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ARTICLE

The impact of physical functions on depressive symptoms in people with multiple sclerosis

O impacto das funções físicas nos sintomas depressivos em pessoas com esclerose múltipla

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ABSTRACT

Background: Multiple sclerosis (MS) is an immune-mediated disease that affects the central nervous system. The impact of MS transcends physical functions and extends to psychological impairment. Approximately 50% of people with MS develop depressive symptoms during their lifetime and depressive symptoms may predict impairment of physical functions. However, prediction of depressive symptoms based on objective measures of physical functions is still necessary. **Objective:** To compare physical functions between people with MS presenting depressive symptoms or not and to identify predictors of depressive symptoms using objective measures of physical functions. **Methods:** Cross-sectional study including 26 people with MS. Anxiety and/or depressive symptoms were assessed by the Beck Depression Inventory-II (BDI-II) and by the Hospital Anxiety and Depression Scale (HADS). Outcomes of physical functions included: the Nnnine-hole Ppeg Ttest (NHPT), knee muscle strength, balance control, the Timed Up and Go Test (TUG), and the 6-minute walk test (6MWT). Perceived exertion was measured using the Borg scale. **Results:** The frequency of depressive symptoms was 42% in people with MS. Balance control during a more challenging task was impaired in people with MS who presented depressive symptoms. Balance could explain 21–24% of the variance in depressive symptoms. 6MWT and TUG presented a trend of significance explaining 16% of the variance in the BDI-II score. **Conclusions:** Impairment in physical functions consists in a potential predictor of depressive symptoms in people with MS. Exercise interventions aiming at the improvement of physical functions, together with the treatment of depressive symptoms and conventional medical treatment, are suggested.

Keywords: Multiple Sclerosis; Depression; Physical Fitness; Walking.

RESUMO

Introdução: A esclerose múltipla (EM) é uma doença imunomediada que afeta o sistema nervoso central. O impacto da doença transcende as funções físicas e se estende a comprometimento psicológico. Aproximadamente 50% das pessoas com EM desenvolvem sintomas depressivos e estes podem predizer o comprometimento das funções físicas. No entanto, a previsão de sintomas depressivos com base em medidas objetivas das funções físicas ainda é necessária. **Objetivos:** Comparar funções físicas entre pessoas com EM que apresentam ou não sintomas depressivos e identificar preditores de sintomas depressivos usando medidas objetivas de funções físicas. **Métodos:** Estudo transversal incluindo 26 pessoas com EM. A ansiedade e/ou sintomas depressivos foram avaliadas pelo Inventário de Depressão de Beck-II (*Beck Depression Inventory* — BDI-II) e pela Escala Hospitalar de Ansiedade e Depressão. Os resultados das funções físicas incluíram: teste de PEG de nove buracos, força muscular do joelho, controle de equilíbrio, teste *Timed Up and Go* (TUG) e teste da caminhada de seis minutos (TC6M). A fadiga percebida foi medida usando a escala de Borg. **Resultados:** A frequência de sintomas depressivos na amostra foi de 42%. O controle do equilíbrio durante tarefa desafiadora foi prejudicado em pessoas com EM e sintomas depressivos. O equilíbrio pode explicar 21–24% da variação nos sintomas depressivos. O TC6M e o TUG apresentaram tendência de significância que explica 16% da variância no escore do BDI-II. **Conclusões:** O comprometimento das funções físicas é potencial preditor de sintomas depressivos em pessoas com EM. São sugeridas intervenções de exercícios físicos visando melhora das funções físicas, juntamente com o tratamento médico convencional e dos sintomas depressivos.

Palavras-chave: Esclerose Múltipla; Depressão; Habilidade Física; Caminhada.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic, immune-mediated disease that affects the central nervous system. The accumulation of demyelinating lesions in different areas of the white and grey matters of the brain and the spinal cord leads to a heterogeneous clinical manifestation of the MS disease[1]. Impairment of physical and cognitive functions increase as the disease progresses, being walking and thinking/memory the most valuable functions according to patients' and physicians' opinion[2]. However, the impact of the disease transcends physical functions and extends to impairments in psychological, cognitive, visual, fatigue, among others domains[3]. Health-related quality of life of people with MS seems to decrease as the perception of the degree of limitation of physical and cognitive functions increases, affecting the emotional state, social functioning and, consequently, the mental health[4,5].

About 25 to 50% of people with MS develop depressive symptoms during their lifetime, a number two to five times higher compared with the general population[6]. However, although these symptoms are common, they are often underdiagnosed[7], and the impacts of the disease, especially for younger people, produce feelings of helplessness and low self-efficacy in MS patients[7,8]. A study[7] investigating factors associated with anxiety and depressive symptoms, using a multivariate model in MS, has suggested that these factors could be grouped as follows:

- the cause of increase in anxiety or depressive symptoms (e.g., male sex, concussion, and other medical conditions);
- the result of anxiety or depressive symptoms (e.g., use of antidepressants or anxiolytic-sedative medications);
- both, the cause and the result (e.g., less physical activity, being unemployed); and
- correlate of anxiety or depressive symptoms or part of the same disease process (e.g., disability).

Regarding impairment of physical functions and impact on anxiety and/or depressive symptoms in people with MS, decrement in subjective walking capacity seems to predict changes in depressive symptoms at a 2-year follow-up[9]. Nevertheless, the baseline subjective walking capacity, measured by the Multiple Sclerosis Walking Scale (MSWS-12), has been associated with depressive symptoms[9], and explained approximately 20% of the variance related to the symptoms[10]. On the other hand, objective short walking tests were not significantly different between depressed and nondepressed people with MS[11], particularly when controlling for age, sex, and the Expanded Disability Status Scale (EDSS)[10]. However, function self-efficacy proved to be associated with walking speed (timed 25-foot walk test, T25FW) and endurance (6-minute walk test — 6MWT)[12], suggesting the importance of mental health related to confidence for performing activities of daily living. Furthermore, a study investigating depressive symptoms as predictors of subjective balance control showed that depressive symptoms explained 11–17% of the variance in balance, suggesting that as the symptoms increase, the capacity of performing functional activities that require balance decreases[13].

Considering that disability, usually measured by walking capacity and sensory functions, which are also related to balance, is a correlate of anxiety and/or depressive symptoms, and might be part of the same disease process, it seems necessary to investigate potential predictors of anxiety and/or depressive symptoms concerning physical functions. Then, the development of strategies, such as physical exercise and/or pharmacologic interventions, focusing on the improvement of these physical determinants could contribute to the treatment of depressive symptoms in people with MS.

Thus, the objectives of this study were to compare physical functions between people with MS presenting depressive symptoms or not and to identify predictors of anxiety and depressive symptoms using objective measures of physical functions.

METHODS

Twenty-six people with MS (24 women/two men) were included in this cross-sectional study. A written informed consent form was obtained prior to the procedures and the study was approved by the Ethics Research Committee of the Department of Health/Brasília – Brazil. Inclusion criteria were being ≥18 years old; having the confirmed diagnosis of relapsing-remitting MS (RRMS) by a neurologist, according to the revised McDonald criteria[14]; being capable of performing the 6MWT; and being relapse free over the past 30 days. Exclusion criteria were being unable to understand the commands of motor tests; being pregnant or having any infectious, neoplastic, and psychiatric diseases (except for mood disorders); receiving treatment with other psychiatric medications, such as antipsychotics and anxiolytics; having non-controlled chronic medical conditions, such as hypertension, diabetes, and heart conditions; and presenting other neurologic conditions in addition to MS.

Disability status was scored using the EDSS by a trained neurologist[15].

Scales of anxiety and/or depressive symptoms

Anxiety and/or depressive symptoms were assessed by two neuropsychologists using two validated scales, namely:

- the Beck Depression Inventory-II (BDI-II), which is a self-report scale with 21 items whose score ranges from 0 to 63 points, with each item scoring from 0 to 3[16,17]; and

- the Hospital Anxiety and Depression Scale (HADS), which rates two components — anxiety (HADS-A) and depression (HADS-D), each consisting of 7 items, whose score ranges from 0 to 21 for each item[18].

Physical functions

Manual dexterity was evaluated using the Nine-hole Peg Test (NHPT), and the average time taken to twice perform the test was used for the analysis[19].

Dynamic muscle strength from the knee extensor and flexor muscles were assessed by an isokinetic dynamometer (Biodex Medical Systems 3, Inc., USA)[20]. The range of motion was kept within 0–80° for the knee joint. Four bilateral isokinetic (concentric/concentric) extensions and flexions of the knee joint were performed at 60° per second. The maximum value obtained between the two legs was considered for the analysis.

Balance control was based upon the displacement of the center of pressure (COP) quantified using a force platform (AccuSway Plus, AMTI Inc, USA). Participants were instructed to stand upright and barefoot on the force platform (stable surface — COP_{stable}) and on a plastic foam placed on the platform (unstable surface — COP_{foam}), keeping their eyes open and looking at a point located 1.5 meters of distance. Data were collected during three trials of 30 seconds with 60 seconds of rest. A sampling rate of 100 Hz and a Butterworth digital filter with cutoff frequency of 10 Hz were used. The COP velocity parameter was used for the analysis[21].

Mobility was evaluated by the Timed Up and Go test (TUG). Patients were instructed to stand up from a standardized chair with arms crossed on the chest, to walk three meters, turn around, walk back, and sit down on the chair. The test was twice performed and the mean time of two attempts, measured in seconds, was used for the analysis[22].

The 6MWT was used to evaluate walking endurance[23]. Participants were instructed to walk as fast and as far as possible without rest or encouragement for six minutes. The 6MWT was completed at a single corridor, with 10-meter in length and cones placed on opposite ends, while performing 180° turns around the cones.

Subjective fatigue was measured by the 15-point Borg scale (which scores from 6 to 20)[24]. The perceived fatigue concerning the overall physical fatigue sensation was asked prior to the 6MWT and after every minute of the test. The rate of perceived exertion in percentage was calculated using the values immediately reported after the 6MWT and before the test.

Statistical analyses

In order to perform the analysis between people with MS presenting depressive symptoms or not, the status of depressive symptoms was identified using a cutoff score of 13 on the BDI-II (17), considering that such cutoff score seems to screen for about 70% of MS patients with significant depressive symptoms in ambulatory people[25]. People with MS with BDI score ≤13 were classified as asymptomatic for depression, whereas those with BDI-II score >13 were classified as symptomatic for depression.

Statistical analyses were performed using descriptive statistics and data are presented as means and 95% confidence interval (95%CI). Shapiro-Wilk test was used to assess data normality. Distribution of data was also visually verified with box-plots, q-q-plots, histograms, and dot-plots. In order to perform parametric tests and the linear regression analysis, data from the NHPT, TUG, and COP_{stable}, and COP_{foam} were transformed ($X_i=1/x_i$^2). To perform comparisons between groups (depressive asymptomatic and symptomatic), the unpaired t-test was used. Simple linear regression analysis was carried out to investigate potential associations between outcomes of depressive symptoms and physical functions. The significance of the R-squared values was used to identify predictors of depressive symptoms. The Pearson correlation test was graphically represented for the significant predictors. The statistical significance level was set at $p\leq0.05$, and trend, at $0.05<p<0.10$. All data analyses were performed using the Statistical Package for the Social Sciences (SPSS) program, 13.0 version (SPSS Inc., USA).

RESULTS

As demonstrated in Table 1, no differences in clinical characteristics were found between depressive asymptomatic and symptomatic people with MS. Concerning mental health, anxiety status (HADS-A) did not differ between groups, and the HADS-D score was significantly higher for

Table 1. Descriptive clinical characteristics, mental health, and physical functions of people with multiple sclerosis. Comparisons between groups concerning the status of depressive symptoms.

	All	Asymptomatic	Symptomatic
Clinical			
n (women/men)	26 (24/2)	15 (15/0)	11 (9/2)
Age, y	36.2 (32.4–40)	36.5 (30.5–42.5)	35.9 (31.2–40.5)
Weight, kg	63 (56.6–69.5)	59.1 (52.9–65.4)	69.6 (54.8–84.4)
Height, cm	160.2 (157–163.3)	158.8 (156–161.6)	163 (154–172)
Disease duration, y	6.1 (4.3–7.9)	5.6 (3.2–7.9)	4.1 (1.1–7.1)
EDSS score	2.6 (2.1–3.1)	2.3 (1.8–2.8)	3.2 (2–4.3)

Continue...

Table 1. Continuation.

	All	Asymptomatic	Symptomatic
Mental health			
HADS-A	8.5 (6.9–10.1)	7.7 (5.2–10.2)	9.7 (7.8–11.6)
HADS-D	6 (4.6–7.4)	4.5 (3.2–5.8)	8.1 (5.4–10.7)a
BDI-II	13.7 (10.2–17.1)	8.1 (6.3–10)	21.2 (16.2–26.2)a
Physical functions			
NHPT, s	19.7 (18.4–21)	19.1 (17.5–20.7)	20.5 (18–23.1)
PTKE, N.m	107 (94.1–119)	106.2 (91.6–120.9)	108 (85–130.8)
PTKF, N.m	47 (39.2–54.9)	49.1 (39.5–58.8)	44.6 (30–59.2)
COPstable, cm/s	1.17 (0.93–1.41)	1.02 (0.90–1.12)	1.37 (0.81–1.93)
COPfoam, cm/s	2.58 (2.2:3)	2.18 (1.9:2.6)	3.12 (2.3:4)a
TUG, s	8.9 (6.2:11.4)	7.2 (6.6:7.7)	11.2 (4.4:18)
6MWT, m	481 (444.5:517.4)	503.8 (469.5:538.2)	443.8 (359.3:528.2)a
RPE, %	33 (18:49)	30 (7:54)	37 (18:57)

EDSS: Expanded Disability Status Scale; HADS-A: Hospital Anxiety and Depression Scale-Anxiety; HADS-D: Hospital Anxiety and Depression Scale-Depression; BDI-II: Beck Depression Inventory-II; NHPT: Nine-hole Peg Test; PT_{KE}: Peak Torque Knee Extensor; PT_{KF}: Peak Torque Knee Flexor; COP: Center of Pressure; TUG: Timed Up and Go Test; 6MWT: 6-minute Walk Test; RPE: Rate of Perceived Exertion. Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$) are denoted by "a": different from depressive asymptomatic people with multiple sclerosis.

the depressive symptomatic participants classified by the BDI-II. Comparisons of physical functions demonstrated a significant higher COP velocity for depressive symptomatic people with MS during the test performed on an unstable surface (COP_{foam}). In addition, a trend of significance was detected in the 6MWT between groups. No statistically significant differences between depressive asymptomatic and symptomatic participants were found in manual dexterity, muscle strength, balance on a stable surface, mobility, and in the increment of perceived exertion.

Tables 2 and 3 present the results from the simple linear regression analysis performed between clinical characteristics/physical functions and BDI-II and HADS-D, respectively. COP_{foam} significantly explained 21% of variance in the BDI-II score, and 24% of the variance in the HADS-D. Furthermore, TUG and 6MWT presented a trend of significance, explaining 16% of the variance in the BDI-II. No statistically significant associations were found between any clinical characteristics and BDI-II and HADS-D scores.

Table 2. Coefficients from the simple linear regression analysis including clinical characteristics/physical functions and the Beck Depression Inventory-II.

	β	95%CI	p-value	R-squared
Age	-0.04	-0.40–0.32	0.81	0.002
Disease duration	-0.08	-0.99–0.66	0.69	0.007
EDSS	0.34	-0.41–4.45	0.10	0.11
NHPT	-0.28	-6689–1499	0.20	0.08
Peak $Torque_{KE}$	-0.25	-0.21–0.05	0.22	0.06
Peak $Torque_{KF}$	-0.34	-0.36–0.03	0.10	0.11
COP_{stable}	-0.18	-10.6–4.2	0.38	0.03
COP_{foam}	-0.46	-56.3:-4.9	0.02	0.21
TUG	-0.40	-868.6–21.3	*0.06*	0.16
6MWT	-0.40	-0.07–0.003	*0.06*	0.16
RPE	0.33	-1.5–9.8	0.14	0.11

95%CI: 95% confidence interval; EDSS: Expanded Disability Status Scale; NHPT: Nine-hole Peg Test; PT_{KE}: Peak Torque Knee Extensor; PT_{KF}: Peak Torque Knee Flexor; COP: Center of Pressure; TUG: Timed Up and Go Test; 6MWT: 6-minute walk test; RPE: Rate of Perceived Exertion. Statistical significance is denoted by the bold letter; the trend is denoted by the italic numbers of p-values.

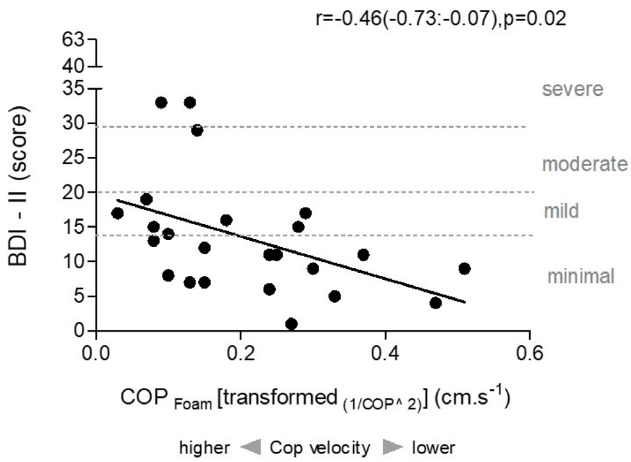
Table 3. Coefficients from the simple linear regression analysis including clinical characteristics/physical functions and the Hospital Anxiety and Depression Scale-Depression.

	β	95%CI	p-value	R-squared
Age	0.14	-0.10–0.20	0.49	0.02
Disease duration	-0.21	-0.50–0.16	0.29	0.04
EDSS	0.15	-0.75–1.6	0.47	0.02
NHPT	-0.23	-2870–924.2	0.29	0.05
Peak $Torque_{KE}$	-0.25	-0.08–0.02	0.24	0.06
Peak $Torque_{KF}$	-0.30	-0.14–0.02	0.15	0.09
COP_{stable}	-0.10	-3.9–2.4	0.62	0.01
COP_{foam}	-0.49	-24.9:-2.1	0.01	0.24
TUG	-0.36	-381–33.2	*0.09*	0.13
6MWT	-0.36	-0.03–0.004	0.10	0.13
RPE	0.22	-1.5–4.2	0.32	0.05

95%CI: 95% confidence interval; EDSS: Expanded Disability Status Scale; NHPT: Nine-hole Peg Test; PT_{KE}: Peak Torque Knee Extensor; PT_{KF}: Peak Torque Knee Flexor; COP: Center of Pressure; TUG: Timed Up and Go Test; 6MWT: 6-minute walk test; RPE: Rate of Perceived Exertion. Statistical significance is denoted by the bold letter, and the trend is denoted by the italic numbers of p-values.

Simple regression results between clinical characteristics/physical functions and HADS-A can be found in the supplementary data.

Figure 1 graphically represents the significant association between balance and the BDI-II scores.



Note: the regression between COP_{foam} was performed using a second-order hyperbolic transformation (1/COP foam ^2). The result must be cautiously interpreted, as the values of velocity are inverted. The grey caption on the right side of the figure indicates the degree of depression according to Beck Depression Inventory-II.

Figure 1. Association between Center of Pressure on an unstable surface (COP_{foam}) and Beck Depression Inventory-II.

DISCUSSION

The main finding of the present study is that the outcome of a more challenging balance test, the COP_{foam}, could significantly predict depressive symptoms, thus explaining 21 and 24% of the variance in the BDI-II and in the HADS-D, respectively. In addition, COP_{foam} was statistically different between depressive asymptomatic and symptomatic people with MS. The prevalence of depression was 42% in the sample of MS patients.

Studies investigating associations between physical functions and mental health have been mostly focused on how mental health, evaluated by mood disorders and self-efficacy, could predict walking capacity[10,12], activities of daily living[11], self-reported physical activity[5], and balance[13]. In this study, balance control during a more challenging task was a significant predictor of depressive symptoms, suggesting that impairment in physical function, such as dynamic balance, can affect mental health. The present results partly corroborate the findings of the study conducted by Alghwiri et al.[13], in which associations between depressive symptoms and balance could also be found. However, in their study, balance was measured by the subjective Activities-Specific Balance Confidence Scale (ABC) and by the Berg Balance Scale (BBS), suggesting that the ability to perform dynamic balance tasks during activities of daily living is affected by the level of depressive symptoms. On the other hand, the present study also showed that a more precise and challenging method of balance control, using a force platform and a plastic foam, could generate an outcome capable of predicting depressive symptoms. Considering these results and those found by Alghwiri et al., it could be inferred that the sensory systems responsible for balance control are impaired in people with MS, consequently affecting their independence in performing activities of daily living and compromising the dynamic balance. Altogether, the loss of independence can affect the mental health of people with MS[8,11]; likewise, the low self-efficacy generated by depressive symptoms can affect physical functions such as walking[9], physical activity, and social functioning[5].

Concerning other aspects of physical function that could predict depressive symptoms, although no statistical significance was found for any of the other functions, a trend of significance was found regarding the 6MWT. The 6MWT distance was slightly shorter for depressive symptomatic people with MS, and it could explain 16% of the variance in the depressive symptoms. In addition, the TUG test, which involves both ambulation and dynamic balance, also presented a trend of significance for predicting depressive symptoms. Kalron et al.[10] showed that depressed people with MS walked significantly slower; however, the differences were no longer significant when controlling for EDSS score, age, and sex. In addition, significant differences could be found between groups (depressed and nondepressed) regarding the MSWS-12, even when controlling for the same parameters. The short walk test performed in their study did not comprise the difficulties presented in ambulation during the daily life, such as fatigability, factor to which the MSWS-12 could be more sensitive. Furthermore, results from another study[9] suggested that MSWS-12 could not only predict depressive symptoms, but also the worsening of the symptoms after two years. However, it is necessary to identify more objective tests regarding physical functions in order to target intervention strategies. As pinpointed in another study investigating associations between self-efficacy and walking[12], the 6MWT was significantly associated with self-efficacy, suggesting the importance of including measures of walking endurance in future studies investigating the impact of physical functions on depressive symptoms.

In the present study, the BDI-II proved to be a more sensitive scale to identify depressive symptoms in people with MS, although differences could be found between depressive asymptomatic and symptomatic patients regarding to the HADS-D, perhaps confirming the consistency of the scales. Concerning tests of physical functions and the outcomes capable of predicting depressive symptoms, the use of more objective tests that can predict the difficulties in performing activities of the daily living and the lower levels of physical activity is suggested. Future studies should consider to include motor-fatigability tests[26,27,28], the sit-to-stand test[29,30], the six-spot step test[31], among others[32]. Furthermore, the use of strategies to improve physical functions are recommended, such as rehabilitation and exercise interventions aimed at adaptations in the neuromuscular system, such as resistance training, as well as dynamic balance training and aerobic exercises. In this context, and considering the high impact of exercise on people with MS, exercise should be prescribed from the early stage of MS together with conventional medical treatment[33]. Moreover, it is worth highlighting the importance of appropriate detection and treatment of depressive symptoms in people with MS.

Although this is the first study, to the best of the authors' knowledge, to include measures of physical functions and to identify the COP outcome from a gold standard balance test that predicts depressive symptom, it also presents some limitations. The sample size may have limited the comparisons between groups. The selection of the participants was not based on their statuses of depressive symptoms and neither on their disability. Most patients were well-functioning and classified with mild MS. Finally, as a cross-sectional study, it could not allow the discussion about the causality of physical functions as for mental health.

In conclusion, the prevalence of people with MS presenting depressive symptoms was 42%. Balance control during a more challenging task was impaired in depressive symptomatic people with MS. Balance could explain 21–24% of the variance in depressive symptoms. 6MWT and the TUG presented a trend of significance explaining 16% of the variance in the BDI-II score. All in all, impairment in physical functions consists in a potential predictor of depressive symptoms in people with MS. Exercise interventions aimed at improving physical functions, together with the treatment of depressive symptoms and conventional medical treatment, are suggested.

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