# The effect of resistance training on the anxiety symptoms and quality of life in elderly people with Parkinson's disease: a randomized controlled trial

O efeito do treinamento resistido sobre sintomas de ansiedade e qualidade de vida em idosos com doença de Parkinson's: ensaio randomizado controlado

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### **ABSTRACT**

**Objective:** To assess the effects of resistance training on the anxiety symptoms and quality of life in patients with Parkinson's disease. **Methods:** Thirty-five elderly patients were randomly divided into two groups: 17 patients in the control group and 18 in the intervention group. All patients maintained standard pharmacological treatment for Parkinson's disease, but the intervention group participated in a 24-week resistance training program. The anxiety symptoms were assessed through the Beck's Anxiety Inventory, and quality of life by the Parkinson's Disease Questionnaire–39. **Results:** There was a significant reduction in anxiety level and increase in quality of life after 24 weeks of resistance training. **Conclusion:** The results of the present study indicate that resistance training is an effective intervention in the reduction of anxiety symptoms and improves the quality of life in elderly people with Parkinson's disease.

Keywords: resistance training; anxiety; Parkinson disease; randomized controlled trial.

### **RESUMO**

**Objetivo:** avaliar os efeitos do treinamento resistido nos sintomas de ansiedade e na qualidade de vida em pacientes com doença de Parkinson. **Métodos:** Trinta e cinco pacientes idosos foram divididos randomicamente em dois grupos: 17 indivíduos no grupo controle e 18 no grupo de intervenção. Todos os sujeitos mantiveram o tratamento farmacológico padrão para a doença de Parkinson, mas o grupo de intervenção participou de um programa de treinamento resistido de 24 semanas. Os sintomas de ansiedade foram avaliados através do inventário de ansiedade de Beck e a qualidade de vida pelo questionário da doença de Parkinson-39. **Resultados:** Houve redução significativa no nível de ansiedade e melhora da qualidade de vida após 24 semanas de treinamento resistido. **Conclusão:** Os resultados do presente estudo indicam que o treinamento resistido é uma intervenção efetiva na redução dos sintomas de ansiedade e melhora a qualidade de vida em idosos com doença de Parkinson.

Palavras-chave: treinamento resistido; ansiedade; doença de Parkinson; ensaio randomizado controlado.

Parkinson's disease (PD) is a neurodegenerative disorder that affects approximately 7 to 10 million individuals worldwide, and is characterized by the degeneration of neurons of the substantia nigra pars compacta<sup>1</sup>. Individuals with PD present mainly with clinical motor findings: tremor, stiffness, progressive bradykinesia and postural instability. In addition, nonmotor symptoms are frequent before and after the PD diagnosis: sleep disorders, behavioral or mood changes, apathy, depression and anxiety<sup>2</sup>.

Anxiety affects approximately 25% to 49% of PD patients, with a higher prevalence in this population than in non-PD populations<sup>3,4</sup>. The etiology of anxiety in PD has not yet been defined, but it may be a reaction secondary to motor and nonmotor symptoms. Studies have shown that anxiety symptoms may contribute to morbidity and are correlated with decreased quality of life in patients with PD<sup>2,5</sup>.

Previous studies have shown positive effects of resistance training on the physical aspects of PD patients, improving

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balance<sup>6</sup>, speed and spatial features of gait<sup>7</sup>, reaction time, functional capacity<sup>8</sup>, muscle strength and power<sup>7,6</sup>.

It is known that physical training, such as resistance training, is able to reduce anxiety symptoms in adults and in people with other chronic diseases<sup>9,10</sup>. Studies have shown that resistance training and other forms of physical exercise are beneficial for central nervous system functions<sup>11</sup> and are important for the control of motor and nonmotor symptoms of PD<sup>12</sup>.

To the best of our knowledge, there are no studies evaluating the anxiety symptoms of individuals with PD undergoing a resistance training protocol. Thus, the main aim of this study was to evaluate the effects of resistance training on anxiety symptoms and quality of life of patients with PD. We hypothesized that resistance training decreases the symptoms of anxiety, improving the quality of life and symptoms of PD.

### **METHODS**

### Trial design and ethics

We conducted an open-label randomized parallel group controlled clinical trial. The study was approved by the ethics committee of the University of the Amazon (43624015.6.0000.5173). The trial was registered in the Brazilian Registry of Clinical Trials (http://www.ensaiosclinicos.gov.br/): RBR-36cw3y. The study was conducted at the Laboratory of Resistance Training and Health, Universidade do Estado do Pará, August 2016 - December 2016.

### Eligibility and trial procedures

Initially, 70 individuals from the Parkinson's Association in the State of Pará were selected. Eligibility criteria included: 1) the diagnosis of PD by a neurologist specialized in movement disorders, according to the clinical criteria proposed by Gelb<sup>13</sup>; 2) age ≥ 60 years; 3) stage 1-3 on the Hoehn and Yahr scale; 4) stable use of medication; 5) participants could not have participated in any exercise protocol in the previous three months. Participants were excluded if: 1) they had a Mini-Mental State Examination score of < 2414; 2) suffered from unstable cardiovascular disease; 3) suffered from other uncontrolled chronic conditions that would interfere with the participant's safety, or our conducting of the training and testing protocol and interpretation of the results; 4) the patient's ability to walk independently; 5) or other neurological, cardiopulmonary, or orthopedic disease.

### Participants and randomization

After assessing the inclusion and exclusion criteria, 35 patients (aged over 60 years, of both genders, with a clinical diagnosis of idiopathic PD and staging between 1 and 3 on the Hoehn and Yahr scale) were randomly divided into two groups: 1) control group (CG) with 17 individuals and 2) resistance training group (RTG) with 18 individuals. The

CG continued with their standard pharmacological treatment for PD and the RTG, in addition to pharmacological treatment, participated in a resistance training protocol (Figure 1). Both groups were followed up by a neurologist throughout the study. The individuals in the sample (n = 35) did not present with other chronic disease (e.g. diabetes mellitus and/or hypertension).

Participants were assigned a number between 1 and 35, and distributed to their group by a research analyst, who was not involved in the study, by the implementation of a publicly-accessible official website designed for research randomization (https://www.randomizer.org). Randomization was stratified using the results of the Beck's Anxiety Inventory (BAI) at baseline and outcome assessors were masked to group allocation. Randomization resulted in a parallel group design with a 1:1 allocation ratio.

### **Assessments**

All assessments were made by a single evaluator who was unable to distinguish participants from either group (blind evaluation). All patients were analyzed when they were in the "on" state of medication (1–1.5 hours after taking medication). During the study period, it was recommended that all patients maintain their medication schedules.

### **Assessment of anxiety symptoms**

The anxiety symptoms of patients with PD were evaluated by the BAI. This inventory was translated and validated in Brazil by Cunha<sup>15</sup> in 2001 and is an anxiety measure that has been carefully designed to avoid confusion with depression. The BAI consists of 21 self-reported items that highlight somatic, affective and cognitive signs of anxiety symptoms. Each item has four possible answers with scores from 0 to 3: 0 = Not at all; 1 = Mild, but it didn't bother me much; 2 = Moderate, it wasn't pleasant at times; 3 = Severe, it bothered me a lot. The total score is 63 points<sup>15</sup>.

# Quality of Life Assessment and Unified Parkinson's Disease Rating Scale

The quality of life (QoL) assessment was performed using Parkinson's Disease Questionnaire (PDQ-39), which is a validated and reliable tool for assessing PD patients<sup>16</sup>. The PDQ-39 has eight domains: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort. Each item can be answered according to five predetermined answers: never; rarely; sometimes; often; and always. The score of each item ranges from 0-4 points. The total score is 0-100 points, and a lower score reflects a higher QoL. The PD symptoms were evaluated using the Movement Disorders Society – Unified Parkinson's Disease Rating Scale (UPDRS)<sup>17</sup>. The UPDRS can be divided into four parts: 1) nonmotor experiences of daily living, 2) motor experiences of daily living, 3) motor examination and 4) motor complications.

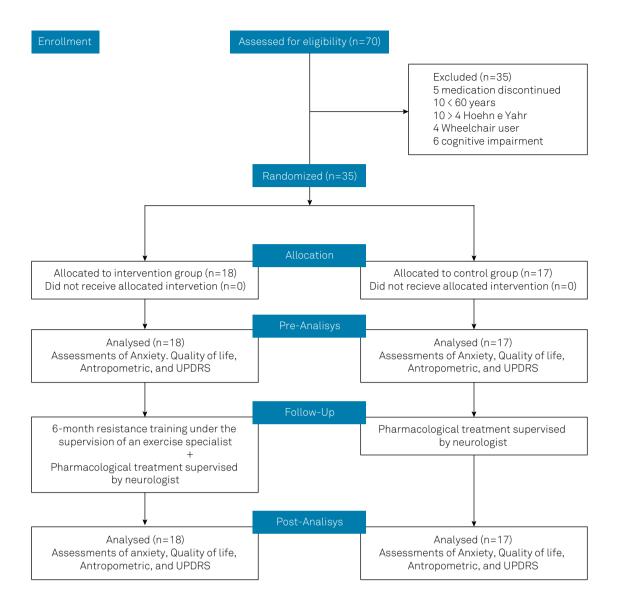


Figure 1. Flow diagram of study.

### **Anthropometry**

Body weight was measured on an analog scale (Filizola, Brazil) with 100 g accuracy and capacity up to 150 kg. Height was measured using the stadiometer coupled to the scale with 1 mm increments. To estimate subcutaneous fat, a skinfold caliper (Harpenden, London, UK) was used according to standards established by the Siri equation using a body density regression model (g.mL<sup>-1</sup>) for three skinfolds. To measure the waist, hip and abdomen circumference, a flexible metal tape with 0.1 cm accuracy was used (Sanny, São Paulo, Brazil). All measurements were performed in triplicate by a single, experienced evaluator.

### Hand grip strength

The participant held the dynamometer in the hand to be tested, with their arm at right angles and elbow by the side of their body. The handle of the dynamometer was adjusted if required—the base should rest on the first metacarpal

(heel of palm), while the handle should rest on the middle of four fingers. When ready, the participant squeezed the dynamometer with maximum isometric effort, which was maintained for about five seconds. No other body movement was allowed. The participant was encouraged to give maximum effort.

### **Training protocol**

The six-month intervention exercise program consisted of resistance training sessions lasting 30–40 minutes, on two nonconsecutive days per week, under the supervision of an exercise specialist. The resistance training program comprised two sets of 8–12 submaximal repetitions for each of the following exercises: bench press, deadlift, unilateral rowing, standing calf raise, and lower abdominal exercise. The interval between sets and exercises was 1–2 minutes. During the first two weeks, the participants became familiar with the exercises. After this phase, training loads were

adjusted following the recommendations of the American College of Sports Medicine<sup>18</sup>. In addition, the following characteristics were observed: tendency to concentric failure, rhythm reduction, apnea, isometry and difficult effort on the OMINI-RES scale.

### Statistical analysis

An *a priori* sample size calculation using G\*Power showed that a total sample across both groups of 34 participants would be sufficient to detect effect sizes of 0.5 from F tests (p > 0.05) with a statistical power of 0.80. Data were analyzed using the SSPS v.20 statistical software. The  $\alpha$  level for significance was p < 0.05 and all tests were one-tailed. To analyze data normality, the Shapiro-Wilk test was used. Due to the normal distribution, anxiety symptom, quality of life, hand grip strength and anthropometry results were reported as mean  $\pm$  standard deviation. The Hoehn and Yahr scale and UPDRS results were presented as median and  $25^{\rm th}{-}75^{\rm th}$  percentile), as they did not show normal distribution. The magnitudes of effect from pre-intervention to post-intervention tests for each group were estimated using calculations of effect size (ES).

The differences between groups at baseline were analyzed using the Mann-Whitney test (variables with nonnormal distribution) and the t-test (variables with normal distribution). Groups were compared using factorial mixed-model  $2 \times 2$  ANOVA [group (RTG x CG) x moment (baseline x after 24 weeks)]. When necessary, multiple comparisons with confidence adjustment using the Bonferroni procedure were used for *post-hoc* analysis. In the RTG, the Spearman's

correlation was used to evaluate the association between the BAI and the UPDRS and Pearson's correlation was used to evaluate the association between the BAI and the PDQ-39.

### **RESULTS**

Thirty-five patients participated in the study and, at baseline, there were no differences between the groups (RTG x CG) in any demographic, anthropometric, clinical and outcome characteristics (Table 1). At baseline, the groups showed no differences in the Hoehn and Yahr scale [RTG = 1 (1–2) and CG = 1 (1–2); U = 0.322; p = 0.273]. All RTG patients completed the training and no adverse events were reported during the trial. At the end of the study, there was a significant decrease in part I of the UPDRS (p = 0.003) and UPDRS total (p = 0.002) in the RTG. The CG showed a significant decrease only in part I of UPDRS (p = 0.038) (Table 2).

The results of the PDQ-39 showed that the RTG patients had an improvement in QoL (ES = -0.156; p = 0.009), while CG patients had no significant difference in QoL (ES = -0.0043; p = 0.959) (Table 3). Before starting the exercise protocol, the RTG patients presented with an anxiety level of  $18 \pm 7.1$  and, after performing resistance training, these patients reported a significant decrease of these symptoms, presenting with a score of  $12.2 \pm 5.5$  (ES = -0.415; p = 0.0001) (Table 3 and Figure 2). Initially, the CG showed an anxiety level of  $21.3 \pm 7.2$  and after six months, with the maintenance of pharmacological treatment, the anxiety level was  $19.9 \pm 9.5$ . This difference was not significant (ES = -0.082; p = 0.37).

Table 1. Characteristics of participants at baseline.

Charactaristics	CG (n = 17)		RTG (n	= 18)	95% CI		n valuat
Characteristics	Mean	SD	Mean	SD	95% CI	t	p-value*
Age (years)	67.6	8.9	64.1	7.0	3.53 (-1.97-9.04)	1.306	0.201
Time since PD diagnosis (years)	4.5	4.0	6.4	2.7	-1.9 (-4.23-0.43)	-1.740	0.091
PDQ-39 (score)	47.4	17.3	38.1	20.2	9.3(-3.67-22.27)	1.471	0.151
Symptoms of anxiety (score)	21.3	7.2	18	7.1	3.3 (-1.62-8.22)	1.381	0.177
Height (cm)	156.7	11.4	156.7	8.8	0 (-6.98-6.98)	2.043	0.447
Weight (kg)	66.9	8.3	67.8	11	-0.9 (-7.63-5.83)	-0.854	0.398
BMI (kg/m²)	27.6	4.7	27.6	3.7	0 (-2.90-2.90)	2.030	0.972
Fat weight (kg)	15.6	2.6	16.4	4.6	-0.8 (-3,39-1.79)	-1.241	0.223
Lean weight (kg)	52.7	5.8	52.8	11.5	-0.1 (-6.42-6.22)	-0.100	0.920
Body fat (%)	23.1	1.9	24.5	7	-1.4 (-4.97-2.17)	-1.945	0.060
Waist (cm)	93.1	9.4	91.9	9.6	1.2 (-0.92-3.32)	2.055	0.777
Hip (cm)	99.6	6.5	97.8	7.7	1.8 (-2.83-6.43)	1.994	0.054
Abdomen (cm)	101.9	9.8	100.7	9.4	1.2 (-5.40-7.80)	1.145	0.260
Drugs (mg)							
Levodopa + Carbidopa	5	0	5	0	=	-	NA
Prolopa	100	0	100	0	-	-	NA
Benserazide	25	0	25	0	=	=	NA
Sifrol	0.19	0.06	0.18	0.06	-	=	NA
Biperiden	157.4	33.1	146.3	25.5	=	=	NA

CG: control group; RTG: resistance training group; SD: standard deviation; PD: Parkinson disease; BMI: body mass index; \* Test t samples independents; DM: difference between mean; NA: not available.

The correlation of anxiety symptoms with age (p = 0.228) and time of PD diagnosis (p = 0.269) was not significant. However, there was a positive correlation between anxiety symptoms with the UPDRS and QoL (Figure 3). At the end of the intervention, there was an increase in training load (Kg)

in all exercises (Table 4). The hand grip strength increased significantly in the RTG (pre = 24.9  $\pm$  7.4; post = 29.4  $\pm$  6.4; ES = 0.31; t = -2.59; p = 0.004). However, in the CG there was a significant decrease in hand grip strength (pre = 25  $\pm$  5.6; post = 23.3  $\pm$  5; ES = -0.16; t = 5.146; p = 0.16).

Table 2. Scoring on the UPDRS of the resistance training group and control group.

RTG						CG				
UPDRS	Pre		Post		$\Delta\%$	Pre		Post		$\Delta\%$
	Median	25 <sup>th</sup> 75 <sup>th</sup>	Median	25 <sup>t</sup> –75 <sup>th</sup>		Median	25 <sup>th</sup> 75 <sup>th</sup>	Median	25 <sup>t</sup> –75 <sup>th</sup>	
UPDRS - Part I	11.5	(8-17.3)	6.5	(5-8.5)*	-43.5	13.5	(7.7-18.5)	8.5	(6-16.2)*	-37
UPDRS - Part II	19	(15.3-20.8)	19	(10-21.5)	0	18	(14-20.7)	17	(12.5-20)	-12.5
UPDRS - Part III	30	(28.5-39.8)	29	(22.8-48)	-3.3	29	(23.75-39)	34	(26.2-34)	17.2
UPDRS - Part IV	2	(0-4.5)	0	=	-100	4.5	(1-7)	6	(5.2-6)	33.3
UPDRS – Total	65.5	(57-74.8)	54.5	(42.5-73.3)*	-16.8	66.5	(56.5-75.7)	69.2	(60-72.2)	4

RTG: resistance training group; CG: control group; median (first quartile-third quartile); UPDRS: Unified Parkinson's Disease Rating Scale; Part I: nonmotor experiences of daily living; Part II: motor experiences of daily living; Part III: motor examination; Part IV: motor complications; \*statistically significant; \( \Delta \)%: percentage difference.

Table 3. Anxiety symptoms and quality of life in elderly people with Parkinson's disease.

Variable N		RTG				CG			
	Mean	SD	95% CI	$\Delta\%$	Mean	SD	95% CI	$\Delta\%$	
BAI									
Pre	18	7.1	14.5-21.5	-32.8%	21.3	7.2	17.60-25	-6.6%	
Post	12.2	5.5	9.5-14.9		19.9	9.5	15.0-24.8		
PDQ-39									
Pre	38.06	20.16	28.03-48.09	-16.7%	47.41	17.27	38.5-56.3	-0.4%	
Post	31.72	19.75	21.9-41.54		47.24	21.34	36.3-58.2		

RTG: resistance training group; CG: control group; 95% CI: 95% confidence interval; SD: standard deviation;  $\Delta$ %: percentage difference; BAI: Beck Anxiety Inventory; PDQ-39: Parkinson's Disease Questionnaire - 39

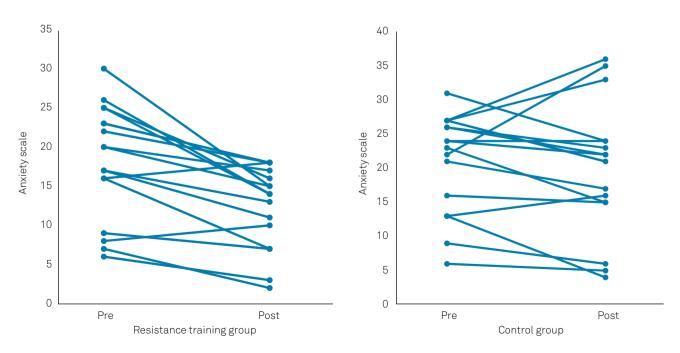
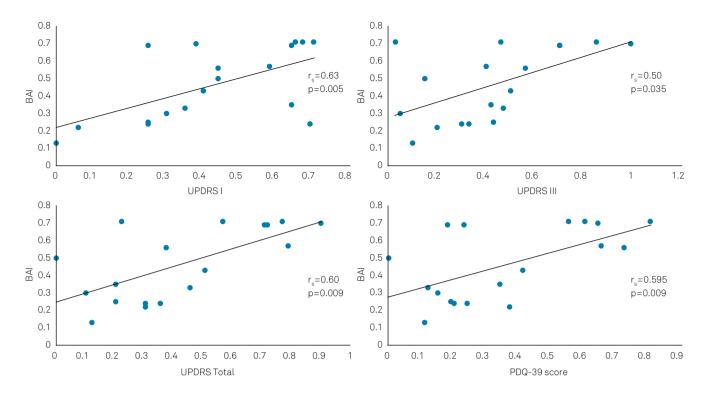


Figure 2. Levels of anxiety in the study groups.



BAI: Beck Anxiety Inventory; UPDRS: Unified Parkinson's Disease Rating Scale; PDQ-39: Parkinson's Disease Questionnaire-39

Figure 3. Correlation between the parts of the UPDRS and the symptoms of anxiety. A: Spearman's correlation of the BAI vs UPDRS III. C: Spearman's correlation of the BAI vs UPDRS total. D: Pearson's correlation of the BAI vs PDQ-39.

**Table 4.** Progression of the load in the exercises of the intervention protocol.

Exercise		Pre-interventio	n	Post-intervention			
Exercise	Mean (kg)	SD (kg)	Min-Max (kg)	Mean (kg)	SD (kg)	Min-Max (kg)	
Bench Press	13.6	5.15	4-24	27.5	11.56	10-48	
Unilateral rowing – Right	14.2	5.65	2-20	28.8	10.36	6-40	
Unilateral rowing - Left	17.5	3.54	15-20	27.5	10.61	20-35	
Deadlift	18.4	11.78	4-45	32.1	13.75	10-60	
Standing calf raise	24.5	11.17	5-45	43.5	15.1	15-65	
Lower abdominal exercise	1	1.05	0-2	4.6	2.32	2-8	

SD: standard deviation; Min: minimum; Max: maximum

### **DISCUSSION**

The main finding of our study showed a significant reduction in the anxiety level of patients with PD after the regular resistance training; however, the CG did not show any changes in this symptom. In previous studies, it had been observed that physical exercise (e.g. resistance training) had potential benefits in the control and reduction of anxiety symptoms in different populations<sup>9,12,19,20</sup>.

Anxiety is associated with increased motor symptoms in PD and decreased QoL of these patients. Therefore, our main explanation for the reduction of anxiety symptoms in the RTG was the reduction of the symptoms of the disease as evaluated through the UPDRS and the consequent improvement in QoL of patients with PD. In addition, a positive association between the BAI and UPDRS and between the BAI

and PDQ-39 was found. It is currently known that patients with PD who practice resistance training have significant improvements in motor and nonmotor symptoms<sup>1,12,21</sup>.

Unlike the localized action of the drug, chronic exercise promotes crosstalk among tissues, providing metabolic, structural and functional adaptations in various cells and organ systems at the same time, improving the ability to gain in the presence of stress<sup>22</sup>. This may explain the response of reduction of anxiety symptoms in virtually all RTG subjects.

The origin of anxiety symptoms in PD has not been clearly explained, but many studies support the hypothesis of sharing underlying biological mechanisms among these pathologies, which involve abnormalities in the dopaminergic system and in other interacting systems such as: noradenergics, serotonergics<sup>2,23</sup>. In addition, a constant stress stimulus is an important determinant for the development of excessive anxiety

symptoms, and PD is a homeostatic disorder that causes this type of stimulation in the central nervous system<sup>24</sup>.

Excessive anxiety symptoms are linked to reduced activity of noradrenergic neurons in the medulla oblongata - locus coeruleus, leading to reduced synthesis of the norepinephrine level, as well as increased expression of 5-hydroxytryptamine (5-HT) and decreased 5-HT 1A and 5-HT 1B autoreceptors by serotonergic neurons of the dorsal raphe nucleus. However, stress promoted by chronic exercise increases the tyrosine hydroxylase activity that transforms the tyrosine into norepinephrine, increasing expression of this neurotransmitter. Triggers in the dorsal raphe lead to greater expression of 5-HT1A autoreceptors, which, when activated, regulate the release of 5-HT $^{24,25}$ .

According to Moteiro-Junior et al. <sup>26</sup>, the exercises may have a neuroprotective potential in patients with PD, by the stimulation of neurotrophic factors responsible for the neurogenesis, neuroplasticity and angiogenesis processes, which are fundamental for mental health. Resistance exercise increases central insulin-like growth factor (IGF1) by stimulating the expression of the IGF1 receptor that activates the Akt pathway, which is critical for angiogenesis, cell growth and proliferation, and neural survival<sup>19</sup>. In addition, it is known that muscle under vigorous contraction releases many endocrine-related factors, such as brain-derived neurotrophic factor, which can cross the blood-brain barrier and trigger neuroplasticity<sup>22</sup>.

Another important mechanism is the mitochondrial turnover disorder that is related to the increase of oxidative stress and consequent neuroinflammation. This process is cyclic, and is responsible for neurodegeneration, which may explain the progression of PD symptoms and psychological disturbances, but chronic exercise by mediated increase in the co-activators of SIRT1 transcription and peroxisome proliferator-activated 1-alpha-receptor co-activator (PGC- $1\alpha$ ) promotes mitochondrial biogenesis, increases antioxidant enzyme activity and decreases reactive oxygen species, reducing the progression of PD symptoms and improving mental health<sup>26,27</sup>.

The relationship between the patients' age and the time of diagnosis of PD with symptoms of anxiety is still unclear<sup>28,29</sup>, but studies have demonstrated that anxiety may precede the onset of PD motor symptoms or may develop after PD diagnosis<sup>2,4</sup>. In the present study, no relationship between the patients' age and time of PD diagnosis was found.

Patients with PD present with a high prevalence of anxiety symptoms<sup>30</sup>, which cause excessive concern and difficulty in social relations, directly affecting their QoL. Our findings have

shown that these symptoms can be attenuated with participation in resistance training programs and the maintenance of pharmacological treatment, under the care of a neurologist.

However, the QoL of patients with PD is influenced by other aspects of the disease, such as: depression, apathy, cognition, insomnia, tremor, rigidity, medication, age and severity of PD<sup>28</sup>. Many patients with PD become confined and abandon social life due to the progression of motor symptoms. This situation further increases the symptoms of depression and anxiety in this population.

Therefore, it is important that therapies, such as resistance training, which are capable of acting on both motor and non-motor symptoms of PD are added to the treatment of this disease<sup>12</sup>. It was observed that in the RTG, the decrease of the total UPDRS, as well as in parts I and II of the UPDRS, correlated with lower BAI scores. However, parts II (motor experiences of the daily living) and part IV (motor complications) were not correlated with the BAI. This demonstrates that understanding the complexity of different PD symptoms is important because they directly influence the patients' anxiety status. Future studies should specifically research this relationship and how much and how it influences the quality of life.

In conclusion, the resistance training was effective in reducing anxiety symptoms and improved quality of life in patients with PD. Therefore, resistance training may be a very important therapeutic intervention in PD.

### Limitations

There were some limitations of this trial. First, all patients were treated and tested during the "on" phase of their medications and the effects of therapy when "off" awaits confirmation. Second, only patients at stages 1-3 of the Hoehn and Yahr scale, without chronic conditions at the study onset, were included. Thus, results cannot be generalized to patients without these characteristics. Third, the level of transmitters associated with anxiety was not investigated. Fourth, the sample size was modest, with 17 control patients and 18 patients in the experimental group, but this was due to the inclusion and exclusion criteria proposed in this study.

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## **Erratum**

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Should be:

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