FUNCTIONAL CAPACITY and quality of life IN CHILDREN AND ADOLESCENTS WITH SICkLE CELL ANEMIA

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Abstract

Objective: To evaluate the functional capacity, pulmonary function and quality of life of children and adolescents with sickle cell anemia (SCA) and to test the reproducibility of functional capacity tests in this population. **Method**: Cross-sectional study with volunteers with SCA genotype Hb-SS (SCAG), aged 6 to 18 years matched in age and gender to the control group (CG). Spirometry, 5-repetition sit-to-stand test (5STS-test), modified shuttle walk test (MSWT), and Pediatric Quality of Life Questionnaire (PedsQL) were performed. The reproducibility of 5STS-test and MSWT was evaluated: **Results**: 48 volunteers of SCAG and 48 of CG were evaluated. Pulmonary function of SCAG (FVC: 92 ± 15% pred.; FEV 1 /FVC: 84 ± 8% pred.) was worse than the CG (104 ± 15% pred.; FEV 1 /FVC: 90 ± 6% pred.) $p < 0.05$. SCAG had worse functional capacity registered by distance walked: 576m (515-672m) and 5STS-test: 8 seconds (7.4-8.9seconds) compared to the CG who showed distance walked: 1010m (887- 1219m) and 5STS-test: 7 seconds (7.0-8.1seconds), $p < 0.001$. SCAG had worse quality compared to CG, $p < 0.05$. The reproducibility was good of MSWT (ICC 0.99 (0.98-0.99 IC-95%)) and 5STS-test (ICC 0.80 (0.69 – 0.88), $p < 0.001$ **. Conclusion**: Children and adolescents with sickle cell anemia showed worse capacity to walk or run, and to perform sit-to-stand test. Additionally, they have poor quality of life when compared with their control peers. The MSWT and 5STS-test showed reproducible to be applied in pediatric individual with SCA.

Introduction

Sickle cell anemia (SCA) is the most common monogenic disease in the world, predominant among people of African descent and brown skin. It is characterized by the occurrence of sickle cells due to the mutant presence of hemoglobin S (HbS).[1] The altered erythrocytes present difficulty in circulating in the blood, which causes vaso-occlusive phenomena and infarction in the affected area. In addition, this altered physiology causes permanent damage to tissues and organs, with the cardiorespiratory system being the target of acute and chronic manifestations.[2] Thus, lung function and cardiovascular impairments changes favor a sedentary lifestyle, reduced functional capacity and worsening quality of life (QOL).[3,5,6] Different tests that assess functional capacity are available. Hostyn[4] et al. (2013), showed higher number of hospitalizations in children and adolescents with SCA (genotype Hb-Sβ^0–thalassemia) who walked shorten distance at the 6-minute walk test (6MWT). This test has been widely used, however there are some limitations as self-paced test, floor effect. Thus, the Modified Shuttle Walk Test (MSWT) in patients with SCA can be an alternative, considering it has already been described in children and adolescents' other chronic conditions.[7 -10]

The MST is simple and low cost, needs corridor of 10 meters (m), limited by symptoms, externally paced, and allows the volunteer walk or run.[4] This test is appropriated to assess exercise intolerance in individuals with different severity status. Additionally, the MSWT can be used to exercise prescription. [11] The sit

and stand movement are considered fundamental for mobility and functional independence. This movement is part of several activities of daily living (ADL) and the literature has already described the 5-repetition sit-to-stand test (5STS-test) as a simple and low coast test to measure lower limb strength, balance control, risk of falling and exercise capacity.[13] Thus, the 5STS-test is another alternative to assess different aspects of functional capacity compared to MSWT. This study aims to evaluate and compare the functional capacity, pulmonary function and quality of life of children and adolescents with SCA with their healthy peers and to analyze the reproducibility of the functional capacity tests on the sickle cell anemia group. The hypotheses are that SCA individuals have reduced exercise capacity, lung function and quality of life.

Methods

This is a cross-sectional study carried out in individuals diagnosed with SCA genotypes (HbS-S) between 6 and 18 years old, from the Pediatric Hematology Outpatient Clinic of Darcy Vargas Children Hospital, Sao Paulo, Brazil. The control group (CG) was composed by healthy individuals matched for age and sex, recruited from educational institutions in the city of Sao Paulo, Brazil. The research was approved by the Research Ethics Committee (Protocol number: 2.843.860). The informed consent form for the study was signed by the legal guardians. All participants signed the consent form and the parents or guardians signed the informed consent form.

Individuals who had neurological or musculoskeletal diseases or did not perform the tests properly were excluded, also those who were hospitalized in the last four weeks. Individuals in the control group who presented lung function $< 80\%$ of the predicted value were also excluded.

Protocol

All evaluations were carried out in a single day. The sickle cell anemia group (SCAG) was evaluated in the Pediatric Hematology Outpatient Clinic of Darcy Vargas Children Hospital, Sao Paulo, Brazil, while the CG was evaluated in public or private schools. Data was performed between October 2018 and July 2019. The present comorbidities and medications in use in the SCAG were obtained from medical records and confirmed in the interview. The mean values of the last three hemoglobin collected in the last 12 months were used to estimate the basal hemoglobin. The assessments were carried out in the following sequence: Pediatric Quality of Life Inventory^{TM} 4.0 (PedsQl^{TM}4.0) quality of life questionnaire, assessment of lung function (spirometry and respiratory muscle strength) and functional capacity (modified shuttle test and 5-repetition sit-to-stand).

Pulmonary function

Spirometry was performed by KOKO Sx1000® device (n-Spire-HealthTM, Longmont, USA) previously calibrated according to recommendations.[12] The variables analyzed were forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) , FEV_1 / FVC ratio, forced expiratory flow between 25-75% of FVC ($FEF_{25-75\%}$) and peak expiratory flow (PEF)[12, 13] Values were expressed in absolute values and as a percentage of the predicted value.[12]

Maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) were measured with a manovacuometer (GERAR®, scale between +120 to –120cmH2O) following the guidelines.[14] To measure MIP, maneuvers were performed from the residual volume; and, to measure MEP from total lung capacity. The patient was asked for a maximum inspiratory or expiratory effort. At least five maneuvers were performed or until reproducible values were obtained.[8] The best value was used for analysis. Values are expressed in absolute terms and as a percentage of the predicted value.[15]

Quality of life

Quality of life was assessed by PedsQl^{TM}4.0 questionnaire applied according to the age group. This questionnaire has versions for five to seven years old (answered by their parents), eight to twelve years old and thirteen to eighteen years old. The domains are physical, emotional, social and school aspects. Each problem was asked for the adolescent or parents in the last month on a five-level response scale (0 = never a problem;

1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). For children aged 5 to 7, the scale is simplified to three points (1 = not at all; 2 = sometimes; 3 a lot), with each answer anchored on a similar scale visual with happy, neutral and sad faces respectively. The items are score-reverse and linearly transformed to a scale from 0 to 100 (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). Therefore, high scores indicate better QOL. PedsQl ^{TM}4.0 scores are computed by adding the items divided by the number of items answered.[16,17]

Functional Capacity

Both 5STS-test and MSWT were performed twice on the same day (test and retest), with an interval of 30 minutes between them. The 5STS-test was performed with the subject sitting on a chair with his arms crossed over his chest. The patient should perform five movements of getting up and sitting down as quickly as possible. The height of the chair was adjusted to reach the angle of flexion of the hips and knees at 90º and feet flat on the floor. The test outcome was the execution time in seconds (s).[18]

The MSWT was performed in a 10 m long corridor according to the original description[19]. It is a test externally paced by an audible signal, in which the speed increases every minute, varying from 1.79 to 10.2 km / h.[20] The test ends when the volunteer is unable to follow the speed or needs to stop the test due to fatigue, dyspnea or when SpO_2 remains below 82%. The outcome is the distance walked in meters and the percentage of the predicted value.[21]

The order of the tests (MSWT and 5STS-test) was randomized. Heart rate (HR), dyspnea and lower limb fatigue (modified Borg scale[22]) were assessed at the beginning and at the end of all the tests.

Statistical analysis

Sample size was calculated based on a pilot study, with the distance walked in the MSWT for the SCAG being 598 ± 129 m and in the CG 900 ± 193 m. Based on power of 95% and alpha of 0.05, the effect size was 1.8, the number of subjects was 10 for each group. The 5STS-test showed an average time of 9 ± 2 seconds for SCAG and 8 ± 1 seconds for the CG in the pilot study. Based on power of 80% and alpha of 0.05, the effect size was 1.0 and the number of subjects was 41 for each group.

The normality of the studied variables was analyzed using the Shapiro Wilk test. Parametric data were represented by mean and standard deviation, and nonparametric data were expressed as median and interquartile range. For comparisons between groups, the unpaired student t test or the Mann-Whitney test was used depending on the normality of the data.

The intraclass correlation coefficient (ICC) and the Bland-Altman analysis were used to test the reproducibility of tests MSWT (distance walked) and 5STS-test (time to perform) test and retest, in the SCAG. The ICC was characterized as follows: low reliability <0.40; moderate reliability 0.40 - 0.75; strong reliability 0.75 - 0.90; excellent reliability <0.90.[23,24]Statistical significance was considered p <0.05. Data analysis was performed with the software SPSS version 22.

Results

One hundred and eighteen volunteers were eligible for this study, of them 22 excluded due to the lack of understanding the execution of some of the tests. In total, 96 volunteers were evaluated, with the sickle SCAG consisting of 48 volunteers (56% female) with mean age of 13 ± 3 years. The characteristics of the volunteers are described in**Table 1** .

Spirometric values of the SCAG were worse when compared to the CG (p <0.05). Regarding respiratory muscle strength, there was difference between groups with lower MEP values in the SCAG compared to the CG, p = 0.03 (**Table 2**).

The SCAG spent more time to perform 5STS-test, 8 seconds (7-9 seconds), compared to the CG, 7 seconds (7-8 seconds), p < 0.001. Similar result was observed at the MST, which distance walked was shorter at SCAG 576m (515-672m), compared to the CG, 1010m (887-1219m), p < 0.001 (**Table 2**).

The SCAG had poorer quality of life scores than the CG according to the Pedsql ^{TM}4.0 domains: physical functioning 66 (59 - 74) vs 94 (79 - 97), emotional functioning 65 (50 - 80) vs 75 (60 - 89), social functioning 80 (66 - 94) vs 95 (81 - 100) and school functioning 50 (40 - 70) vs 87 (74 - 91), p <0.05.

To test the reproducibility between the SCAG functional capacity tests, the outcomes were compared between test and retest. The ICC was excellent between the two MSWT: 0.99 (0.98-0.99 IC-95%) p <0.001. The Bland-Altman analysis showed bias of -1.6m (-42m - 39m) were observed (**Figure 1A**). Similar results were observed at 5STS-test with an excellent ICC: 0.8 (0.7 – 0.9) p <0.001. The Bland Altman's analysis showed bias of 0.36 seconds was observed (-2.6 - 3.3 seconds) (**Figure 1B**).

Discussion

In the present study, we identified that children and adolescents with SCA showed reduced functional capacity, quality of life and pulmonary function when compared to their healthy peers. Additionally, the clinical field tests MSWT and 5STS-test proved to be reproducible to assess the functional capacity in these volunteers. As far as we know, this is the first study that includes these tests of functional capacity in the evaluation of individuals with SCA.

Cardiorespiratory morbidity of SAC contributes to functional capacity decreasing.[25,26] This can be associated with anthropometric variables such as weight and height that were worse in patients of the SCAG compared to control group.[26]Several studies have shown that the resting energy expenditure of these patients is up to 20% higher when compared to healthy individuals, this is due to erythropoiesis, increased cardiac work, chronic hemolysis and hypoxia in tissues.[22,27,28]

Studies have already pointed out the relationship between low hemoglobin and decreased performance in the 6MWT in children with SAC.[29,30] The status of chronic anemia and the reduction in hemoglobin transport in the SCAG, may have caused a lower carrying of the oxygen and may have provided worse performance during the tests. In this study, the mean Hb of the SCAG was 8 ± 1g/Dl. The chronic hemolysis may impair the performance in the MSWT for promoting greater fatigue. Additionally, patients with SCA tend to have sedentary behavior due to the chronicity of the disease, which is an important aspect in reducing functional capacity.[31,32]

Hospital admissions due to cardiopulmonary complications occur due to frequent episodes of acute chest syndrome (ACS) and lower lung function. In SCA, patients tend to have the syndrome of high cardiac output, described as the disease that most increases cardiac output at rest, contributing to the lower performance in activities such as walking fast or running and playing.[33] In this study, both groups reached higher values of heart rate (more than 80% of the maximum heart rate), at the peak of the MSWT. However, the patients of the SCAG reached these values with a much shorter distance than the CG, which highlights the aspect of sedentary lifestyle, lower exercise capacity and chronicity of the disease.[34,35]

Children and adolescents with SCA are exposed to several factors that contribute to the decrease in QOL in the physical and social fields. The results of this study showed a significant difference in all domains of the PedsQl.[16, 17] In the physical functioning domain, several studies reported that pain has a greater impact on QoL in patients with SCA, although its intensity is variable and depends on the individual characteristics of each patient. Pain is the main symptom that lead to frequent hospital admissions and higher school absenteeism.[42,43,44] Acute or chronic pain affect functional status, which predisposes these children and adolescents to remain at rest and sedentary behavior.[25,28,44]

The 5STS-test and MSWT showed to be reproducible in SACG. Additionally, we observed an excellent value in the ICC and Bland Altman analysis with a small difference between the measurements and acceptable limits of agreement. Similar results for the MST were observed in pediatric patients with cerebral palsy[45] and cystic fibrosis.[46] Bohannon et al, described test and retest reliability for 5STS-test from strong to excellent in the ICC analysis for healthy adults.[47] This shows that two test (5STS-test and MSWT) should be performed to assess functional capacity in SAC individuals.

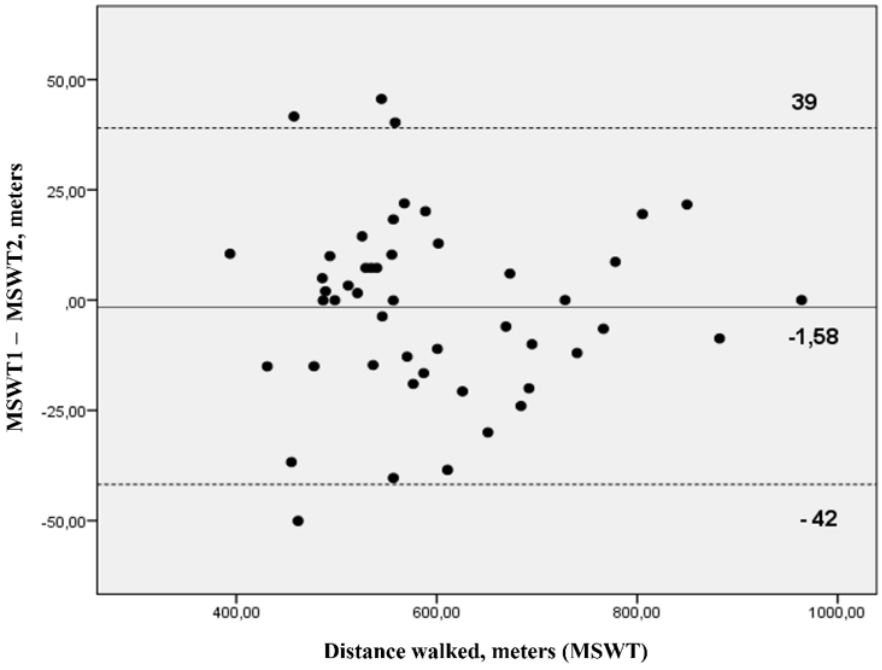
The main limitation of the study was the lack of stratification of patients by disease severity; however, the

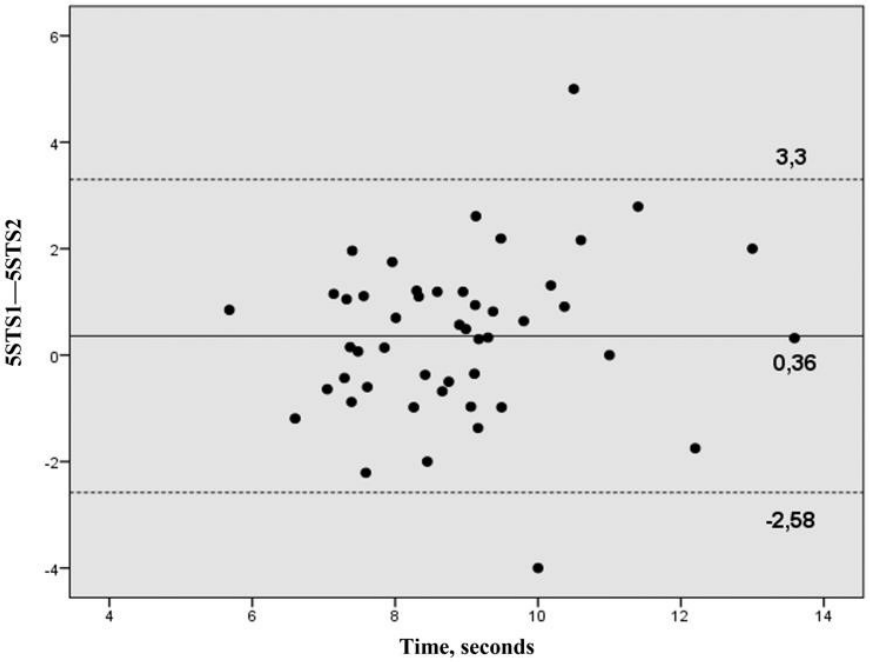
choice was made to select the group with the greatest impairment, so that a greater number of individuals were evaluated.

We conclude that children and adolescents with SCA-HbS-S genotype have reduced functional capacity when compared to their healthy peers, as well as having a worse quality of life and lung function. Additionally, MSWT and 5STS-test proved to be reproducible in this population and can be used as an alternative to evaluate functional capacity.

List figure legends:

Figure-1 Bland Altman of the distance in meters in the first and second MSWT (A) and the time in seconds in the first and second 5STS-test (B). Solid lines indicates the reference mean bias and the dashed lines indicate the central mean bias and the upper and lower limits of 95% agreement between tests.





Variables	Control Group (n=48)	Sickle Cell Anemia Group (n=48)	p
Age, years	13 (10 -15)	13 (9 -15)	0.811
Height, cm	159 (140 -167)	147 (132 -158)	0.003
Weight, Kg	47 (35.7 -58.3)	37 (28 -51)	0.012
BMI, Kg/m²	19 (16.2 -21.8)	17 (15.5 -20.1)	0.086
Hb, g/Dl	-	8 ± 1	-
Use of Hydroxyurea, n (%)	-	34 (70.8%)	-
FVC, L (%prev.)	3.3 ± 1.0 (104 ± 15)	2.4 ± 0.8 (92 ± 15)	<0.001
FEV_1, L (%prev.)	2.91 ± 0.9 (101 ± 13)	2.0 ± 0.6 (83 ± 15)	<0.001
FEV_1/FVC, %	90 ± 6	84 ± 8	<0.001
PEF, L (%prev.)	5.7 ± 1.8 (92 ± 18)	3.9 ± 1.3 (72 ± 22)	<0.001
$FEF_{25-75\%}$, L (%prev.)	3.5 ± 1.2 (108 ± 22)	2.3 ± 0.7 (82 ± 22)	<0.001

Variables	Control Group (n=48)	Sickle Cell Anemia Group (n=48)	p
cm: centimeters; Kg: kilogram; Kg / m2: kilogram per square meter; BMI: body mass index; Hb: hemoglobin; g / dL: grams deciliters; FVC: forced vital capacity, L: liters; % pred: percentage of predicted; FEV1: forced expiratory volume in the first second; FEV_1/FVC: ratio of forced expiratory volume in the first second divided by forced vital capacity; PEF: peak forced expiratory flow; FEF25-75%: forced expiratory flow 25-75 percent.	cm: centimeters; Kg: kilogram; Kg / m2: kilogram per square meter; BMI: body mass index; Hb: hemoglobin; g / dL: grams deciliters; FVC: forced vital capacity, L: liters; % pred: percentage of predicted; FEV1: forced expiratory volume in the first second; FEV_1/FVC: ratio of forced expiratory volume in the first second divided by forced vital capacity; PEF: peak forced expiratory flow; FEF25-75%: forced expiratory flow 25-75 percent.	cm: centimeters; Kg: kilogram; Kg / m2: kilogram per square meter; BMI: body mass index; Hb: hemoglobin; g / dL: grams deciliters; FVC: forced vital capacity, L: liters; % pred: percentage of predicted; FEV1: forced expiratory volume in the first second; FEV_1/FVC: ratio of forced expiratory volume in the first second divided by forced vital capacity; PEF: peak forced expiratory flow; FEF25-75%: forced expiratory flow 25-75 percent.	cm: centimeters; Kg: kilogram; Kg / m2: kilogram per square meter; BMI: body mass index; Hb: hemoglobin; g / dL: grams deciliters; FVC: forced vital capacity, L: liters; % pred: percentage of predicted; FEV1: forced expiratory volume in the first second; FEV_1/FVC: ratio of forced expiratory volume in the first second divided by forced vital capacity; PEF: peak forced expiratory flow; FEF25-75%: forced expiratory flow 25-75 percent.

Table 1. Characteristic of the included volunteers.

Table 2. Comparison of modified shuttle walk test (MSWT) and 5-repetition sit-to-stand test (5STS-test), and muscle strength between groups.

Variables	Variables	Control Group (n=48)	Sickle Cell Anemia Group (n=48)	P
MSWT	**MSWT**	**MSWT**	**MSWT**	**MSWT**
Distance walked, m	Distance walked, m	1010 (887 - 1219)	576 (515 - 672)	<0.001
Distance walked, %prev.	Distance walked, %prev.	101 (89 - 111)	58 (50 - 64)	<0.001
Heart rate, maximal, bpm	Heart rate, maximal, bpm	200 (193 - 203)	193 (185 - 199)	0.058
Borg Dyspnea	Borg Dyspnea	5 (3 - 7)	5 (4 - 7)	0.344
Borg Lower limb	Borg Lower limb	5 (3 - 7)	5 (3 - 7)	0.227
SpO_2%	SpO_2%	97 (96 - 98)	91 (89 - 96)	<0.001
5STS-test	**5STS-test**	**5STS-test**	**5STS-test**	**5STS-test**
Time, seconds	Time, seconds	7 (7 - 8)	8 (7 - 9)	<0.001
SpO_2%	SpO_2%	97 ± 1	93 ± 3	<0.001
Heart rate, maximal, bpm	Heart rate, maximal, bpm	106 ± 17	109 ± 13	0.409
Borg, Dyspnea	Borg, Dyspnea	0 (0-1)	0 (0-1)	0.352
Borg, Lower limb	Borg, Lower limb	1(1-2)	1(1-3)	0.411

Variables	Variables	Control Group (n=48)	Sickle Cell Anemia Group (n=48)	P
Muscle strengh	**Muscle strengh**			
MIP, %pred	MIP, %pred	91 (80-111)	91(78-103)	0.205
MEP, %pred	MEP, %pred	96(87-108)	87(71-107)	0.039

MIP: maximal inspiratory pressure; MEP: maximum expiratory pressure.

Table 3. Reproducibility of modified shuttle walk test (MSWT) and 5-repetition sit-to-stand test (5STS-test) at the sickle cell anemia group (N= 48).

Variables	Test 1	Test 2	P
MSWT			
Distance walked, m	595 ± 123	596 ± 126	0.602
Distance walked, %prev.	58 ± 12	58 ± 13	0.723
Heart rate maximal, bpm	189 ± 10	192 ± 9	0.002
5STS-test			
Time, seconds	9 ± 1	8 ± 1	0.108
Hear rate, maximal, bpm	110 ± 14	109 ± 13	0.268

m: meters; % prev: percentage of predicted; HRmax: maximum heart rate; bpm: beats per minute, s: seconds

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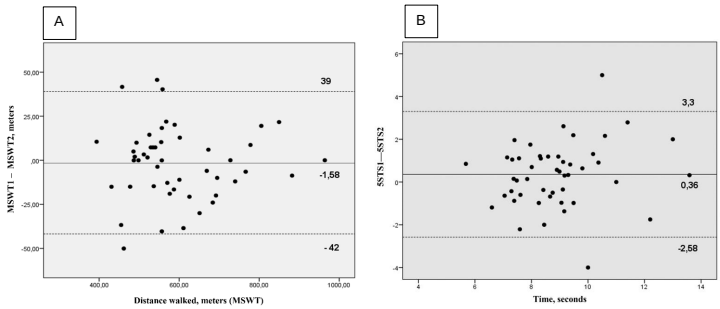

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