Association of 6-Minute Walk Test (6MWT) Data with Cardiopulmonary Factors in Hispanic Systemic Sclerosis Patients

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Objective: Systemic Sclerosis (SSc) is an autoimmune disease with significant morbidity and mortality secondary to pulmonary manifestations. The six-minute walk test (6MWT) has been used in SSc studies to measure respiratory complications, particularly pulmonary hypertension. In this study, we evaluated whether the six-minute walk distance (6MWD), measured during the 6MWT, is associated with clinical SSc symptoms in Puerto Rican patients in a rheumatology clinic.

Methods: We prospectively collected 6MWT data for 37 consecutive SSc patients at the University of Puerto Rico every three months for one year between 2013 and 2015. A linear mixed regression model was used to investigate the effects of the SSc clinical features and subtypes on average 6MWD over time.

Results: The average baseline distance walked by SSc patients was $365.2 (\pm 8.1)$ meters, with no significant differences over time. No statistically significant differences (p>0.05) were found in the six-minute walk distance (6MWD) at different time intervals for SSc subtypes. Two clinical features, palpitations and lung crackles, were associated with a significantly shorter 6MWD(p<0.05).

Conclusion: Our study showed that the 6MWT can be used to evaluate SSc patients. No association was found between 6MWD and most clinical SSc symptoms in our population. Two clinical symptoms, lung crackles and palpitations, were associated with decreased 6MWD.

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Key words: Systemic Sclerosis, 6-minute walk disease, Pulmonary disease

ystemic Sclerosis (SSc) is an autoimmune disease with significant morbidity and mortality driven by cardio-pulmonary complications, including pulmonary hypertension and interstitial lung disease. The six-minute walk test (6MWT), a measure of aerobic exercise capacity, can assess functional capacity and monitor disease progression in SSc patients with pulmonary complications (1). SSc patients have a significantly reduced six-minute walk distance (6MWD) compared to healthy individuals, possibly due to the impact of the disease on lung function, cardiovascular function, and muscle weakness (1). A shorter 6MWD in SSc patients is associated with a poor prognosis, including increased mortality (2). Despite these utilities, using the 6MWT in SSc patients is limited because other extrapulmonary manifestations of SSc, including joint pain and contractures, can affect the patient's performance (1,3,4). Our study aims to evaluate if selected cardiopulmonary features (e.g., palpitations, fatigue, dyspnoea) have a significant association with the 6-Minute Walk Distance (6MWD) after a serially administered 6-Minute Walk Test (6MWT).

Methods

Study design

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Study population

Using the 1980 American College of Rheumatology (ACR) criteria for the classification of SSc, 37 consecutive patients with SSc, seen between 2013 and 2015, were recruited from the outpatient clinics of the Rheumatology Division of the Department of Medicine at the University of Puerto Rico (UPR) School of Medicine (5). Patients were divided into two groups based on disease subtype, limited SSc or diffuse, according to the classification criteria proposed by LeRoy (6). The study was approved by the UPR-Medical Sciences Human Research Subjects Protection Office (IRB#), and all patients signed informed consent forms before participating.

Variables

Study visits included a complete medical history and physical examination. Data on demographic parameters, clinical manifestations, laboratory tests, diagnostic studies, and pharmacologic therapy received were collected using a structured data sheet. Clinical manifestations of SSc in all organ systems

For this study, we used a longitudinal cohort design to evaluate the association of selected cardiopulmonary features and the 6MWD after administering the 6MWTs. The tests were performed every 3 months for a year.

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were determined using medical history, physical examination, and medical record review. Skin manifestations were evaluated using the modified Rodnan skin score (MRSS) (range, 0 to 51), the presence or absence of calcinosis, and/or sclerodactyly (7). Musculoskeletal involvement was defined as synovitis, tendon friction rubs, joint contractures, and muscle weakness. Cardiopulmonary features evaluated include palpitations, dyspnoea, cough, lung crackles, and fatigue.

Six-minute walk test

One experienced operator performed the 6MWT according to published guidelines (8). Two tests were done with at least 10 minutes between them, and data from the longer of the two walks was used. Subjects rated their dyspnoea using the modified Borg scale at the beginning and end of the exercise. The test was repeated at intervals of 3 months for 1 year. Blood pressure, oximetry, heart rate, and Borg indices were measured at baseline and after the 6MWT.

Statistical analyses

The study population was characterized by their sociodemographic and clinical traits at baseline, utilizing frequencies and proportions for categorical variables and measures of central tendency and dispersion (e.g., mean, standard deviation, median, and interquartile range) for continuous variables. We used linear mixed regression models to evaluate the impact of the systemic scleroderma subtype and time (baseline, 3, 6, 9, and 12 months) on the average six-minute walk distance. The interaction between scleroderma type and follow-up time was analyzed using the likelihood ratio (LR) test. The LR test was also employed to examine potential interactions between specific clinical characteristics and follow-up time concerning the sixminute walk distance outcome. We reported the results of the "main-effect only" models for clinical features that showed no significant interactions with time. We considered fixed effects (such as systemic scleroderma subtype, time, and their interaction) and random effects (addressing individual variability) in our linear mixed model. The model coefficients and their 95% confidence intervals were displayed in tables.

Additionally, residual analyses were conducted, and any observations with extreme and influential values were excluded from the final analysis. However, no evaluation of confounders was performed for this analysis. All statistical analyses were performed using STATA version 17, and p-values less than 0.05 were considered statistically significant.

Results

The cohort had a mean age of 50.2 ± 12.1 years, with 34 out of 37 female patients (91.9%). Most patients presented with the limited subtype (62.9%) and had a mean modified Rodnan Skin Score (mRSS) of 11.2 ± 6.7 at baseline. The mean disease duration was 10.2 ± 8.1 years. Most had not received education beyond high school (56.8%), and 75.7% had public health care insurance. Additionally, 48.7% were married, and 70.3% self-identified as non-smokers. The average baseline distance walked by all study participants was 365.2 ± 8 meters. Further details on the baseline clinical characteristics of the patients can be found in Table 1.
 Table 1. Summary of Sociodemographic/Clinical characteristics of participants at baseline (n=37).

Sociodemographic/Clinical Characteristic	Total n (%)		
Sex Male Female	3 (8.11) 34 (91.89)		
Age ≤ 50 years > 50 years	17 (45.95) 20 (54.05)		
Education High School or Less Graduate or more	21 (56.76) 16 (43.24)		
Insurance Type Public Private	28 (75.68) 9 (24.32)		
Smoking history Non smoker Previous smoker	26 (70.27) 11 (29.73)		
Distance Walked (meters) Mean (SD) Median (P ₂₅ -P ₇₅)	365.16 ± 89.26 357.1 (325 - 415)		
SSc subtype Limited Diffuse	23 (62.16) 14 (37.84)		
Time with disease (y) Mean (SD) Median (P ₂₅ -P ₇₅)	10.17 ± 8.13 7 (5 - 13)		
Modified Skin Score Mean (SD) Median (P ₂₅ -P ₇₅)	11.14 ± 6.70 9 (6 - 13)		
Calcinosis	10(27.03)		
Sclerodactyly	31(83.78)		
Digital pitting scars	23(62.16)		
Palpitations	14(38.89)		
Dyspnoea	22 (59.46)		
Cough	18 (48.65)		
Lung crackles	13 (35.14)		
GI reflux	31 (83.78)		
Muscle weakness	8 (21.62)		
Joint contractures	19 (51.35)		
Fatigue/malaise	24 (64.86)		
Immunosuppressive therapy	20 (54.05)		

Abbreviations: SE: Standard Error of the Mean;, SSc= Systemic Sclerosis, GI: Gastrointestinal

We evaluated the average six-minute walk distance (6MWD) over time for each systemic sclerosis (SSc) subtype but found no statistical significance (p-value > 0.05; data not shown) over time. This trend was also observed in the Linear Mixed Model Regression, where no statistically significant differences were found between SSc subtypes and the average 6MWD over time (baseline, 3, 6, 9, and 12 months) (see "main effect model," Table 2).

 Table 2. Linear Mixed Regression Model for evaluating Scleroderma subtypes and 6-minute walk distance over time.

6 MWD	Estimate Coefficient (95% CI)	p-value
Fixed Effects		
Intercept	376.44 (347.10; 405.78)	< 0.0001
Scleroderma Type Limited SSc Diffuse SSC	Reference -29.81 (-64.98, 5.36)	0.097
Time (in months) Baseline 3 months 6 months 9 months 12 months	Reference 3.96 (-10.76; 18.67) 2.67 (-11.90; 17.24) 3.81 (-11.53; 19.14) 14.0 (-1.33; 29.32)	0.598 0.719 0.627 0.074

Abbreviations: 6 MWD = Six-minute walk distance; SSc= Systemic Sclerosis

Similarly, no statistically significant differences were observed in the average 6MWD over time for most clinical features (p > 0.05; data not shown). After evaluating the log-likelihood ratio test, Dyspnea, joint contractures, fatigue, and immunosuppressive treatment did not significantly interact with time (p > 0.05). After adjusting for the type of SSc and follow-up time, no other significant associations were observed between the above clinical features and the average 6MWD (Table 3).

However, a significant group-by-time interaction was identified for two clinical features: palpitations and lung crackles; thus, the interaction-term model results for these variables are shown. In patients experiencing palpitations at the 3-month evaluation, the average six-minute walk distance was significantly higher [coef.: 55.47 (95%CI: 16.49; 94.45)]. To further evaluate the cause of the interaction between palpitations and time, we assessed the effect of heart rate on the average 6MWD. As a result, in patients with palpitations specifically, time and heart rate were significantly associated with the average 6MWD. Several additional significant findings emerged among patients with palpitations. The average 6MWD was significantly lower at the six-month evaluation [coef.: -222.11 (95%CI: -406.47; -37.75)] compared to patients without palpitations. An inverse relationship was found between heart rate and 6MWD [coef.: -3.79 (95%CI: -5.53; -2.04)]. Significant interactions were observed between heart rate and 6MWD at 3 months [coef.: 4.82 (95%CI: 0.36; 9.28)] and 6 months [coef.: 3.37 (95%CI: 1.03; 5.70)]. Additionally, a significant interaction was identified between 6MWD at 6 months and having a diffuse scleroderma [coef] diagnosis: -89.06 (95%CI: -134.10; -44.03)] (data not shown).

An interaction was also observed between lung crackles and 6MWD at 3-, 9-, and 12-month intervals. For patients with lung crackles, there was a significant decrease in the average 6MWD at 3 months [coef.: -32.25 (95%CI: -62.94; -1.56)], 9 months [coef.: -43.69 (95%CI: -81.93; -5.45)], and 12 months [coef.: -65.91 (95%CI: -104.79; -27.03)]. No further evaluation was made for this group of patients.

Discussion

In this prospective study, we present 6MWT data for 37 Hispanic patients, who were majority female with the limited SSc subtype and a moderate mRSS. We found two clinical features of SSc, palpitations and lung crackles, were significantly associated with a shorter 6MWD. In this cohort, the mean distance walked was 365.2 ± 8.1 meters, with no significant differences at followup visits. This is markedly decreased compared to healthy adults and other groups of SSc patients (mean=484.20, SD=92.65) (9,10). As in other longitudinal studies of SSc patients, we found no significant differences in 6MWD at different time points (3). Other studies have found patients with diffuse SSc have shorter 6MWDs compared to those with limited subtypes (11). In our study, no significant differences were found between subtypes. This finding can be attributed to similar skin scores in both groups.

In our study, we found that when the heart rate increases, the average six-minute walk distance significantly decreases. Sanges et al. also found an independent association between variations in heart rate and 6MWD (12). This finding can be explained by exercise intolerance in SSc patients, specifically on impaired chronotropic response to exercise. We identified a gradual decrease of the average 6MWD in patients who presented with lung crackles on physical exam, a clinical finding of pulmonary fibrosis. Previous studies also found an association between pulmonary fibrosis and decreased 6MWD (12,13).

This study was limited by the small sample size, which directly affects the study's statistical power and the analysis conducted. Having a few patients precluded us from incorporating additional variables into the analysis, estimating the relationships of interest, and controlling for confounding factors. Furthermore, data from several sources (pulmonary function test, echocardiograms, chest computer tomography) are missing, precluding an objective assessment of cardio-pulmonary involvement.

In conclusion, our study demonstrated that serial 6MWTs can be administered to SSc patients with good tolerance. No significant differences among subtypes were observed in 6MWD at 3, 6, 9, and 12 months. Two clinical features of SSc, lung crackles and palpitations, were associated with a decreased 6MWD. Conducting similar studies to enhance our understanding of the topic and inform future research and interventions is essential.

Resumen.

Objetivo: Esclerosis Sistémica (ES) es una enfermedad con alta morbilidad y mortalidad debido a sus manifestaciones pulmonares. La caminata de seis minutos (6MWT) se utiliza en estudios de ES para medir complicaciones cardio-respiratorias, en particular hipertensión pulmonar. El objetivo de este estudio es evaluar si la distancia caminada de seis minutos (6MWD) se asocia con síntomas clínicos de ES en pacientes evaluados en una clínica de reumatología en Puerto Rico. Métodos: Se recopilaron, de forma prospectiva, datos del 6MWT en 37 pacientes diagnosticados con ES cada tres meses durante un año para el periodo de 2013 - 2015. Se utilizó un modelo de regresión lineal mixto para

Table 3. Mixed Linear Regression of the average six-minute walk distance for selected clinical features

	Clinical Feature						
6 MWD	Palpitations ' β (95% CI)	Dyspnoea β (95% CI)	Lung Crackle ⁷ β (95% Cl)	Joint contractures β (95% CI)	Fatigue β (95% CI)	Immunosuppressive β (95% Cl)	
Fixed Effects							
Intercept	377.82 (347.66; 407.98)	381.27 (351.38; 411.16)	364.19 (333.08; 395.30)	381.08 (350; 411.24)	376.59 (346.29; 406.88)	377.32 (342.89; 411.76)	
Clinical Feature No Yes	Reference -1.48 (-26.26; 23.29)	Reference -8.67 (-22.72; 5.38)	Reference 33.10 (3.87; 62.32)*	Reference -12.03 (-30.15; 6.09)	Reference -0.23 (-11.92; 11.47)	Reference -1.48 (-31.76; 28.79)	
Scleroderma Type Limited SSc Diffuse SSC	Reference -21.55 (-57.00; 13.90)	Reference -28.94 (-63.78; 5.90)	Reference -21.09 (-57.90; 15.74)	Reference -25.75 (-61.37; 9.87)	Reference -29.80 (-64.98; 5.37)	Reference -30.02 (-65.47; 18.86)	
Time (in months) Baseline 3 months	Reference -9.60 (-27.12: 7.92)	Reference 1.77 (-13.38: 16.92)	Reference 14.35 (-2.86: 31.58)	Reference -0.64 (-16.81: 15.52)	Reference 3.95 (-10.77: 18.67)	Reference 4.04 (-10.78: 18.86)	
6 months	-1.07 (-18.94; 16.80)	0.57 (-14.41; 15.55)	(-8.33; 25.90) 15.82	-3.05 (-19.87; 13.78)	2.65 (-11.96; 17.26)	(1011 0; 10100) 2.75 (-11.90; 17.40) 3.86	
12 months	(-16.50; 18.72) 5.93 (-12.83; 24.68)	(-13.17; 17.89) 11.81 (-3.92; 27.55)	(-1.24; 32.87) 29.60 (12.51; 46.70)*	(-19.19; 15.60) 8.86 (-8.21; 25.92)	(-11.60; 19.16) 13.89 (-2.21; 30.00)	(-11.51;19.23) 14.03 (-1.32; 29.39)	
Interactions between the clinical feature							
category and time Clinical feature: Yes,		-		-	-	-	
time: baseline Clinical feature: Yes,	Reference 55.47	-	Reference -32.25	-	-	-	
time: 3 months Clinical feature: Yes,	(16.49; 94.45)* 8.33	-	(-62.94; -1.55)* -12.52	-	-	-	
time: 6 months Clinical feature: Yes,	(-23.93; 40.60) -6.98	-	(-44.42; 19.38) -43.69	-	-	-	
time: 9 months Clinical feature: Yes,	(-51.92; 37.96) 23.52	-	(-81.93; -5.45)* -65.91	-	-	-	
time: 12 months	(-11.08; 58.12)	-	(-104.79; -27.03)*	-	-	-	

Abbreviations: 6 MWD = Six-minute walk distance; SSc= Systemic Sclerosis; *Statistically significant coefficients(p<0.05).

determinar la asociación de la medida promedio de la distancia caminada a los 6 minutos y los subtipos de ES, para un grupo selecto de características clínicas. Resultados: Al comienzo del estudio, la distancia promedio recorrida por los pacientes con ES fue de 365.2 (\pm 8,1) metros; sin embargo, no se observaron diferencias significativas durante el tiempo. De igual forma, no se encontraron diferencias estadísticamente significativas (p >0.05) en la distancia promedio del 6MWD y el tiempo para los subtipos de ES. Se observó que solo dos características clínicas, palpitaciones y crepitaciones pulmonares, mostraron tener una asociación significativa con tener un 6MWD más corto (p<0.05). Conclusión: Nuestro estudio demostró que el 6MWT puede ser utilizado para evaluar pacientes con ES. En nuestra población, no se encontró asociación entre el 6MWD y la mayoría de los síntomas clínicos de ES, excepto crepitaciones pulmonares y palpitaciones.

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