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Treadmill in Parkinson's: influence on gait, balance, BDNF and Reduced Glutathione

Esteira em Parkinson: influência sobre marcha, equilíbrio, BDNF e Glutationa Reduzida

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Abstract

Introduction: Parkinson's disease (PD) is characterized by nigrostriatal degeneration, with dopaminergic depletion, and inflammatory and oxidative changes in the brain, leading to movement and coordination disorders. Recent studies have shown that treadmill training can be beneficial for these patients, but there is little evidence assessing the related blood parameters, such as oxidative stress and neurotrophin levels. **Objective:** Assess the influence of treadmill training for patients with Parkinson's on gait, balance, Brain-Derived Neurotrophic Factor (BDNF) and reduced glutathione. **Methods:** Twenty-two patients with PD (Hoehn and Yahr II and III), older than 40 years, were randomly allocated to two groups: CG (n = 12) - drug treatment and IG (n = 10) - treadmill. Assessments related to functional capacity (quality of life, static and dynamic analysis of gait) and blood parameters such as GSH and BDNF were conducted before and after the eight-week intervention. **Results:** The demographic data of the groups were homogeneous in terms of age,

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sex, height, weight, time since disease onset, mini mental examination and the geriatric depression scale. Significant intergroup differences were found for the mental component summary, surface variation, latero-lateral oscillation, antero-posterior oscillation and mean velocity in the post-intervention period. The IG exhibited a strong association between BDNF and GSH, with statistically significant values. **Conclusion:** It was concluded that controlled treadmill walking improves static balance, quality of life and plasma BDNF and GSH levels in patients with PD.

Keywords: Parkinson's Disease. Gait. Oxidative Stress. Neurotrophin.

Resumo

Introdução: *A doença de Parkinson (DP) é caracterizada pela degeneração nigroestriatal, com depleção dopaminérgica, alterações inflamatórias e oxidativas cerebrais levando a prejuízo no controle do movimento e coordenação. Trabalhos recentes mostram que a atividade física em esteira pode ser benéfica para estes pacientes, mas há poucas evidências avaliando os parâmetros sanguíneos relacionados, como estresse oxidativo e níveis de neurotrofinas.* ***Objetivo:*** *Avaliar a influência da esteira em Parkinson sobre a marcha, equilíbrio, Brain-Derived Neurotrophic Factor (BDNF) e Glutationa Reduzida.* ***Métodos:*** *Vinte e dois pacientes com DP (Hoehn e Yahr II e III), acima de 40 anos, foram aleatorizados em dois grupos: GC (n = 12) - tratamento medicamento e GI (n = 10) - esteira ergométrica. As avaliações relacionadas à capacidade funcional (qualidade de vida, análise estática e dinâmica da marcha) e parâmetros sanguíneos como GSH e BDNF foram realizadas antes e após as oito semanas de intervenção.* ***Resultados:*** *Os dados demográficos dos grupos foram homogêneos quanto às variáveis idade, gênero, altura, peso, tempo de doença, teste mini mental e teste da escala de depressão. Diferenças significativas foram encontradas para o coeficiente mental sumarizado, variação de superfície, oscilação látero-lateral, oscilação ântero-posterior e velocidade média entre os grupos no período pós-intervenção. No GI, viu-se associação forte entre BDNF e GSH com valores de significância estatística.* ***Conclusão:*** *Conclui-se que a caminhada controlada na esteira melhora o equilíbrio estático, qualidade de vida e os níveis plasmáticos de BDNF e GSH em pacientes com DP.*

Palavras-chave: *Doença de Parkinson. Marcha. Estresse Oxidativo. Neurotrofina.*

Introduction

Parkinson's (PD) is a chronic progressive disease, considered the second most common neurodegenerative disorder worldwide, affecting 1 to 2% of the population aged 65 years and older, with a prevalence of 4% for individuals older than 85 years (1). Given that quality of life and life expectancy has been improving around the world, an estimated 8.7 million cases of PD are expected by 2030 (2).

A number of risk factors are highlighted in the literature, such as advanced age, a slightly higher prevalence in men (3) and hereditary factors. However, the sporadic form is more common (4). Other causes are environmental toxins, drugs, oxidative–induced viruses and damage resulting from neuronal cells (5).

The neuropathological characteristics of PD include the death of 50% of dopaminergic neurons in the substancia nigra pars compacta leading to an 80% loss in striatal dopamine (6), causing the classic signs of bradykinesia, rigidity, resting tremor and postural instability (2).

Freezing of gait in Parkinson's disease is a brief absence or marked reduction of forward movement, despite the intention to walk, and may be accompanied by rapid steps with increasingly shorter length, not affecting everyone equally (7). This phenomenon affects mobility and can lead to falls, compromising the emotional state of individuals and causing depression due to social isolation, which may have a direct influence on their quality of life (8).

Physical exercises are adjuvant therapy for PD, and oscillations in clinical status related to the drug

intake period must be considered. The ultimate goal should be joint flexibility, muscle strengthening, balance and motor coordination. Exercise also contributes to improving the emotional state of the patient (9, 10).

Stride training and low-to-moderate intensity treadmill exercise seem to enhance motor performance in terms of walking and daily activities. Furthermore, they increase cardiovascular capacity, improve gait evolution, contributing to extension, velocity, stride length and a reduction in the double-leg stance phase. They also help maintain balance in unstable conditions and minimize falls, due to the increased vigor in ischiotibial, quadriceps and gastrocnemius muscles (11). Other important muscles involved in gait are the gluteus maximus, gluteus medius and soleus. Stimulation of neurogenesis, neuronal plasticity and an increase in antioxidants are determined by measuring blood parameters such as the Brain-Derived Neurotrophic Factor (BDNF) and reduced glutathione (GSH), suggesting central degenerative control in these cases (12).

Given the aging population and the prevalence of PD at advanced ages, and considering the public health costs and compromised quality of life, this study sought to analyze new assessment mechanisms and propose adjuvant therapies for individuals with Parkinson's. As such, the aim of the study was to assess the influence of treadmill training for patients with Parkinson's disease on gait, balance, BDNF and reduced glutathione.

Methods

This is an open randomized quantitative study conducted at the Laboratory of Human Movement Analysis, affiliated with the Center for Integrated Medical Attention (NAMI) of the University of Fortaleza (UNIFOR), between August 2013 and May 2014.

Participants were recruited by consecutive non-probability sampling at the neurology outpatient facility of the General Hospital of Fortaleza (HGF), totaling 22 patients diagnosed with PD (Hoehn and Yahr II and III) (13), aged older than 40 years, undergoing treatment for Parkinson's disease (dopaminergic drugs – levodopa or dopamine agonist at a dose of 70 to 100mg, twice a day and with no dementia, as measured by the Mini Mental State Examination (> 21) (14).

The participants were randomized into two groups: those undergoing gait recovery on a treadmill (Intervention Group-IG / n = 10) and those not submitted to any physiotherapeutic intervention, remaining only under clinical treatment (Control Group-CG / n = 12).

Assessment procedures

The following were applied to all participants before and 8 weeks after intervention: anthropometric and demographic assessment (weight, height, time since disease onset and physical activity), assessment of mental state (Mini Mental State Examination), Geriatric Depression Scale (15), Medical Outcomes Study, 36-Short-Form Health Survey (SF-36) (16), Static and Dynamic Analysis of Gait and Assessment of Plasma Measures of BDNF levels and reduced glutathione (GSH) concentration.

Gait assessment

Static and dynamic analysis of gait was conducted using an electronic baropodometer (FootWalk Pro, AM CUBE, France) and FootWork Pro 3.7.0.1 software. All the participants underwent an equipment adaptation period before data collection, in order to minimize changes and non-habituation to the medium. The tests were carried out in the off phase of the dopamine cycle, that is, with subjects not under the effect of the drug.

Static analysis assessed the surface values of the left (L) and right (R) foot (cm^2), antero-posterior and latero-lateral oscillations of the L and R foot (cm). For dynamic analysis, the second consecutive lap of the patient around the track was measured, assessing mean right and left velocity (mm/s), calculated by the fraction between stride length and cycle time, both generated by the software.

Quantification of plasma measures

Blood samples were taken from the patients, with no prior use of PD medication, around twelve

hours later. The samples were collected in the morning after a 12-hour fast, at the study site, and identified. Reduced glutathione (GHS) was determined (17) to evaluate performance in the activity carried out as well as BDNF levels (18) to measure neuroplasticity.

Training protocol

To determine the ability of participants to perform treadmill exercises (Movement RT 250 treadmill), G1 subjects were submitted to the Harbor protocol (19). They walked on the treadmill with no incline and minimum velocity of 0.1cm/s for one minute, which was doubled every minute until the individual expressed fatigue, at which time the machine was turned off.

After the velocity immediately before fatigue was identified, the protocol was implemented, whereby the subjects underwent training for 10 minutes, adding 5 minutes every week until reaching a time of 30 consecutive minutes, a duration that was used until the end of training. Two 30-minute weekly sessions were held over an 8-week period, for a total of 16 sessions (19).

Statistical analysis

The data obtained were analyzed using the Statistical Package for the Social Sciences (SPSS) 18.0 program. The Kolmogorov-Smirnov test of normality was applied to assess sample homogeneity. Descriptive analysis was carried out using means, standard deviations and percentage. Intragroup and intergroup results were compared using the paired and independent student's t-tests, respectively. Analysis of the association between variables was conducted by applying Pearson's correlation coefficient. A p-value < 0.05 was considered statistically significant.

Ethical aspects

The study was approved by the University of Fortaleza Ethics Committee (COÉTICA), under protocol number 442.563, in compliance with the ethical and legal principles of Resolution no. 466/12 of the National Health Council (CNS) (20).

Results

Sample characteristics

Twenty-one patients were clinically eligible to take part in the protocol. Of these, 45.4% (n = 10) belonged to the IG, with mean age of 68.4 years ± 12.8 years, and 54.55% (n = 12) to the CG (Figure 1). Of the 12 CG patients, four did not finish the protocol due to a domestic fall, precluding further participation.

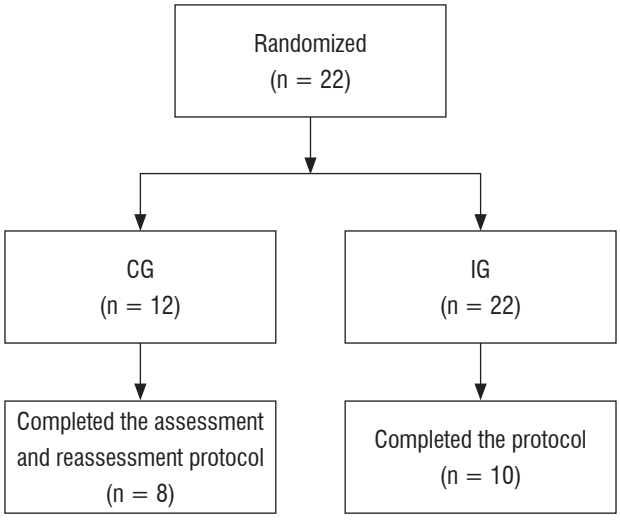

Figure 1 - Flowchart of the study patients.
Note: CG = control group, IG = intervention group.

With respect to the initial characteristics of the study groups, there was no statistically significant difference in the variables analyzed, demonstrating sample homogeneity (Table 1).

Table 1 - Pre-intervention demographic, anthropometric and clinical characteristics

Variables	CG (n = 8)	IG (n = 10)	*P*
Age (years)	67.8 ± 10	68.4 ± 12.8	0.8
Sex (M/F)	5/3	6/4	0.1
Height (cm)	165 ± 5	159 ± 6.5	0.3
Weight (Kg)	67.5 ± 7	65.2 ± 9	0.8

(To be continued)

(Conclusion)

Table 1 - Pre-intervention demographic, anthropometric and clinical characteristics

Variables	CG (n = 8)	IG (n = 10)	*P*
Time since disease onset (months)	48.3 ± 12.3	82.7 ± 64	0.1
Mini Mental State Examination	25.8 ± 2.8	26.4 ± 12.8	0.3
Depression Scale	6.6 ± 4.6	3.7 ± 1.4	0.6
Time engaged in physical activity (months)	18 ±42	27.6 ± 28.9	0.8

Note: CG = Control group; IG= Intervention group; n = number of individuals; M = male, F = female; cm = centimeters; Kg = kilograms; Independent student's t-test, $p < 0.05$.

Quality of life

A comparison of post-intervention quality of life between the CG and IG shows a statistically significant difference in the mental component summary (MCS) (p = 0.04). However, the physical component summary (PCS) exhibited no significant difference (p = 0.3).

After 8 weeks, there was a negative correlation between MCS and the depression scale in the CG (r = -0.8; p = 0.008) and the IG (r = -0.7; p = 0.01).

Baropodometric assessment

Intragroup analysis of surface variation on the R foot of CG individuals demonstrated an increase in values (Table 2), albeit not significant (p = 0.1). However, there was a statistically significant decrease in the IG for the R foot (p = 0.001) (Table 2).

In relation to the surface variation of the L foot, intergroup analysis between the CG and IG was statistically significant (p = 0.001) pre-intervention, with a tendency to a post-intervention increase (Table 2).

In latero-lateral oscillation of the R foot, the CG exhibited a post-intervention increase, although not statistically significant (p = 0.5). The IG showed a statistically significant reduction post-intervention (p = 0.01). With respect to antero-posterior oscillation in the L foot, there was a statistically significant decline (p = 0.01) in the IG (Table 2).

A comparison between the CG and IG before and after intervention, in terms of mean velocity, showed a statistically significant difference (p = 0.04) for the R foot (Table 2).

The other variables that underwent barometric analysis in both groups exhibited no statistically significant results.

Table 2 - Lateral (frontal plane) and antero-posterior (sagittal plane) oscillation of the right and left foot, respectively and mean velocity of the right foot

Variable		CG (n = 8)	IG (n = 10)	*P*
Δ R surface (cm^2)	Pre	1.36 ± 0.8cm^2	5.3 ± 6.8 cm^2	0.2
	Post	1.74 ± 0.85 cm^2	1.9 ± 3 cm^2	0.8
	p	0.1	0.001*	
Δ L surface (cm^2)	Pre	1.17 ± 0.95	12.8 ± 33	0.001*
	Post	1.19 ± 0.78	1.79 ± 2.8	0.6
LLORF (cm)	Pre	0.74 ± 0.25	1.37 ± 0.95	0.2
	Post	0.84 ± 0.31	0.71 ± 0.34	0.8
	p	0.5	0.01*	
APOLF (cm)	Pre	2.10 ± 1	3.77 ± 2.84	0.4
	Post	2.17 ± 0.86	2.60 ± 2.21	0.6
	p	0.1	0.01*	
Mean Vel. R (mm/s)	Pre	468.3 ± 177.8	356.6 ± 42.5	0.04*
	Post	426.3 ± 196.1	324.3 ± 103.6	0.04*

Note: CG = control group; IG = intervention group; L = left foot; R = right foot; LLORF: latero-lateral oscillation right foot; APOLF = antero-posterior oscillation left foot; Mean Vel. = mean velocity. Intragroup – paired student's t-test; Intergroups – independent student's t-test *$p < 0.05$.

Analysis of reduced glutathione and BDNF plasma measures

With respect to plasma measures, the GSH and BDNF parameters showed no significant post-intervention changes. However, when BDNF and GSH were correlated before and after the 8-week intervention, a positive correlation was obtained for the IG (Table 3).

Table 3 - Correlation between BDNF and GSH.

	BDNF CG	BDNF IG
GSH (μg/mL)	r = 0.2; p = 0.5	r = 0.8; p = 0.001*

Note: BDNF CG = Brain-Derived Neurotrophic Factor control group; BDNF IG = Brain-Derived Neurotrophic Factor intervention group; GSH = reduced glutathione. Pearson's correlation coefficient. *$p < 0.05$.

Discussion

The present study used the 8-week treadmill training protocol proposed by Filippin et al. (19), in order to determine the influence on the gait, balance and plasma BDNF and GSH levels of patients with Parkinson's disease.

It is known that physical activity helps prevents a wide range of pathologies and associated risks, such as chronic degenerative disorders, thereby increasing life expectancy by 0.68 year (21).

An inverse relationship was found between the risk of PD and exercise in studies by Xu et al. (22), regardless of age range. With respect to sex, men engaged in vigorous exercise have 50% less risk for PD compared to those exhibiting lower activity levels. The results obtained by the women were not statistically significant. The author attributes this to the pathogenesis of the disease, with a slight predominance in men, although this has not been explained to date.

Different factors associated with PD can have a direct or indirect influence on the quality of life of these individuals. Mental component summary values were statistically significant when the CG and IG were correlated at the end of the protocol, confirming the importance of the intervention suggested for the mental well-being of the patients studied here.

Dauwerse et al. (23) proposed qualitative analysis to describe the factors that influence the QOL of patients with PD and observed that health perspectives, personal relationships, individual care, communication and society directly affect the health of these subjects, as corroborated in the present research.

The baropodometric data between the CG and IG showed a post-intervention decline, possibly due to improved static balance, thereby decreasing the incidence of falls. The mean velocity of gait demonstrated that, although the IG exhibited lower pre-intervention velocity than that of the CG, an even greater post-intervention decrease was found in the R foot, compared to the CG, which also experienced a decline. Corroborating this study, Bello et al. (24) obtained positive results in terms of walking velocity and stride length in groups studied before and after a treadmill training program, which was sustained 1 month after the completion of training.

Gait disorders and falls are frequent in elderly individuals and patients with common neurological diseases. Approximately 30% of adults aged 65 years or older fall at least once a year. In individuals with PD, this index increases to 60-80% (25). Most falls occur during walks, despite reduced gait velocity and stride length. The consequences are greater caution during walks, fear, functional dependence and social isolation (26), data that corroborate the dynamic changes in gait in the patients analyzed.

Reuter et al. (27) reported that physical exercise in subjects with PD promotes motor improvements, including gait, strength and balance, in addition to relieving pain, which has a significant influence on their quality of life, findings that agree with those of the present study in terms of static balance.

According to Tambosco et al. (28), it is important to consider that compromised gait may result in greater energy expenditure and fatigue during activities of daily living, which is not as evident when the patient maintains a static posture.

The GSH and BDNF parameters at the start and end of the 8-week training period revealed no significant evidence in the pathogenesis of PD. Seifert et al. (29) suggest that 7 consecutive days of training are needed to release substantial levels of BDNF. Moreover, these levels are unstable in terms of emotional parameters, which are difficult to control in a study.

The relationship between BDNF and GSH in the IG showed a strong and statistically significant association, suggesting that treadmill

exercise intensifies neuroprotection via different mechanisms. Given that GSH is the primary antioxidant defense in the organism, it is assumed that exercise in Parkinson's disease contributes to the rise in this marker, an important instrument for adjuvant therapy, minimizing the production of free radicals and in turn, neurodegeneration (30).

Its multifactorial causes, motor and non-motor dysfunctions (31) and effect on memory and learning mean Parkinson's disease is the object of constant research aimed at elucidating etiopathogenic mechanisms, therapeutic measures and effective prophylactics, in order to improve the functional capacity and quality of life of these patients.

This study exhibited limitations in terms of sample size, given the limiting motor repercussions displayed by numerous patients who were excluded during the data collection period.

Conclusion

In conclusion, controlled treadmill walking improves the static balance of patients with Parkinson's disease, and positively influences quality of life, especially mental health parameters, which exhibit significant gains in exercise protocols that offer social contact between the patients.

Furthermore, the relationship between BDNF and GSH is also an important finding, showing a strong association at high levels, and playing an important neuroprotective role through different mechanisms.

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