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ORIGINAL RESEARCH

Exercise capacity and daily physical activity levels in children and adolescents with cystic fibrosis: association with nutritional status, lung function, hospitalization and antibiotic use

Capacidade de exercício e nível de atividade física diária de crianças e adolescentes com fibrose cística: associação com estado nutricional, função pulmonar, hospitalização e uso de antibióticos

Capacidad de ejercicio y nivel de actividad física diaria de niños y adolescentes con fibrosis quística: asociación con estado nutricional, función pulmonar, hospitalización y uso de antibióticos

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ABSTRACT | To evaluate the exercise capacity and daily physical activity level among children and adolescents with cystic fibrosis, and its association with nutritional status, lung function, hospitalization time, and days taking antibiotics. This is a cross-sectional study in individuals with cystic fibrosis aged 6 to 18 years. Information on clinical profile, history of hospitalizations and antibiotic use were collected. Participants were submitted to spirometry, bioimpedance, and an assessment of exercise capacity with modified shuttle test (MST), and the level of physical activity was measured with the International Physical Activity Questionnaire (IPAQ) using an accelerometer for 5 days. In total, 30 individuals participated, aged 11.2±3.6 years, and 68.0±24.8% in forced expired volume in the first second (FEV_1). The median distance covered in the MST was 820 meters (66.3%), showing association with lung function (r=0.78), nutritional status (r=0.38), hospitalization time (r=-0.42) and antibiotic use (r=-0.46). According to the questionnaire, 20 patients (64.6%) were classified as sedentary, the accelerometer revealed that the individuals spend 354.2 minutes in sedentary activities and only 14.9 minutes in moderate to vigorous activities per day. The higher the percentage of time in moderate to vigorous physical activity, the higher the body mass index (BMI) and the shorter the hospitalization time. Exercise capacity and level of physical activity in children and adolescents with cystic fibrosis is reduced and associated with lower BMI values and with an increase in hospitalization time.

Keywords | Cystic Fibrosis; Exercise Capacity; Physical Activity Level; Antibiotics; Hospitalization.

RESUMO | O objetivo deste trabalho é avaliar a capacidade de exercício e nível de atividade física diária de crianças e adolescentes com fibrose cística e associar com estado nutricional, função pulmonar, tempo de hospitalização e uso de antibióticos. Trata-se de estudo transversal em indivíduos com fibrose cística entre 6 e 18 anos, registrando-se informações sobre perfil clínico, histórico de hospitalizações e uso de antibióticos. Os participantes foram submetidos

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à espirometria, bioimpedância, avaliação da capacidade de exercício com teste de Shuttle modificado (MST), o nível da atividade física foi medido por meio do questionário internacional de atividade física (IPAQ) e usando acelerômetro por 5 dias. Participaram 30 indivíduos com idade de 11,2 ± 3,6 anos e volume expirado forçado (VEF_1) de 68,0 ± 24,8%. A mediana da distância percorrida no MST foi de 820 metros (66,3%) e demonstrou associação com a função pulmonar (r = 0,78), estado nutricional (r = 0,38), tempo de hospitalização (r = -0,42) e uso de antibióticos (r = -0,46). De acordo com o questionário, 20 pacientes (64,6%) foram classificados como sedentários, o acelerômetro revelou que os indivíduos passam 354,2 minutos em atividades sedentárias e apenas 14,9 minutos em atividades moderadas a vigorosas por dia. Quanto maior a porcentagem de tempo em atividade física moderada a vigorosa, maior o índice de massa corpórea (IMC) e menor o tempo de hospitalização. Assim, a capacidade de exercício e nível de atividade física em crianças e adolescentes com fibrose cística apresentou-se reduzida e associada com menores valores de IMC e aumento do tempo de hospitalização.

Descritores | Fibrose Cística; Capacidade de Exercício; Nível de Atividade Física; Antibióticos; Hospitalização.

RESUMEN | El propósito de este trabajo fue evaluar la capacidad de ejercicio y el nivel de actividad física diaria de los niños y adolescentes con fibrosis quística, así como asociarlos con el estado nutricional, la función pulmonar, la duración de la permanencia hospitalaria y el uso de antibióticos. Este es un estudio transversal realizado con individuos con fibrosis quística con edades comprendidas entre los 6 y los 18 años, y que registra información sobre el perfil clínico, los antecedentes de hospitalizaciones y el uso de antibióticos. Los participantes se sometieron a la espirometría, la bioimpedancia, la evaluación de la capacidad de ejercicio con la prueba de *Shuttle* modificada (MST); para medir el nivel de actividad física se aplicó el Cuestionario Internacional de Actividad Física (IPAQ) y el uso del acelerómetro durante 5 días. Participaron 30 personas de entre 11,2 ± 3,6 años de edad y volumen espirado forzado (VEF_1) de 68,0 ± 24,8%. La mediana de la distancia recorrida en el MST fue de 820 metros (66,3%) y se mostró asociación con la función pulmonar (r=0,78), el estado nutricional (r=0,38), la duración de la permanencia hospitalaria (r=-0,42) y el uso de antibióticos (r=-0,46). El cuestionario reveló que 20 pacientes (64,6%) estaban sedentarios, y el acelerómetro evidenció que ellos pasan 354,2 minutos en actividades sedentarias y solo 14,9 minutos en actividades moderadas a intensas al día. Cuanto mayor sea el porcentaje de tiempo dedicado a la actividad física moderada a intensa, mayor será el índice de masa corporal (IMC) y menor la duración de la permanencia hospitalaria. Por lo tanto, la capacidad de ejercicio y el nivel de actividad física de niños y adolescentes con fibrosis quística fueron menores y están asociadas con bajos valores de IMC y con una permanencia hospitalaria más prolongada.

Palabras clave | Fibrosis Quística; Capacidad de Ejercicio; Nivel de Actividad Física; Antibióticos; Hospitalización.

INTRODUCTION

Cystic Fibrosis (CF) is an autosomal recessive genetic disease that affects several organic systems, including the respiratory, with persistent infections, airway obstruction and progressive reduction of forced expired volume in the first second (FEV_1), resulting in dyspnea, exercise intolerance and sedentary lifestyle[1,2]. Moreover, the involvement of the gastrointestinal system causes nutritional deficit, contributing to the reduction of muscle mass, physical inactivity[3-5], osteopenia, osteoporosis and functional loss[6].

Epidemiological data indicate that 27% of children and 41% of adolescents with CF suffer one or more episodes of respiratory exacerbations, requiring hospitalization for 10 to 11 days on average. The hospitalization period removes the individual from the school and family environment, affecting quality of life[7]. The number of exacerbations and less than six months between such events increase morbidity and mortality by CF[8].

Studies show that aerobic capacity is a predictor for hospitalization and mortality in CF patients. Reduction in exercise capacity is multifactorial in origin, including airway obstruction, age, nutritional status, respiratory and peripheral muscle strength[9-11]. Schneiderman-Walker et al. state that exercise capacity influences the respiratory system, improving airway clearance and slowing the decline in lung function[12].

Donadio et al. demonstrated that exercise capacity does not necessarily follow the expected decline in lung function over time[9]. Ledger et al. found a reduction in the need for antibiotic use during the year of intervention with physical exercises, playing an important role in the decline of pulmonary function[13]. A systematic review conducted in 2019 showed that the risk of mortality in individuals with CF was 4.9 times higher when considering maximum

oxygen consumption (VO_2)<82% of the predicted or 45mL/kg/ml[14].

Thus, the evaluation of exercise capacity in CF patients is extremely important, being a potential marker for disease progression. The cardiopulmonary exercise test is considered the gold standard in the evaluation of exercise capacity; however, its application is limited, so field tests such as the modified shuttle test (MST) become a viable option, demonstrating better sensitivity and specificity in individuals with CF[15,16].

Furthermore, studies indicate that the longer the time spent in moderate physical activities daily, the lower the frequency of exacerbations and the need for hospitalization in CF patients[17,18]. A recent systematic review pointed out a strong association between the level of physical activity, measured objectively through accelerometer, and clinical outcomes and exercise capacity; however, the review also concluded that the number of studies that used the accelerometer is limited and present methodological weaknesses[19].

Studies using exercise tolerance tests and evaluation of the level of daily physical activity using accelerometer devices are important to better understand the associations with clinical variables predicting prognosis, improve the follow-up of CF patients in referral centers and direct therapy, aiming at maintaining pulmonary function and reducing exacerbation and hospitalization events.

Therefore, the objective of this study was to evaluate the exercise capacity and level of physical activity using an accelerometer device and associate it with nutritional status, pulmonary function, hospitalization time and antibiotic use in children and adolescents with cystic fibrosis.

METHODOLOGY

This is a cross-sectional study with a sample of patients with Cystic Fibrosis, aged between 6 and 18 years, who were followed-up at the Reference Center of the state of Espírito Santo between March and December 2018. The clinical diagnosis confirmed by sweat test or genetic test, to ensure stable clinical conditions and preserved cognitive function, was used as a criterion for the participation in this study. The exclusion criteria considered complications in the 30 days before the research and individuals who had difficulties to perform the proposed tests. Finally, 47 patients were eligible. Considering that the level of physical activity and exercise capacity are the main objects of the study, sample size calculation was based on the study by Savi et al.[20]. Based on standard deviations stipulated in two, 95% power, 5% significance index and 0.5 as the minimum correlation between the variables, a sample size of 28 individuals was estimated.

Initially, the informed consent and informed assent forms were delivered, read and signed in two copies. The following information were taken from the medical records: age, gender, Shwachman-Kulczycki (SK) score, presence and type of chronic colonization, hospitalization time and antibiotic use in the last year.

Spirometry was performed using a KoKo device (nSpire Health, Inc., Circle Longmont, USA), duly calibrated, following the criteria of the American Thoracic Society. The following variables were analyzed: forced vital capacity (FVC); FEV_1; forced expired flow between 25 and 75% ($FEF_{25-75\%}$); and the FEV_1/FVC relation. The predicted values were obtained using the global lung initiative 2012 equation[21].

Bioimpedance was used to assess nutritional status with Inbody 720 equipment (InBody Co., Los Angeles, USA), which uses the multifrequency segment direct measurement method with tetrapolar electrodes in eight tactile points. Participants were instructed to follow some recommendations before the exam, such as fasting for 12 hours, not performing strenuous physical exercises and not consuming caffeine-based beverages in the 24h before and urinating prior to the examination. Data on weight, skeletal muscle mass, fat mass and body mass index (BMI) were obtained.

Next, the exercise capacity was evaluated using the maximal effort test, the modified shuttle test (MST), validated for the Cystic Fibrosis population. For the test, a 10-meter track was used, on which the participant was instructed to walk within the rhythm determined by sound signals until fatigue or presence of limiting symptoms. The test was interrupted when the patient presented inability to maintain rhythm or reached the maximum heart rate. Peripheral oxyhemoglobin saturation (SpO_2) and heart rate were recorded at the end of each level of the test using a Nonin brand finger oximeter, fixed to the patient's finger throughout the test. Blood pressure, heart rate, SpO_2 and respiratory rate were measured before and after the test. The variables provided by the MST were the maximum distance traveled, maximum speed reached, blood pressure, heart rate, stage and route where the test was interrupted. The predicted distance was calculated using the equation proposed in the study by Lanza et al.[22].

The short form of the international physical activity questionnaire (IPAQ-SF) was used to assess the level of daily physical activity. For subjects up to 12 years of age, IPAQ-C was used, and individuals were classified as active (≥3 points) or sedentary (<3 points). For individuals over 12 years of age, IPAQ-A was used, and they were classified as active when there was a sum of at least 150 minutes per week of moderate intensity physical activities, subdivided into at least three times/week, and physical activities for at least three 20 minute/week sessions[23]. Finally, participants used a wGT3X-BT triaxial accelerometer (Vermont, San Sebastian, Spain), fixed on the left side of the waist to objectively assess the level of daily physical activity for five consecutive days. The results were expressed as mean counts/min, being classified as sedentary (<100 counts), mild (≥100 counts) and moderate to vigorous (>2296 counts)[24].

Data normality was assessed by the Shapiro-Wilk test. The normal continuous data were expressed in mean and standard deviation and the asymmetric data in median and interquartile interval. Spearman's correlation was used to correlate the variables of exercise capacity and levels of daily physical activity with clinical variables. The interpretation of the correlation coefficient (r) was weak when r<0.4, moderate when r>0.4 and r<0.7, and strong when r>0.7. All data analysis and processing were performed in the SPSS 20.0 program. The significance level adopted was 5% (p<0.05).

RESULTS

Thirty children and adolescents aged 11.2±3.6 years participated in this study, most female, 16.6±3kg/m2 BMI, FEV_1 was 68.8±24.8% of the predicted value, and 10 (33.3%) had severe pulmonary function, the mean hospitalization time was 6±13.9 days and the time of antibiotic use were 33.9±26.9 days in the last year (Table 1).

Table 1. Demographic, anthropometric and clinical profile of the sample studied

Variables	n=30
Age	11.2±3.6
Female (%)	19 (63.3)
White race (%)	17 (56.6)
Mutation Type (%)	
Heterozygous F508del	14 (46.6)
Colonization (%)	
Staphylococcus aureus	20 (65)
SK Score	
SK Total*	86.0±13.3
Nutritional status	
BMI	16.6±3
BMI Z Score	-0.74±1.16
SMM (Kg)	13.3±5
FM (Kg)	7.0±5
Pulmonary Function	
FEV_1%	68.0±24.8
FVC%	77.7±21.8
$FEF_{25-75\%}$	53.0±30.0
Hospitalization (days/year)	6.0±13.9
Antibiotic (days/year)	33.9±26.9

Caption: SK: Shwachman-Kulczycki; BMI: body mass index; SMM: skeletal muscle mass; FM: fat mass; FEV_1%: forced expired volume in the first second; FVC%: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow between 25-75%

The exercise capacity measured by the MST was 820 meters distance covered, corresponding to 66.3±23.3% of the predicted value. According to the IPAQ questionnaire, 20 individuals (64.6%) were classified as sedentary. The evaluation of the level of physical activity, through the accelerometer, showed that the participants dedicate about 354.2 min/day (54.7%) to performing sedentary activities, and only 14.9 min/day (2.4%) in moderate and vigorous activities. The data on exercise capacity and daily physical activity level are shown in Table 2. We observed a positive and moderate correlation (r=0.55) between moderate and vigorous physical activity time and the percentage of distance traveled in the shuttle test (p=0.002).

Table 2. Exercise capacity and level of physical activity

Variables	n=30
Modified Shuttle Test – MST	
Level	10.8±2
Distance (meters)*	820 (350 -1400)
Predicted distance (%)	66.3±23.3
Before MST	
Heart rate	99.4±14
Respiratory rate	24.7±8
SpO_2(%)	97±2
Borg dyspnea	0.3±1
After MST	
Heart rate	190±15
Respiratory rate	41.7±10
SpO_2(%)	95.9±5
Borg dyspnea	6.9±3

(continues)

Table 2. Continuation

Variables	n=30
Accelerometer (n=30)	
Sedentary (min/day^{-1})*	354.2 (246.2–488.5)
Sedentary (%)	42.9±15
Light activity (min/day^{-1})*	479.7 (371.2–561.3)
Mild activity (%)	54.7±13.5
Moderate to vigorous activity (min/day^{-1})*	14.9 (2.1–36.9)
Moderate to vigorous activity (%)	2.4±2.4
International physical activity questionnaire (IPAQ)	
Sedentary (%)	20 (64.6)

MST: Modified Shuttle Test; Min: Minutes; SpO_2: Oxyhemoglobin saturation; IPAQ: international physical activity questionnaire.
*Asymmetric variables, expressed in median and interquartile range.

Exercise capacity showed a positive and strong correlation with FEV_1 (r=0.78) and weak correlation with BMI score (r=0.38), and inversely proportional correlation to hospitalization time (r=-0.42) and antibiotic use (r=-0.46) (Figure 1).

The higher the percentage of time that individuals spent developing moderate to vigorous activities, the higher the BMI Z score (r=0.51) and the shorter the hospitalization time (r=-0.37). Moreover, the higher the percentage of time in sedentary activities, the lower the BMI Z score (r=-0.43) (Figure 2). All correlations between exercise capacity and level of physical activity with clinical variables are shown in Table 3.

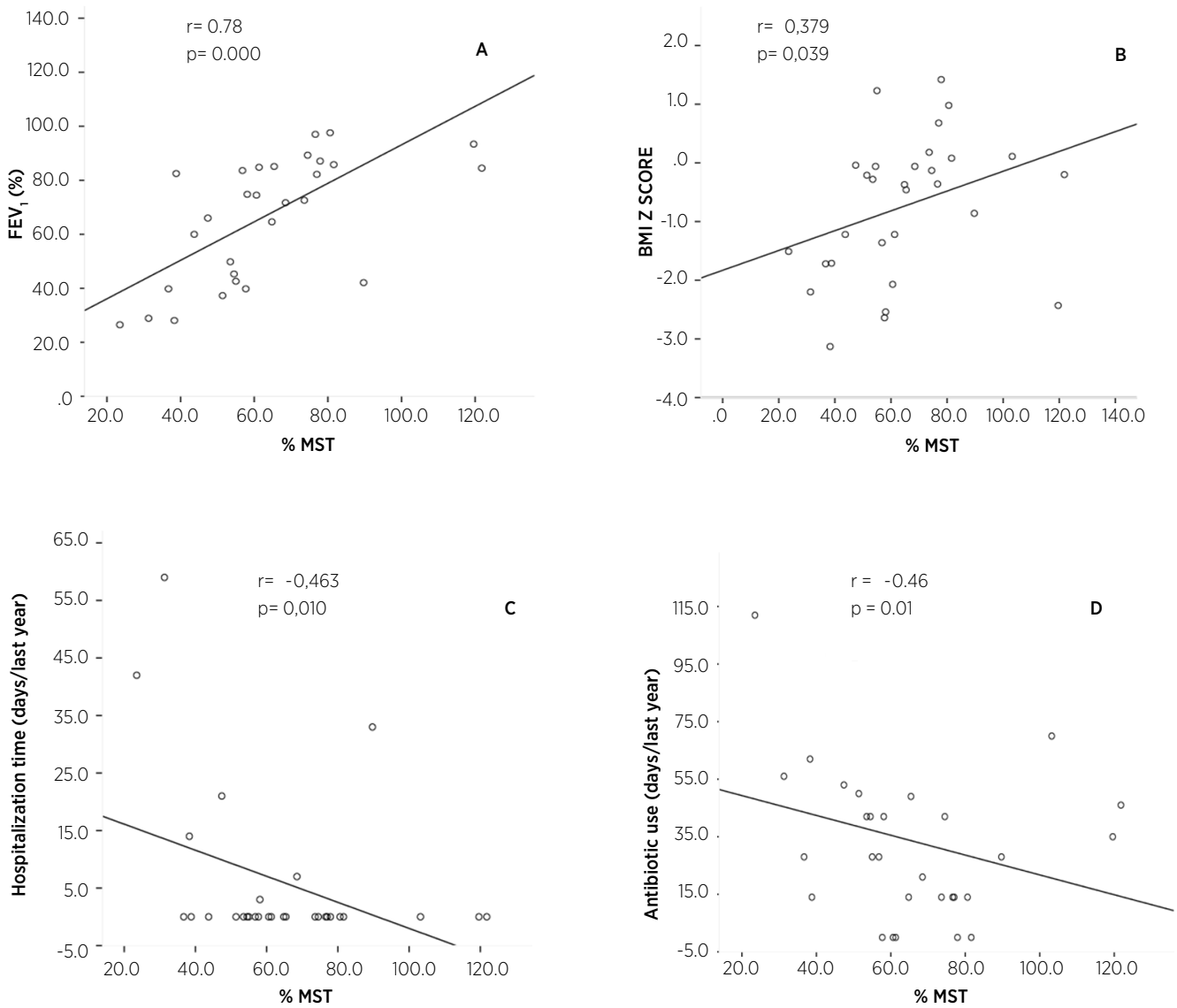

Figure 1. Correlation of exercise capacity with: (A) forced expired volume in the first second (FEV_1%); (B) Body mass index (BMI) Z Score; (C) hospitalization time; and (D) Antibiotic use

Table 3. Correlation between exercise capacity and level of physical activity with pulmonary function, nutritional status, time of hospitalization and antibiotic use.

		% MST Distance	Sedentary min/day	% Sedentary/day	Moderate and vigorous min/day	% Moderate and vigorous/day
Hospitalization (days/year)	r	**-.423***	.272	.279	-.341	**-.371***
	p	**.020**	.147	.136	.065	**.044**
Antibiotic (days/year)	r	**-.463***	-.108	-.038	-.058	-.072
	p	**.010**	.571	.840	.760	.705
FEV_1(%)	r	**.782****	.359	.339	.069	.076
	p	**.000**	.051	.067	.715	.688
$FEF_{25-75\%}$ (%)	r	**.665****	-.255	-.305	**.421***	**.417***
	p	**.000**	.175	.101	**.020**	**.022**
BMI (Kg/m2)	r	.342	**.415***	**.450***	-.169	-.152
	p	.064	**.023**	**.013**	.373	.424
BMI Z Score	r	**.379***	**-.372***	**-.426***	**.508****	**.511****
	p	**.039**	**.043**	**.019**	**.004**	**.004**

MST: modified shuttle test; Kg: kilogram; BMI: body mass index; FEV_1%: forced expired volume in the first second; $FEF_{25-75\%}$: forced expiratory flow between 25-75%.

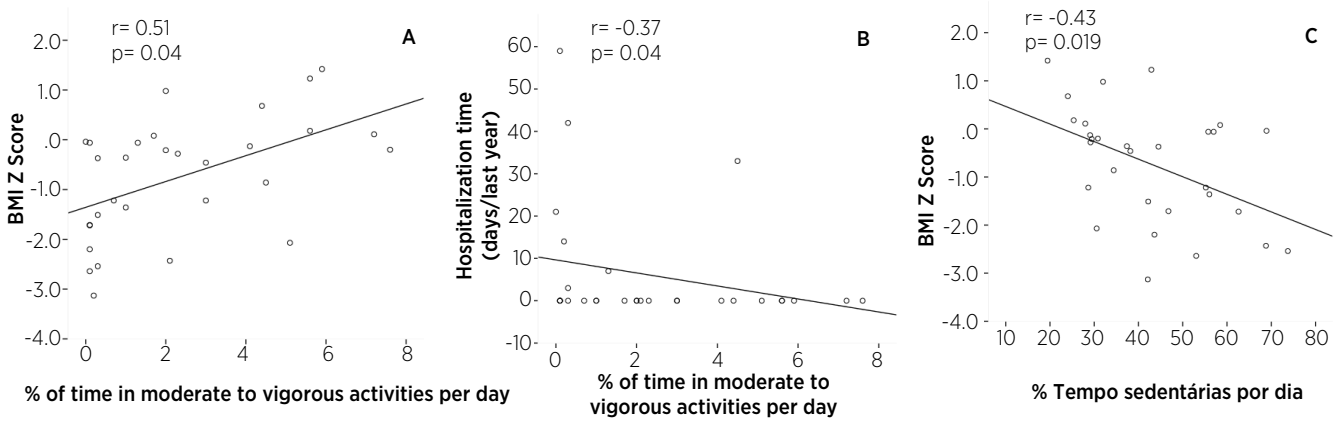

Figure 2. Correlation of % of moderate to vigorous daily physical activity with Z score of body mass index (A) and with days of hospitalization (B). Correlation % of daily sedentary physical activity and Z score of body mass index (C)

DISCUSSION

Our findings show that more than half of the sample is sedentary, spending 354 minutes in sedentary activities – corresponding to 42% of the daytime – and only 14.9 minutes per day performing moderate or vigorous activities. The physical activity level, assessed by applying a questionnaire, revealed that 64.6% of children and adolescents self-reported as sedentary.

The World Health Organization recommends at least 60 minutes of moderate to vigorous physical activity per day for children[25] and sedentary lifestyle is both a public health problem and one for the population studied, as it leads to the progression of the disease with physical and functional impairment[26]. Studies show that individuals with CF are susceptible to malnutrition and inactivity[3,27]; when we analyzed the correlation between physical activity level and nutritional status, an inversely proportional correlation was found (r=-0.46).

Aerobic exercise improves cardiorespiratory and muscle fitness, and the application of vigorous activities via seven metabolic equivalent tasks (METs) for children and adolescents, thus improving cardiopulmonary resistance, body composition, muscle strength, muscular endurance, and flexibility[28]. Some authors show that patients with cystic fibrosis often present limitation in physical exercise practice, progressively reducing their activities of daily living[29,30]. A recent systematic review conducted by Shelley et al. showed a positive association between exercise capacity and physical activity level measured by accelerometer, however the number of studies is limited and of low methodological quality[19]. Our findings corroborate this association, demonstrating that the longer the time in moderate and vigorous daily physical activity, the better the tolerance to exercise.

Saglam et al., in their study on individuals with CF, normal pulmonary function and mild disease, reported that MST has a moderate to strong correlation with pulmonary function ($p<0.05$)[10], corroborating the findings of our study, in which MST ($r=0.69$).

Nutritional follow-up and guidance are crucial for CF patients, and BMI values above the 50th percentile are recommended, although often difficult to achieve[31]. Nutritional status influences in the pulmonary function, as cases of severe malnutrition lead to significant worsening in lung function and increased risk of mortality[32]. Prospectively data collected in 319 children showed that 1kg in weight gain is associated with increased FEV_1 by 32mL. The study concluded that the children with the highest FEV_1 evolution, were those with the highest weight gain[33].

We observed a correlation between exercise capacity and nutritional status, in which higher BMI values follow a greater distance covered in the MST ($r=0.39$). Saglam et al. state that MST has similar moderate-strong correlations with age, height, weight ($p<0.05$), in which BMI measurement contributed to the distance covered in the MST ($p<0.001$)[10]. The present study found a moderate correlation between MST and skeletal muscle mass ($r=0.52$) and BMI Z score ($r=0.43$, $p>0.05$).

Regarding the hospitalization time and use of antibiotics in pediatric patients with CF, an association of these variables with exercise capacity obtained in the MST was found. Both the hospitalization time ($r=-0.42$) and the antibiotic use ($r=-0.46$) present moderate negative correlation with exercise capacity. The literature has shown that these variables lead to impairment of the functional capacity of the individual[9].

Donadio et al. demonstrated that individuals with CF who walked <577.5 meters were four times more at risk of being hospitalized and that the assessment of functional capacity is associated with a lower risk of hospitalization in the five-year period[9]. Furthermore, Waters et al. showed an association between antibiotic use and decline in pulmonary function in patients with cystic fibrosis, suggesting that pulmonary exacerbations, treated with intravenous antibiotics, may be a risk factor for the decline of pulmonary function[8]. Furthermore, another study demonstrated that individuals with reduced VO_2, obtained by assessing exercise capacity, present a mortality risk almost five times higher, indicating that it may be an important prognostic indicator in the follow-up of people with cystic fibrosis[14].

The present study presents some limitations, including its cross-sectional design, which does not allow us to accurately evaluate the cause-effect relationship. Moreover, it was impossible to use the cardiopulmonary stress test, considered the gold standard for assessing exercise capacity. However, we believe that the use of MST, which has already been validated for use in CF patients and holds a strong correlation with VO_2, was adequate for evaluation of exercise tolerance in the sample studied.

CONCLUSION

Exercise capacity in children and adolescents was reduced and associated with increased hospitalization time, antibiotic use, reduced lung function and nutritional status. The time spent in moderate and vigorous intensity physical activity per day was correlated with walking distance in the shuttle test and was associated with shorter hospitalization time and better nutritional status, however, the time that children and adolescents spend in this type of activity is much lower than recommended.

The evaluation of exercise capacity and the monitoring of the level of daily physical activity may be important predictors of prognosis in children and adolescents with CF combined with known indicators, such as FEV_1 and nutritional status; these are useful tools in the routine follow-up of patients with cystic fibrosis, guiding the multidisciplinary therapeutic approach to reduce exacerbation and hospitalization episodes, improving the patients' prognosis and quality of life.

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