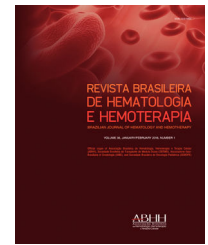




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Original article

Physical activity level and performance in the six-minute walk test of children and adolescents with sickle cell anemia



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ABSTRACT

Background: To establish determinants of maximum walking distance in the 6-minute walk test of children and adolescents with sickle cell anemia, and to compare the performance in this test with physical activity level between patients and healthy controls.

Methods: A cross-sectional study was performed in which the participants answered the Physical Activity Questionnaire for Older Children and Adolescents, and completed the 6-minute walk test.

Main results: Fifty-seven patients and 58 controls were studied. By univariate analysis of the patients, age ($p < 0.0001$) and indirect bilirubin ($p = 0.008$) were associated with maximum walking distance in the 6-minute walk test. In multivariate analysis, age was positively associated ($p < 0.0001$; beta: 0.75), while body mass index was inversely associated with distance walked ($p = 0.047$; beta: -0.32). This yields the following equation: maximum distance walked = $487.7 (\text{age} \times 18.3) - (12 \times \text{body mass index})$ meters. Patients reported a lower physical activity level however there was no significant difference in the distance walked in six minutes between patients (500.6 ± 88.7 m) and controls (536.3 ± 94 m).

Conclusion: The determinants for the 6-minute walk test in children and adolescents with sickle cell anemia were age and body mass index. There was no significant difference in the 6-minute walk test but patients with sickle cell anemia had a lower physical activity level compared to healthy controls.

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Introduction

Sickle cell anemia (SCA) is the most common monogenic hereditary disease in Brazil. The main characteristic is the inheritance of the beta-globin gene S (gene β^s), which is responsible for a mutant hemoglobin (Hb), Hb S. It is estimated that 2–8% of the Brazilian population is heterozygous for Hb S.¹

Several clinical manifestations are commonly observed in patients with SCA, such as occlusive crisis, acute chest syndrome, stroke, chronic hemolysis and chronic organ dysfunction.² These clinical manifestations also appear to be associated with changes in physical capacity, higher basal metabolic rate,³ lower levels of Hb, pulmonary and vascular diseases, and myopathy.⁴

Different methods are available in the clinical practice to assess physical capacity, such as the six-minute walk test (6MWT), whose main response variable is the maximum walking distance (6MWD), and cardiopulmonary stress test. The 6MWT is a simple and inexpensive test that is widely used in chronic diseases such as chronic obstructive pulmonary disease and heart failure.⁵

Recently, results of the 6MWT in the evaluation of patients with SCA were published^{6,7} in an attempt to assess the adequacy of the instrument in this study population. A previous study showed that the determinants of the 6MWD in SCA patients were low Hb level, low concentration of fetal Hb and reduced deformability of red blood cells.⁸ However, there are no studies in the Brazilian population, which, being multiracial, does not allow the direct extrapolation of results obtained in more genetically homogeneous populations.⁹

In this sense, recurring complications and hospitalizations appear to be associated with low physical activity levels (PAL) in patients with SCA.³

The 6MWT and specific questionnaires, with the main advantages of safety and low cost, are widely used to evaluate the physical capacity and PAL.¹⁰⁻¹² Assessment of the PAL in patients with SCA, whether by questionnaires or by direct testing,^{13,14} shows a tendency of a sedentary lifestyle.¹⁵

The adapted Borg scale¹⁶ is intended to classify the subjective and individual perception of effort in performing the 6MWT in a scale from 0 to 10. This may be analyzed in association with exercise-induced desaturation, that is, the reduction in transcutaneous saturation oxygen by three or more percentage points after testing compared to baseline, both measured using a portable digital oximeter.¹⁷

The aim of this study was to establish the determinants of the 6MWD in children and adolescents with SCA, as well as to compare PAL and performance in the 6MWT between SCA patients to healthy controls.

Methods

This is a cross-sectional study conducted in an Outpatients' Clinic of a tertiary teaching hospital in northeastern Brazil. This hospital is the regional referral center for the treatment of patients with SCA.

The project was approved by the Ethics Committee of the Universidade Federal de Sergipe (UFS – protocol: 30661314.0.0000.5546). The legal guardians of both patients and controls signed a written informed consent form.

Patient group

Patients were enrolled from October 2014 to May 2015. Of the patients with SCA (Hb SS) confirmed by Hb electrophoresis, those who were from 6 to 18 years old, in steady-state, with no blood transfusions in the previous three months and with no acute symptoms for at least one month prior to study entry were considered eligible for this study. Results of molecular tests and a family study were not available. Patients with neurological or orthopedic impairment were excluded.

Clinical and laboratory data

Hematological data (Hb, hematocrit, the red blood cell, platelet, leukocyte and reticulocyte counts, indirect bilirubin, mean corpuscular volume and lactate dehydrogenase), Hb electrophoresis (fetal Hb and Hb S) and spirometry data were obtained from an electronic database created especially for this research. All the exams were carried out within four weeks before the test and under stable clinical conditions. All the tests were performed at the central laboratory of the hospital, using standard techniques and equipment.

Current medication intake

All patients were taking folic acid supplement (2 mg/day). Those who were taking hydroxyurea received an initial dose of 15 mg/kg/day and were receiving the standard dose of 20–35 mg/kg/day for at least 12 months.¹⁸

Data collection

Data on variables considered potentially associated with the 6MWD were collected. These included age, gender, hydroxyurea therapy, body mass index (BMI), resting heart rate, heart rate at the end of the test, and transcutaneous oxygen saturation at rest and at the end of testing. Furthermore, blood tests were performed including Hb, hematocrit, red blood cell, platelet, leukocyte, neutrophil and reticulocyte counts, indirect bilirubin, mean corpuscular volume, lactate dehydrogenase, and Hb fetal and Hb S concentrations. Moreover, the scores obtained with the application of the Physical Activity Questionnaire for Older Children and Adolescents (PAQ-C) and the adapted Borg Scale¹⁶ were included as variables.

Physical activity questionnaire for older children and adolescents

Immediately before the 6MWT, all the patients answered the Brazilian version of the PAQ-C,^{10,19} composed of nine questions about sports, games and other physical activities at school and for recreation. This questionnaire aims to provide a complete picture of the type of activities that the participant had been performing during the previous seven days. Each question was scored on a scale of 1 to 5: very sedentary (1),

sedentary (2), moderately active (3), active (4) or very active (5). The sum of scores was calculated to determine the final score.

The 6-minute walk test

The 6MWT was performed according to the standardization proposed by the American Thoracic Society.^{7,11} A single 6MWT was performed along a flat and straight corridor of 30 m on a hard surface. Standard verbal encouragement was used during the test. Patients were instructed to stop when they felt tired. At the end of testing, the maximum distance walked (6MWD) was determined, and the perception of effort was recorded according to the adapted Borg scale.

Control group

The control group consisted of healthy children and adolescents enrolled in a local public school with similar characteristics of the schools the cases usually attended. Controls were matched with cases by age and gender. They performed the 6MWT and answered the PAQ-C.

Data analysis

Continuous quantitative variables are expressed as means \pm standard deviation and range, and categorical variables are expressed as percentages. Factors associated with the 6MWD were evaluated using the Pearson coefficient. Variables with $p < 0.20$ in the univariate analysis were selected by a backward stepwise model and included in the multivariate analysis. An equation was established to predict the 6MWD and its reliability was assessed using the Bland and Altman plot²⁰ in a second independent group of six patients (10% of the sample). The Kolmogorov-Smirnov test was used to verify how the data were distributed. The Pearson correlation and independent *t*-test were used for parametric data and Spearman correlation and Mann-Whitney test for nonparametric data. The level of significance was set for $p < 0.05$. The Statistical Package for the Social Sciences (SPSS) (Chicago, IL, USA) version 13.0 was used for analysis.

Results

Sixty-six patients in a database of patients with SCA who regularly attended the clinic ($n = 352$ children and adolescents) and were considered eligible were selected, but nine were later excluded due to orthopedic disabilities, neurological deficits or because they refused to participate (Figure 1).

All 57 patients and 58 controls completed the 6MWT without any complications. The clinical characteristics of both groups (SCA patients and healthy controls) are shown in Table 1. The groups were similar in respect to age and gender, as well as for heart rate before and after the 6MWT.

There were statistically significant differences between groups in relation to BMI, peripheral oxygen saturation at rest and at the end of the 6MWT and the score obtained using the Borg scale.

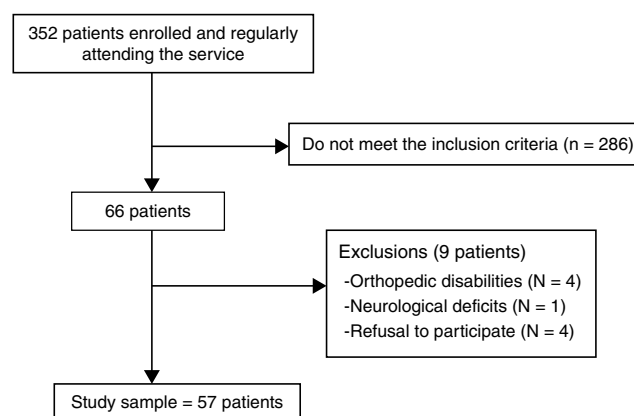


Figure 1 – Patients included in the study.

The following variables with $p < 0.20$ were selected to identify which were independently associated with the 6MWD in the patients group: age ($p < 0.0001$), BMI ($p = 0.118$), heart rate after the test ($p = 0.069$), peripheral oxygen saturation at the end of the test ($p = 0.125$), hematocrit ($p = 0.188$), red blood cell count ($p = 0.056$) and indirect bilirubin ($p = 0.008$). By multivariate analysis, age was found to be positively associated ($p < 0.0001$; beta: 0.75) and BMI was inversely associated ($p = 0.047$; beta -0.32) with the 6MWD.

The following equation was derived from the multivariate analysis, and aims to estimate the likely 6MWD from the variables age and BMI: estimated 6MWD = $487.7 + (\text{age} \times 18.3) - (\text{BMI} \times 12)$ with 6MWD being expressed in meters, age in years and BMI in kg/m^2 . A second and independent group of six patients (10% of the sample) was analyzed to assess the reliability of this equation. The real 6MWD was 480.5 ± 63.1 m which represented $99\% \pm 2\%$ of the estimated 6MWD. The correlation between the real 6MWD and estimated 6MWD was strong according to the Spearman coefficient ($r = 0.98$).

All participants completed the PAQ-C. The average score obtained by patients was 1.6 ± 0.39 with 63.1% of patients with SCA categorized as very sedentary and the remaining 36.9% as sedentary (Table 1). There was no significant difference between the sedentary and very sedentary individuals in respect to the 6MWD (530 ± 84 versus 497 ± 87 m, respectively; $p = 0.16$; 95% confidence interval: -14.19 to 80.75). The score of the controls was 3.2 ± 0.38 , with 17.2% being sedentary, 75% being moderately active and 6.8% being active.

Table 2 shows the comparison of the PAL between the different categories of activity identified by the PAQ-C and shows that patients with SCA reported a lower PAL in all categories compared to the healthy controls. However, the mean 6MWD was not significantly different between patients (500.6 ± 88.7 m) and controls (536.3 ± 94 m) as shown in Figure 2.

Spirometry was performed to evaluate pulmonary function in 23 of the 57 patients (40.3%). Of these, a restrictive pattern was observed in 13 patients (56.5%) and the results were normal in 10 patients (43.4%). No significant difference was found in respect to the 6MWD on comparing restrictive and normal results of the spirometry test. Except for the neutrophil count, no other significant difference was observed

Table 1 – Characteristics of patients and controls in the 6-minute walk test and patients' laboratory results.

Variable	Patients (n = 57)	Range	Controls (n = 58)	Range	p
Age – years	11.9 ± 3.5	6–18	11 ± 3.1	6–18	0.20
Gender male – %	57.9	–	58	–	0.91
BMI – kg/m ²	16.3 ± 2.3	13.01–23.48	18.1 ± 3.7	12.37–29.1	0.01
Resting heart rate – bpm	91.9 ± 13.3	67–122	90.6 ± 15.6	60–130	0.63
End of test heart rate – bpm	124.8 ± 31.3	73–227	117.5 ± 32.2	66–207	0.22
Resting peripheral oxygen saturation – %	93.2 ± 5.6	65–99	98.1 ± 0.9	95–99	<0.001
Peripheral oxygen saturation at 6th minute – %	89.1 ± 8.4	54–99	97.6 ± 1.6	93–99	<0.001
Borg scale at 6 minutes	4.1 ± 1.4	2–7	1.17 ± 1.1	0–4	<0.001
Hb – g/dL	8.3 ± 1.2	5.8–10.9	–	–	–
Hematocrit – %	24.1 ± 4.3	14.2–38.1	–	–	–
RBC count – 10 ¹² /L	2.7 ± 0.6	1.6–5.18	–	–	–
Platelet count – 10 ⁹ /L	429.4 ± 139.7	109–878	–	–	–
Leukocyte count – 10 ⁹ /L	12.4 ± 3.6	4.1–20.7	–	–	–
Neutrophil count – %	48.1 ± 9.6	30–78	–	–	–
Reticulocyte count – %	9.2 ± 4.3	07–19.2	–	–	–
Indirect bilirubin – mg/dL	3.1 ± 3	03–17.09	–	–	–
MCV – fL	92.2 ± 12.7	64–125	–	–	–
LDH – U/L	961.9 ± 475	100–2127	–	–	–
Hydroxyurea therapy – n (%)	26 (45.6)	–	–	–	–
Hb F – %	11.3 ± 7.6	0.9–31.7	–	–	–
Hb A1 – %	3.9 ± 5.4	0–18.7	–	–	–
PAQ-C score	1.6 ± 0.39	0.8–2.4	3.2 ± 0.38	2.4–4.1	<0.001
EIHOD – n (%)	29 (50.8)	–	–	–	–
Distance walked in 6-minute-walk test (m)	500.6 ± 88.7	360–746	536.3 ± 94	247.3–787.4	0.09

Results are expressed as mean, standard deviation and range unless otherwise indicated.

BMI: body mass index; Hb: hemoglobin; RBC: red blood cell; MCV: mean corpuscular volume; LDH: lactate dehydrogenase; Hb F: fetal hemoglobin; Hb A1: hemoglobin A1; PAQ-C: Physical Activity Questionnaire for older children and adolescents; EIHOD: exercise-induced hemoglobin oxygen desaturation.

between the variables associated with the profile and the spirometry results (Table 3).

Twenty-six patients (45.6%) were taking hydroxyurea. There was no significant difference in the 6MWD when the groups were compared according to the use of the medication. Only the mean corpuscular volume presented a significant difference (Table 3).

Discussion

This study identified that the variables independently associated with the 6MWD in the 6MWT of children and adolescents

with SCA were age (positively) and BMI (inversely). Other factors had been previously associated with 6MWD: low Hb level,²¹ increased hemolysis and low oxygen saturation at the beginning and after the exercise,¹⁷ and low levels of fetal Hb and reduced deformability of red blood cells.⁸ However, these associations were not found in this study. In addition, an equation to estimate the 6MWD of children and adolescents was established and tested.

As expected, there was a significant difference in the means of the BMIs between patients and controls.²² In addition, the average 6MWD in the group with SCA was numerically lower than the control group, albeit without

Table 2 – Physical activity levels assessed by the Physical Activity Questionnaire for Older Children and Adolescents (PAQ-C) of patients and controls.

	Patients			Controls			p
	Mean ± SD	Median	Min–Max	Mean ± SD	Median	Min–Max	
Spare-time activity	0.77 ± 0.37	0.8	0–1.6	2.37 ± 0.55	2.3	1.4–3.7	<0.001
Activity during PEC	1.77 ± 0.68	2	1–3	3.2 ± 0.55	3.2	2–5	<0.001
Lunch-time activity	1.4 ± 0.53	1	1–3	3.1 ± 0.72	3	2–5	<0.001
After school activity	1.77 ± 0.92	1	1–4	3 ± 0.61	3	2–4	<0.001
Evening activity	1.63 ± 0.77	1	1–4	3.22 ± 0.77	3	2–5	<0.001
Weekend activity	2 ± 0.75	2	1–3	3.44 ± 0.77	4	2–5	<0.001
AF during the last 7 days	2.26 ± 0.76	2	1–4	3.43 ± 0.62	3	2–5	<0.001
AF during each day last week	1.63 ± 0.53	1.7	0.1–3	3.21 ± 0.50	3.1	2.3–4.3	<0.001
Score	1.64 ± 0.39	1.7	0.8–2.4	3.2 ± 0.38	3.1	2.4–4.1	<0.001

PEC: Physical education classes; AF: Activity frequency; Data expressed as mean ± standard deviation, median and range (minimum and maximum). Independent t-test and Mann-Whitney U test were used to compare the two groups when the variables presented parametric and non-parametric distribution, respectively.

Table 3 – Comparison of laboratory and 6-minute walk test results with the results of spirometry and the use of hydroxyurea.

Variable	Pattern of spirometry (n = 23)		p	Hydroxyurea (n = 57)		p
	Restrictive (n = 13)	Normal (n = 10)		Yes (n = 26)	No (n = 31)	
Age (years)	14.3 ± 1.9	13.6 ± 3.1	0.51	12.9 ± 2.8	11.6 ± 4.1	0.21
Gender male (%)	53	40	0.68	65.3	51.5	0.26
BMI (kg/m ²)	16.8 ± 2.5	16.9 ± 2.6	0.96	16.7 ± 2.2	16.1 ± 2.4	0.40
Resting heart rate (bpm)	92.7 ± 14.6	92.1 ± 13.2	0.91	91.9 ± 13.2	92.2 ± 13.9	0.94
End of test heart rate (bpm)	131.9 ± 34.7	129.8 ± 38.1	0.89	125.6 ± 27.1	124.5 ± 35.4	0.89
Resting peripheral oxygen saturation (%)	92.4 ± 4.3	95.4 ± 3.6	0.10	92.9 ± 6.9	93.5 ± 4.4	0.72
Peripheral oxygen saturation at 6 min (%)	90.3 ± 5.2	91.6 ± 4.3	0.53	89.3 ± 7.4	88.1 ± 9.2	0.60
Borg scale at 6 min	4.3 ± 1.6	4.3 ± 1.4	0.99	4.1 ± 1.4	4 ± 1.4	0.74
Hb (g/dL)	8.4 ± 1.1	7.9 ± 0.8	0.24	8.2 ± 1.3	8.3 ± 1.1	0.94
Hematocrit (%)	24.6 ± 3.1	23.8 ± 2.7	0.54	24.2 ± 4.1	24.2 ± 3.4	0.98
RBC (10 ¹² /L)	2.7 ± 0.5	2.5 ± 0.6	0.37	2.6 ± 0.5	2.7 ± 0.6	0.55
Platelet count (10 ⁹ /L)	459.1 ± 161.6	468.7 ± 151.1	0.88	480.1 ± 260	434.68 ± 147.7	0.62
Leukocyte count (10 ⁹ /L)	11.7 ± 3.3	13.1 ± 4.4	0.38	11.9 ± 4.3	12.6 ± 3.1	0.38
Neutrophil count (%)	41.7 ± 7.6	50.6 ± 7.1	0.02	44.1 ± 9.1	48.9 ± 9.7	0.19
Reticulocyte count (%)	156.5 ± 98.8	110.8 ± 171.6	0.67	149.7 ± 146.6	119.6 ± 156.7	0.68
Indirect bilirubin (mg/dL)	4.9 ± 2.1	2.7 ± 0.9	0.08	4.4 ± 4.8	2.8 ± 2.2	0.50
MCV (fl)	91.3 ± 13.6	98.3 ± 12.4	0.25	97.2 ± 11.5	87.8 ± 12.2	0.04
LDH (U/L)	1098.7 ± 411.2	1235 ± 233	0.62	863.9 ± 581.2	968.4 ± 368.3	0.26
Hb F (%)	7.3 ± 3.3	10.8 ± 9.7	0.43	11.9 ± 6.8	10.7 ± 8.3	0.81
Hb A1 (%)	6.3 ± 4.5	3.3 ± 7.3	0.38	6 ± 7.4	2.4 ± 2.8	0.10
PAQ-C score	1.7 ± 0.4	1.5 ± 0.5	0.32	1.6 ± 0.4	1.7 ± 0.3	0.54
EIHOD (number, %)	7, 53.8	6, 60	0.40	12, 46.1	17, 54.8	0.41
Distance walked in 6-minute walk test (m)	527.2 ± 93.2	521.9 ± 106.7	0.90	522.7 ± 82.3	500.9 ± 90.6	0.35

Results are expressed as mean, standard deviation and range unless otherwise indicated.

BMI: Body mass index; Hb: hemoglobin; RBC: red blood cells; MCV: mean corpuscular volume; LDH: lactate dehydrogenase; Hb F: fetal hemoglobin; HbA1: hemoglobin A1; PAQ-C: Physical Activity Questionnaire for older children and adolescents; EIHOD: exercise-induced hemoglobin oxygen desaturation.

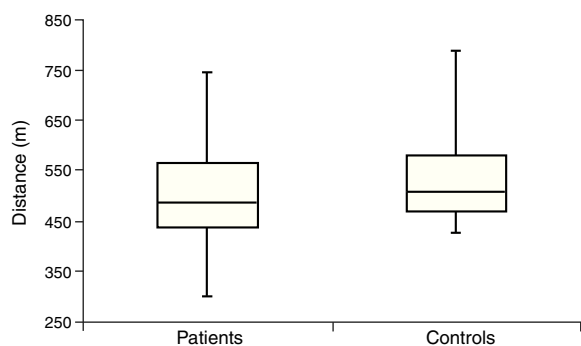


Figure 2 – Maximum distances in the 6-minute walk test of patients and controls (Mann-Whitney test).

statistical significance. In a recent study, adults with SCA had 6MWD below the value expected for the 6MWT.²³ Although there was no statistically significant difference in the means of 6MWD between the patients and controls in this study, it was observed that the perceived effort measured by the Borg scale was higher in patients with SCA. A previous study showed that the 6MWD was positively associated with maximal oxygen consumption and negatively to the degree of hypertension.²⁴

This study demonstrated that children and adolescents with SCA had lower PAL than healthy individuals, thus corroborating a previous study, which found that SCA patients had

physical capacity below that expected for their age.¹³ Another study showed that children with SCA had lower energy expenditure with physical activity than healthy children, which, in combination with growth impairment, indicates a chronic energy deficiency.²⁵

Recurrent painful crises may have contributed to the impairment of physical capacity.²⁶ Pain interferes in the functional status²⁷ and predisposes affected individuals to a more sedentary lifestyle, less muscular work, which may lead to peripheral muscle weakness and to reduced functional capacity, as was observed in this study, even though the test was accomplished in patients without painful crises for at least one month. In a previous study, the authors evaluated 30 children and adolescents with SCA by exercise testing with the results showing moderate to severe impairment of PAL correlated to the baseline Hb level.⁶

There is compelling evidence that hydroxyurea can reduce complications and hospitalizations in children with SCA at all ages.¹⁸ Nevertheless, there was no significant difference in the 6MWD or PAL correlated with the use of this medication. This finding may be justified by the fact that the indication of hydroxyurea is restricted to patients with more acute complications, which, in the long term, result in chronic organ and system involvement, with possible repercussions on the 6MWT.

Although patients with SCA eventually present lung function impairment, in this study there was no significant difference in the 6MWD between the groups with restrictive

and normal patterns by spirometry, thus corroborating previous results.^{8,23}

SCA patients in general adapt to chronic anemia and the consequent lower tissue oxygenation. Thus, compensatory mechanisms, such as increased heart rate and decreased peripheral vascular resistance that increases the supply of oxygen to tissues, result in transcutaneous oxygen saturation near to normal.¹⁷ However, this partial adaptation may be insufficient, especially during exercise, when the need for higher oxygen saturation increases the demand for energy.

Physical exercise induces notable metabolic changes, such as lactate production by the active muscles. Thus, reduced physical capacity can be explained by the presence of anemia, because levels of Hb below normal values induce rapid transition from aerobic to anaerobic respiration during exercise, which can trigger the polymerization of Hb S and promote microvascular occlusions. Furthermore, although habitual moderate exercise can improve immune function, intense exercise can cause temporary dysfunction with transient increases in circulating cytokines,²⁸ reducing blood flow in the microcirculation and causing veno-occlusive crises.²⁹

A limitation of this study was using clinical and laboratory data from medical records and not those evaluated on the same day of the test. However, the tests were carried out in steady-stable and the 6MWT was performed under the same conditions. Moreover, PAL was based on self-reported data and thus might be biased by socially desirable responses. A study of patients with fibromyalgia³⁰ showed that the reported information can overstate the PAL when confronted with data acquired using accelerometers, indicating no association between direct and indirect measures in the evaluation of the PAL. However, although it is not the only available option, self-reporting is a practical and cheap manner to acquire this information. Furthermore, by using the same strategy in both the study and control groups, the potential bias is equally distributed in both groups.

Conclusion

This study found that the determinants of the 6MWD in children and adolescents with SCA were age (positive relationship) and BMI (inverse relationship). Furthermore, it was observed that the evaluated patients have lower PAL compared to healthy individuals.

There was no statistically significant difference in the 6MWD between study and control groups. None of the hematologic parameters was associated with the 6MWT performance. It is possible that aspects related to complications of SCA may be related to the low PAL values and physical capacity in this study; this association should be studied in the future.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Stuart MJ, Nagel RL. Sick cell disease. *Lancet*. 2004;364(9442):1343-60.
2. Rees DC, Williams TN, Gladwin MT. Sick cell disease. *Lancet*. 2010;376(9757):2018-31.
3. Petto J, de Jesus JB, Vasques LMR, Pinheiro RLS, Oliveira AM, Spinola KAB, et al. Resting blood lactate in individuals with sickle cell disease. *Rev Bras Hematol Hemoter*. 2011;33(1):26-30.
4. van Beers EJ, van der Plas MN, Nur E, Bogaard H-J, van Steenwijk RP, Biemond BJ, et al. Exercise tolerance, lung function abnormalities, anemia, and cardiothoracic ratio in sickle cell patients. *Am J Hematol*. 2014;89(8):819-24.
5. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J*. 1985;132(8):919-23.
6. Liem RI, Nevin MA, Prestridge A, Young LT, Thompson AA. Functional capacity in children and young adults with sickle cell disease undergoing evaluation for cardiopulmonary disease. *Am J Hematol*. 2009;84(10):645-9.
7. Connes P, MacHado R, Hue O, Reid H. Exercise limitation, exercise testing and exercise recommendations in sickle cell anemia. *Clin Hemorheol Microcirc*. 2011;49(1-4):151-63.
8. Waltz X, Romana M, Hardy-Dessources M-D, Lamarre Y, Divialle-Doumido L, Petras M, et al. Hematological and hemorheological determinants of the six-minute walk test performance in children with sickle cell anemia. *PLoS One*. 2013;8(10):e77830.
9. Bandeira FM, Leal MC, Souza RR, Furtado VC, Gomes YM, Marques NM. Hemoglobin "S" positive newborn detected by cord blood and its characteristics. *J Pediatr (Rio J)*. 1999;75(3):167-71.
10. Kowalski KC, Crocker PRE, Faulkner RA. Validation of the Physical Activity Questionnaire for older children. *Pediatr Exerc Sci*. 1997;9(2):174-86.
11. Crapo RO, Casaburi R, Coates AL, Enright PL, MacIntyre NR, McKay RT, et al. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-7.
12. Du H, Newton PJ, Salamonson Y, Carrieri-Kohlman VL, Davidson PM. A review of the six-minute walk test: its implication as a self-administered assessment tool. *Eur J Cardiovasc Nurs*. 2009;8(1):2-8.
13. Hostyn SV, Carvalho WB, Johnston C, Braga JA. Evaluation of functional capacity for exercise in children and adolescents with sickle cell disease through the Six Minute Walk Test. *J Pediatr (Rio J)*. 2013;89(6):588-94.
14. Marouf R, Behbehani N, Zubaid M, Al Wazzan H, El Muzaini H, Abdulla R, et al. Transthoracic echocardiography and 6-minute walk test in Kuwaiti sickle cell disease patients. *Med Princ Pract*. 2014;23(3):212-7.
15. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med*. 1994;330(23):1639-44.
16. Carvalho VO, Bocchi EA, Guimarães GV. The Borg scale as an important tool of self-monitoring and self-regulation of exercise prescription in heart failure patients during hydrotherapy. A randomized blinded controlled trial. *Circ J*. 2009;73(10):1871-6.
17. Campbell A, Minniti CP, Nouraie M, Arteta M, Rana S, Onyekwere O, et al. Prospective evaluation of haemoglobin oxygen saturation at rest and after exercise in paediatric sickle cell disease patients. *Br J Haematol*. 2009;147(3):352-9.
18. Strouse JJ, Heeney MM. Hydroxyurea for the treatment of sickle cell disease: efficacy, barriers, toxicity, and management in children. *Pediatr Blood Cancer*. 2012;59(2):365-71.
19. Silva RC, Malina RM. Nível de atividade física em adolescentes do Município de Niterói, Rio de Janeiro, Brasil. *Cad Saude Publica*. 2000;16(4):1091-7.

20. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1(8476):307-10.
21. Setty BN, Stuart MJ, Dampier C, Brodecki D, Allen JL. Hypoxaemia in sickle cell disease: biomarker modulation and relevance to pathophysiology. *Lancet*. 2003;362(9394):1450-5.
22. Al-Saqladi A-WM, Cipolotti R, Fijnvandraat K, Brabin BJ. Growth and nutritional status of children with homozygous sickle cell disease. *Ann Trop Paediatr*. 2008;28(3):165-89.
23. Ohara DG, Ruas G, Walsh IA, Castro SS, Jamami M. Lung function and six-minute walk test performance in individuals with sickle cell disease. *Braz J Phys Ther*. 2014;18(1):79-87.
24. Anthi A, Machado RF, Jison ML, Taveira-DaSilva AM, Rubin LJ, Hunter L, et al. Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. *Am J Respir Crit Care Med*. 2007;175(12):1272-9.
25. Barden EM, Zemel BS, Kawchak DA, Goran MI, Ohene-Frempong K, Stallings VA. Total and resting energy expenditure in children with sickle cell disease. *J Pediatr*. 2000;136(1):73-9.
26. Ohara DG, Ruas G, Castro SS, Martins PR, Walsh IA. Musculoskeletal pain, profile and quality of life of individuals with sickle cell disease. *Rev Bras Fisioter*. 2012;16(5):431-8.
27. Taylor LE, Stotts NA, Humphreys J, Treadwell MJ, Miaskowski C. A review of the literature on the multiple dimensions of chronic pain in adults with sickle cell disease. *J Pain Symptom Manage*. 2010;40(3):416-35.
28. Gleeson M. Immune function in sport and exercise. *J Appl Physiol* (1985). 2007;103(2):693-9.
29. Makis AC, Hatzimichael EC, Bourantas KL. The role of cytokines in sickle cell disease. *Ann Hematol*. 2000;79(8):407-13.
30. McLoughlin MJ, Colbert LH, Stegner AJ, Cook DB. Are women with fibromyalgia less physically active than healthy women? *Med Sci Sports Exerc*. 2011;43(5):905-12.