (mean ± SD)	23 (92) 42.6 ± 33.9	4 (14.8) 26 ± 24.8
Steroid, *n* (%) Months (mean ± SD)	25 (100) 48 ± 48.0	22 (81.5) 29.1 ± 33.1
ERA, *n* (%) Months (mean ± SD)	15 (60) 24.6 ± 30.2	-
DMARDs (MTX), *n* (%) months (mean ± SD)	24 (96) 49.2 ± 45.4	3 (11) 27.3 ± 13.3
DMARDs (MMF), *n* (%) Months (mean ± SD)	13 (52) 9.2 ± 14.6	3 (11) 10.6 ± 11.7
CYC, *n* (%)	13 (52)	4 (14.8)
Biologic agents, *n* (%)	4 (16)	2 (7.4)

jSSc juvenile systemic sclerosis, *jSLE* juvenile systemic lupus erythematosus, *LSSc* limited systemic sclerosis, *DSSc* diffuse systemic sclerosis, *PAH* pulmonary arterial hypertension, *FVC* forced vital capacity, *DLCO* diffusing capacity for carbon monoxide, *ANA* anti-nuclear antibody, *mRSS* modified Rodnan Skin Score, *J4S* Juvenile Systemic Sclerosis Severity Score, *SLEDAI-2k* Systemic Lupus Erytematosus Disease Activity Index 2000, *CCB* calcium channel blockers, *ERA* endothelin receptor antagonists, *DMARDs* disease-modifying antirheumatic drugs, *MTX* methotrexate, *MMF* mycophenolate mofetil, *CYC* cyclophosphamide

446.5 (415–538) m] than those without myalgia [median distance 493.5 (428–580) m] ($p = 0.04$).

Borg Scale

The level of patient respiratory effort and fatigue score, as reflected by Borg dyspnea index, was recorded. Moderate levels of dyspnea (Borg scale > 2) were reported only by jSSc patients: ($n = 7$, 8.5%). Fourteen (58.3%) jSSc and ten (41.7%) jSLE patients complained of moderate levels of fatigue (Borg scale > 2). Participants presented with fatigue ($n = 24$, 29.3%) were found to walk less (mean 482.8 ± 55.1 m) than those who show no signs of fatigue (mean 532.5 ± 48.7 m) ($p = 0.038$).

In addition, we performed analysis of correlation between Borg score of dyspnea and fatigue and walking distance. We found significant correlation ($p < 0.001$) between Borg score and 6MWD; $r = -0.5$ and $r = -0.4$ for dyspnea and fatigue, respectively.

Discussion

Walking distance of patients with jSSc is significantly decreased, comparing to jSLE patients and healthy controls. There are few factors that possibly influence the walking distance in jSSC patients. Previous data from literature report that cardiopulmonary involvement have an impact on the results of 6MWD in systemic sclerosis patients. In addition, musculoskeletal complaints including myalgia and fatigue could imply the results of the test.

Although it is generally used on variety of conditions, the role of 6MWT in SSc-related pulmonary diseases is still debatable in most studies among adults. As far as we know, this is the first study evaluating the 6MWT in juvenile SSc patients.

In a study among 95 adult patients, it has been demonstrated that 6MWD is a surrogate marker for disability and complaints in systemic sclerosis [10]. Therefore, 6MWD could provide a valuable outcome parameter, although it lacks organ specificity. In our study, we found that jSSc patients had significantly disturbed 6MWD, comparing to patients with jSLE and healthy controls. However, in the literature, we have not found the study comparing the 6MWT results of SSc patients to healthy population. In addition, this is the first study evaluating 6MWT in jSSc patients, which make our results hard to discuss.

Systemic sclerosis has been proposed to be subclassified into limited and diffuse forms based on the extent of cutaneous changes. In a study by Vandecasteele et al [11] among 286 adults, patients with diffuse subtype of the disease walked less, comparing to those with limited disease form.

We could not make such a comparison due to low frequency of limited systemic sclerosis patients in juvenile cohort.

Meta-analysis of 43 included studies (3185 SSc-all patients) evaluated the role of 6MWT in adult systemic sclerosis patients with pulmonary involvement [12]. The results revealed that SSc–PAH patients walk less than SSc–noPAH patients and SSc–ILD–PAH patients walk less than SSc–ILD and SSc–noILD patients during test. However, 6MWD in SSc patients without pulmonary involvement was not denoted in this study. We compared jSSc patients with and without ILD and/or PAH to identify the impact of pulmonary involvement on exercise capacity. In contrary, we have not found significant relation between lung involvement and 6MWD in our cohort. This is probably due to low frequency of lung involvement in jSSc patients comparing to adults [13].

Among adult patients with systemic sclerosis, the PAH prevalence is estimated to be 10–15%, whereas in children, it was reported to be 7% [14, 15]. Similarly, 2 patients (8%) had PAH in our cohort. The low frequency of PAH in our cohort (only 2 out of 25 jSSc patients) makes the comparison irrelevant and inappropriate for the interpretation. The studies of PAH among jSSc patients are insufficient and there is a need for further investigations.

Previous studies reporting the usefulness and the prognostic value of 6MWD in children with PAH have been contradictory. Recently, Lammers and colleagues [16] found 6MWD to be a strong predictor of outcome in a selected group of pediatric PAH patients, with a mean age of 11.4 years, after relatively short follow-up time. Douwes et al. [17] confirm this finding within an unselected national pediatric PAH cohort with longer term follow-up. Therefore, prospective evaluation of the same patients in terms of exercise capacity and pulmonary involvement would give us more relevant data on the disease follow-up.

A declining DLCO and elevated FVC/DLCO (%) ratio are very useful as predictors of the presence of PAH or its advanced development [14]. According to the data from the literature, 6MWT resulted to be weakly correlated with these functional parameters [5, 10]. Garin et al. [18] compared SSc patients with idiopathic pulmonary fibrosis (IPF) in a retrospective study and revealed that FVC and DLCO were more strongly predictive of 6MWD in IPF than in SSc, emphasizing exclusion of SSc subjects with pain limitation improved the predictive value. We could not find any significant relation between 6MWD and these parameters, suggesting a multifactorial basis for the limited exercise capacity in jSSc patients.

Because of its multisystemic nature, the effects of other systems can potentially limit exercise capacity in patients with SSc during the 6MWT. Garin et al. [18] pointed out the importance of pain as a limitation of the 6MWT in adult SSc patients. They reported that 6MWT distance is not always a reflection of the lung capacity. The test interpretation should always include the vascular and musculoskeletal factors. In our cohort, patients with myalgia had significantly disturbed results. Similarly, Impens et al. [5] emphasized that the 6MWT does not correlate with cardiovascular and pulmonary functioning measures in systemic sclerosis. They suggested the need for a systemic sclerosis-specific measure of exercise capacity. In another study including 18 adult patients, it has been accentuated that the interpretation of the 6MWT should take into consideration cardiovascular, pulmonary, and skeletal limitations. Besides, they pointed to a possible role of joint mobility interventions in improving the functional capacity of SSc patients [19]. We have not found any significant difference when we compared walking distances of our jSSc patients with and without limited ROM. Limited number of patients could be a reason for the non-significant results.

Fatigue is now recognized as a very major symptom in most patients with SSc, with a number of recent studies describing fatigue and its associates including pain and poor physical function [20]. As a result of our study, in addition to low extremity pain, fatigue could influence the exercise capacity so the 6MWD, since all of our SSc patients reported fatigue as a main complain. Moreover, the severity of fatigue influences the walking distance of patients. We found a significant correlation ($p < 0.001$) between Borg score and 6MWD as we expected.

In addition to the 6MWD, the magnitude of desaturation and heart rate recovery after performing the 6MWT have been reported as additional predictors of outcome in cardiopulmonary diseases. Similarly, to the results of the study by Douwes et al. [17], heart rate increased significantly in all our study groups without significantly difference between patients and healthy control. In addition, in our jSSc cohort, a significant difference was obtained in comparison of oxygen saturation measured before and at the end of the test. Multiple mechanisms, including ventilation–perfusion mismatching, oxygen diffusion limitation, and low mixed venous oxygen, have been shown to contribute to the oxygen desaturation in SSc [14, 15]. Oxygen saturation change during exercise tests have been shown to predict survival in patients with SSc [21, 22].

The main advantage of our study is that this is the first evaluation of 6MWT in juvenile patients with systemic sclerosis. All of the previous results have been obtained from the studies with adult patients. Comparing data from literature are shown in Table 4.

There are several limitations of our study that we would like to mention. This is a cross-sectional study with limited number of patients due to rarity of systemic sclerosis in children and adolescents. We could not make a differentiation between diffuse and limited form of the disease, since the limited systemic sclerosis is extremely rare in young

Table 4 Results of the studies evaluating the six-minute walk test in children and adults

Author	n	Age (years)	Study population	6MWD (m)
Garin et al. [18]	128 (F/M:86/42)	52 (46–60)	IPF (*n*:48) SSc + ILD (*n*:33) SSc + PAH(*n*:13) SSc + ILD + PH (*n*:19) SSc-Neither (*n*:15)	Median (range) 379 (347–411) 349 (302–397) 315 (243–387) 312 (251–372) 313 (244–382)
Vandecasteele et al. [11]	286 (F/M:216/70)	51.5 ± 13.7	SSc (All) LSSc (*n*:71) LcSSc (*n*:167) DcSSc (*n*:48) SSc-extensive ILD (*n*:16) SSc-limited ILD (*n*:94) SSc-PAH (*n*:7) SSc-no ILD-noPAH (*n*:165)	(Mean ± SD) 457 ± 111 475.3 ± 108.8 460.1 ± 106.2 416.2 ± 121.4 357.2 ± 123.5 449.8 ± 107.4 328.8 ± 147.3 484 ± 93
Douwes et al. [17]	47 (F/M:29/18)	10.8 (7.3–14.4)	PAH (All) PAH (No shunt-defect) PAH (Shunt-defect)	(Mean ± SD) 350 ± 106 366 ± 111 317 ± 87
Deuschle et al. [10]	95 (F/M: 85/10)	56.0 (25–80)	LSSc (*n*:61) DSSc (*n*:34)	Median (range) 491 (86.0–664.5)
Our study	82 (F/M:59/23)	16.2 ± 2.9	JSSc (*n*:25) jSLE (*n*:27) Healthy controls (*n*:30)	Median (min–max) 470 (415–480) 518 (376–618) 562 (493.5–618)

6MWD six-minute walk distance, *F* female, *M* male, *IPF* idiopathic pulmonary fibrosis, *ILD* interstitial lung disease, *PAH* pulmonary arterial hypertension, *LSSc* limited systemic sclerosis, *DSSc* diffuse systemic sclerosis, *LcSSc* limited cutaneous systemic sclerosis, *DcSSc* diffuse cutaneous systemic sclerosis, *jSSc* juvenile systemic sclerosis, *jSLE* juvenile systemic lupus erythematosus

population. In our cohort, the majority of jSSc and jSLE patients was female due to disease nature. However, about half of the healthy control was male. A lack of universal reference values for the 6MWT in children could led to misinterpretations of the results. It is well known that the lung involvement, namely, PAH, influences the results of 6MWT. The low frequency of PAH in our cohort makes the comparison irrelevant and inappropriate for the interpretation. Moreover, comparing the results of the CHAQ test to the 6MWT results could give us more reliable data. Unfortunately, we do not perform CHAQ routinely in our practice. Further well-designed prospective trials with higher number of patients should be able to identify the precise role of 6MWT in evaluation of jSSc patients.

In conclusion, the findings of our study showed that patients with jSSc have limited walking distances. Despite the decreased walking distance among jSSc patients with ILD and/or PAH, the limited number of patients makes the results of our study inappropriate for interpretation. On the other hand, low extremity pain and fatigue influence the walking capacity of jSSc patients. Therefore, 6MWT is sensitive to some other disease manifestations that may influence the walk distance. Since there are a limited number of studies regarding the role of six-minute walk test in the evaluation of jSSc, we believe that the results of our study will enlighten the future studies.

Author contributions OK contributed to the conception and design of the study, interpretation of the data, OK and AA contributed to the data collection, data analysis and drafting article, KB and REO contributed to the acquisition and evaluation of the data, MY and SS participated in data collection and performing the statistical analysis. All authors read and approved the manuscript.

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Compliance with ethical standards

Conflict of interest Author O.K, Author A.A, Author S.S, Author M.Y, Author K.B, Author R.E.O, and Author O.K declare that they have no conflict of interest including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials.

Ethical approval Approval was obtained for the study from the Ethics Committee of the Cerrahpasa Medical School (approved: 08/02/2018-53142). Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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