

Aquatic exercise program-modulated oxidative stress markers in patients with Parkinson's disease

Caroline Dani^{1,4,*}, Isabel Teixeira Proença¹, Jessica Marinho¹, Pâmela Peccin², Ivy Reichert Vital da Silva¹, Simone Nique², Vera Striebel², Daniela Pochmann¹, Viviane Rostirola Elsner^{1,2,3}

1 Programa de Pós Graduação em Biociências e Reabilitação do Centro Universitário Metodista-IPA, Porto Alegre, RS, Brazil

2 Curso de Fisioterapia do Centro Universitário Metodista-IPA, Porto Alegre, RS, Brazil

3 Programa de Pós Graduação em Ciências Biológicas: Fisiologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

4 Programa de Pós Graduação em Farmacologia e Terapêutica, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

Funding: This study was financially supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) for financial support.

Abstract

Parkinson's disease is a neurodegenerative disease. Oxidative stress, i.e., the imbalance between the generation of reactive oxygen species and the antioxidant defense capacity of the body, plays an important role in the pathogenesis of this disease. Physical exercise can regulate oxidative stress. The purpose of this study was to analyze the short- and long-term effects of an aquatic exercise program on oxidative stress levels in patients with Parkinson's disease. The aquatic exercise program was carried out during 1 month with two sessions per week (1 hour/session). Blood samples were collected at four different time points: pre-intervention, immediately, 48 hours, and 30 days after the first session of aquatic exercise program. Our results revealed that water-based programs modulated antioxidant enzyme activity, increased superoxide dismutase activity, reduced catalase activity, and increased the ratio of superoxide dismutase activity to catalase activity in patients with Parkinson's disease. Compared with pre-intervention and 48 hours after the first session of aquatic exercise program, superoxide dismutase activity was higher and catalase activity was lower immediately and 30 days after the first session. Our results demonstrated that aquatic exercise program could modulate oxidative stress, mainly by the effect of antioxidant enzyme activity. These results could better help understand the target of oxidative stress in Parkinson's disease. This study was approved by the Ethics Committee of Centro Universitário Metodista IPA (approval No. 1.373.911) on August 9, 2019 and registered with REBEC (registration number: RBR-6NJ4MK).

Key Words: antioxidant enzyme; antioxidants; aquatic exercise; exercise therapies; neurodegenerative disease; oxidative stress; Parkinson's disease

Chinese Library Classification No. R493; R741

Introduction

Parkinson's disease (PD), a chronic neurodegenerative disease, affects 1–2% of the elderly population and is characterized by bradykinesia, rigidity, resting tremor, and postural instability (Lang and Lozano, 1998). This disease involves the progressive loss of dopaminergic neurons in the substantia nigra (SN), leading to depletion of striatal dopamine (Huot et al., 2006). Furthermore, it is known to be mediated by oxidative stress, which contributes to the cascade leading to dopamine cell degeneration (Jenner, 2003).

Oxidative stress is the imbalance between the generation of reactive oxygen species and the antioxidant defense capacity of the body, and usually, it is associated with degenerative process (Monteiro-Junior et al., 2015). This process has some components, such as mitochondrial dysfunction and inflammation (Monteiro-Junior et al., 2015). Oxidative stress is associated with PD (Jenner, 2003); however, until now, it is difficult to know whether this process leads to or is a consequence of these events. For example, in PD, reactive species cause damage to different compounds from cells, and toxic products of oxidative damage, such as 4-hydroxynonenal

(HNE), can react with proteins to impair cell viability.

There is evidence that nitric oxide reacts with superoxide to produce peroxynitrite and hydroxyl radical, the worst free radical, and this is capable of inducing irreversible damage (McNaught and Jenner, 2000). For homeostasis and detoxification, some enzymes are essential, including catalase (CAT) and superoxide dismutase (SOD) (Gonzalez-Billault et al., 2018). SOD acts as a critical antioxidant defense mechanism against oxidative stress by catalyzing the dismutation of superoxide into oxygen and hydrogen peroxide and CAT, the hydrogen peroxide and water, and oxygen (Gonzalez-Billault et al., 2018). Carbonyl level (protein oxidation marker) and malondialdehyde (MDA; product for lipid peroxidation) are essential to measure oxidative damage (Wei et al., 2018). The failure of the antioxidant defense system to protect against free-radical generation damages all components of the cell, including DNA, lipids, and proteins, eventually leading to cell death, which has been considered to be involved in the development of PD (Wei et al., 2018).

PD can be delayed and its consequences can be attenuated through the regular practice of physical activity (LaHue et

*Correspondence to:

Caroline Dani, PhD,
carolinedani@yahoo.com.br.

orcid:

0000-0003-0046-7148
(Caroline Dani)

doi: 10.4103/1673-5374.276337

Received: September 9, 2019

Peer review started: October 11, 2019

Accepted: December 10, 2019

Published online: May 11, 2020

al., 2016). Several scientific studies suggest that a combination of aerobic activities, strength, balance and gait training, functional activities and exercises that require agility at moderate to high intensity are crucial strategies to induce beneficial impact on clinical outcomes in these patients (Fisher et al., 2008; Goodwin et al., 2008).

Relevant studies have shown exercise-mediated beneficial effects in different populations such as athletes, older adult patients with PD, and healthy individuals, after oxidative stress modulation (Radak et al., 2005; Monteiro-Junior et al., 2015). Fisher et al. (2008) reported differences between acute and chronic effects of exercise, and exercise exerts acute effects through the induction of oxidative stress because there was increased ROS production. However, the chronic effects of exercise are presented as reduced oxidative stress possibly by the increased antioxidant effects from the antioxidant and non-antioxidant defense (Radak et al., 2005; Monteiro-Junior et al., 2015). In a PD experimental model, continuous aerobic training (during 8 weeks) induced an increase in antioxidant enzyme activities (SOD and CAT) and reduced the lipoperoxidation and protein oxidation (Tuon et al., 2012). This effect could be explained by the production of neuroprotective factors and the optimized antioxidant mechanisms, which slow PD progression.

Despite these findings, it is essential to note that these studies are focused on land-based exercise programs, while data regarding the impact of aquatic exercise protocols on oxidative stress modulation in PD patients are scarce. The physical properties of the water and the safe conditions offered by the aquatic environment are an exciting topic to be investigated since it enables individuals with PD to move more efficiently while reducing the fear of falling (Pleash and Leavitt, 2014; Volpe et al., 2014). In this sense, the improvement in several outcomes such as balance and functional mobility was also reported following aquatic therapy in this population (Volpe et al., 2014). It was also demonstrated that PD individuals who underwent aquatic therapy showed better improvement in many outcome measures compared to the group that was submitted to a traditional land-based physical therapy (Volpe et al., 2014), confirming that aquatic therapy exhibited greater effectiveness than traditional land-based physical therapy.

Our group recently showed that an aquatic exercise program might offer a potential strategy able to attenuate immune responses and also modulated brain-derived neurotrophic factor (BDNF) levels in PD individuals (Pochmann et al., 2018). However, no evidence has reported the modulation of oxidative stress levels following this intervention in aquatic exercises. Given these considerations, the purpose of this study was to evaluate the effect of PD on oxidative stress markers and the short- and long-term outcomes of an aquatic exercise program on oxidative stress markers in peripheral blood of patients with PD.

Participants and Methods

Participants

Blood sample was collected from 12 patients with idiopathic

PD (PD group) and 14 healthy controls (control group). All included subjects were of either gender and were aged 51 years or older. It is important to note that the cohort of control and PD groups was the same as that included in the previous study by our research group (Pochmann et al., 2018).

The patients with idiopathic PD confirmed by a neurologist and who used levodopa therapy were included in the PD group. Those who had cardiopulmonary, vascular or other internal medical conditions, neoplastic illness, or infection, those who received oral or local corticosteroids, or those who had a history of undergoing neurosurgical procedure were excluded from this study. In addition, the included subjects must be physically inactive (less than 1 hour of physical exercise in the previous 3 months).

Subjects in the PD and control groups had similar ages (PD group: 62.55 ± 5.57 years; control group: 60.21 ± 10.33 years). In the PD group, the duration of levodopa use was 2–4 years in 50% of patients, 6–8 years in 25% of patients, and 10–17 years in 25% of patients. According to Hoehn & Yahr Scale (Hoehn and Yahr, 1967), the majority of patients were in stage 2.5 (41.66%), while data regarding the Unified Parkinson's Disease Rating Scale (Ramaker et al., 2002) were 15.83 ± 7.54 .

This study was approved by the Ethics Committee of Centro Universitário Metodista IPA (approval No. 1.373.911) on August 9, 2019, and performed in accordance with the *Declaration of Helsinki*. The participants gave their written consent before participation in the study.

Three patients in the PD group were excluded because of difficulties in blood sample collection. No participants withdrew during the intervention, and nine completed the proposed 30 days of aquatic exercise program. All of them completed the program with a minimum attendance of 90% of the sessions. It is important to describe no medication or drug dose change during the intervention.

Study design

The study design included two sessions. At the first session, before the intervention, we collected blood from control and PD patients. At the second session, aquatic exercise program was performed in PD patients. Blood samples were then collected at four time points: pre-intervention, immediately after the first session, 48 hours after the first session, and 30 days after the first session.

Prior to intervention, 15 mL of blood was collected from the antecubital vein to measure the levels of oxidative stress markers. After that, patients in the PD group were subjected to 30 days of aquatic physiotherapy program in the indoor swimming pool (depth 1.1 m, mean water temperature 32°C) of the Centro Universitário Metodista – IPA, twice a week (on Wednesdays and Fridays) frequency, 60 minutes/session (from 2 pm to 3 pm) in groups based on previous studies (Jones et al., 2006; Bote et al., 2014). During the sessions, the patients were stimulated and encouraged with verbal commands to perform at their best. The intervention was performed following the recommendations of the American College of Sports Medicine (ACSM, 2000) and in accordance

with a previous study (Pochmann et al., 2018). The intervention mentioned above was characterized by a concurrent exercise protocol (combination of aerobic and resistance training) outlined by the following activities (a) warm-up with passive stretching of lower limbs, dissociation of waists and double-task exercises (10 minutes); (b) resisted exercises composed by exercise to strengthen paravertebral and posterior chain of trunk and limbs, gait exercise, balance exercise, and proprioception exercise (20 minutes); (c) integration exercises that consisted of dual-task exercise in combination with games with playful connotations to stimulate group integration (20 minutes); (d) relaxation (10 minutes).

Blood collection

Venous blood samples were collected in tubes with EDTAK3. Plasma was separated from the tube by centrifuging at $21,952 \times g$ for 10 minutes and frozen at -20°C for future analysis.

Chemicals

2,4-Dinitrophenylhydrazine, 5,5'-dithiobis (2-nitrobenzoic acid), and thiobarbituric acid were obtained from Sigma-Aldrich, St. Louis, MO, USA. All other reagents were from Merck (Darmstadt, Germany) and Hexapur (Bangalore, Karnataka, India) and solvents were from Nuclear (Diadema, SP, Brazil). They were of analytical grade.

Oxidative stress measurement

To evaluate lipid peroxidation, we used the test to measure the level of thiobarbituric acid reactive substances (TBARS). A heated acidic reaction was performed to generate TBARS. This method was considered sensitive to quantitate the levels of lipid peroxidation, as previously described by Wills (1966). In general, samples were mixed with 10% trichloroacetic acid (TCA) and 0.67% thiobarbituric acid (TBA) and then were heated in a boiling water bath for 15 minutes in sealed tubes. The level of TBARS was determined by absorbance at 535 nm (SP-2200 Spectrophotometer, Bioespectro, Curitiba, Brazil).

Oxidative damage to tissue proteins was measured by determining the carbonyl levels and was based on the reaction with dinitrophenylhydrazine (DNPH), according to Levine et al. (1990). DNPH reacts with protein carbonyls to form hydrazones which can be measured spectrophotometrically at 370 nm (T80 UV/VIS Spectrometer, PG Instruments, Leicestershire, UK).

The non-enzymatic sulfhydryl technique was used to determine defenses. This assay was based on the reduction of 5,5'-dithiol-bis (2-nitrobenzoic acid) (DTNB) by thiol groups, generating a yellow compound (TNB), which was its absorbance determined spectrophotometrically at 405 nm (SP-2200 spectrophotometer). The sulfhydryl content was inversely correlated with oxidative protein damage.

The activity of SOD was determined spectrophotometrically by measuring the inhibition of the rate of adreno-

chrome formation at 480 nm (T80 UV/VIS spectrometer) in a reaction medium containing 1 mM adrenaline and 50 mM glycine (Bannister and Calabrese, 1987). The results were expressed as U/mg of protein. The assay for assessing the activity of CAT was performed according to the method described by Aebi (1984), which determines the rate of hydrogen peroxide decomposition (H_2O_2) to 240 nm (T80 UV/VIS spectrometer).

Statistical analysis

All collected data were inserted in a spreadsheet (Microsoft Excel[®], Redmond, WA, USA) and analyzed using SPSS 22.0 software (IBM, Armonk, NY, USA). The normality was verified using the Shapiro-Wilk test. The Student's *t*-test or Mann-Whitney *U* test was used for comparison between control and PD groups. The outliers were detected by the Outlier calculator from GraphPad Prism software version 7 (GraphPad Software Inc., La Jolla, CA, USA), and the values were removed. The repeated measures analysis of variance and Tukey's *post hoc* test were performed for comparison between the various times in PD patients. All data were presented as the mean \pm standard deviation or median (quartile range), and a level of $P < 0.05$ was considered statistically significant.

Results

PD patients showed lower levels of lipid peroxidation compared with the healthy controls ($P < 0.05$; **Figure 1A**). PD patients showed higher CAT activity (**Figure 1E**), lower SOD activity, and lower ratio of SOD/CAT activities compared with the healthy controls (**Figure 1D** and **F**). SOD activity was found to be related with CAT activity (**Figure 1E**). There were no significant differences in carbonyl (**Figure 1B**) and sulfidryl levels (**Figure 1C**) between control and PD groups.

The effects of aquatic exercise program prior to intervention, immediately, 48 hours, and 30 days after the first session on oxidative stress levels are illustrated (**Figure 2**). TBARS level measured at 30 days after the first session of aquatic exercise program was significantly higher than that measured prior to intervention ($P < 0.05$; **Figure 2A**). There were no significant differences in carbonyl (**Figure 2B**) and sulfhydryl levels (**Figure 2C**) between prior to intervention and 30 days after the first session of aquatic exercise program ($P < 0.05$). SOD activity was increased significantly immediately after the first session of aquatic exercise program compared with that measured prior to intervention ($P < 0.05$; **Figure 2D**). CAT activity was significantly decreased immediately and 30 days after the first session of aquatic exercise program than that measured prior to intervention (**Figure 2E**; $P < 0.05$). The ratio of SOD/CAT activities were increased immediately after the first session of aquatic exercise program compared with that prior to intervention and it decreased to the level measured prior to intervention at 48 hours after the first session (**Figure 2F**).

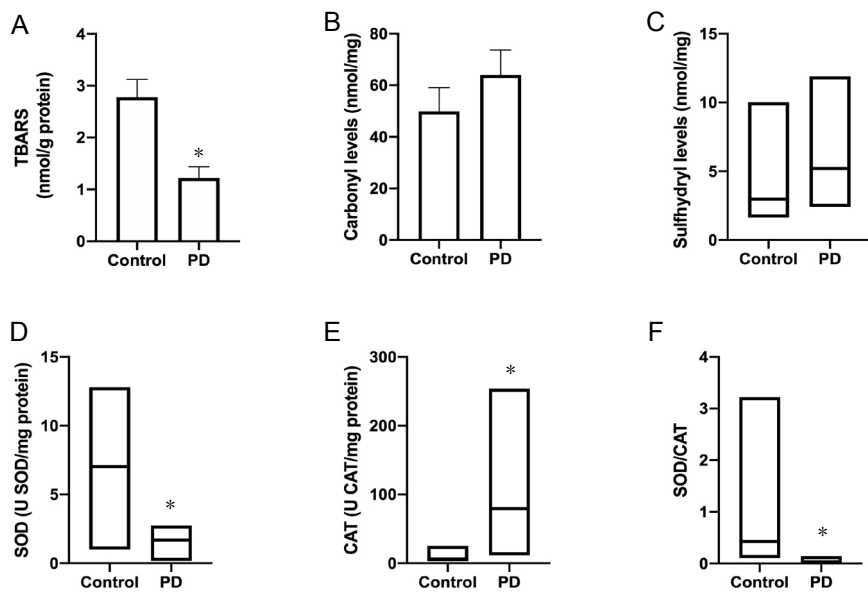


Figure 1 Oxidative stress parameters in plasma from the control and PD groups.

Lipid peroxidation-TBARS (A), protein carbonyl level (B), glutathione-sulfhydryl level (C), SOD activity (D), CAT activity (E) and SOD/CAT activity ratio (F). Sample size: 12 controls and 12 patients with Parkinson's disease. Student's *t*-test or Mann-Whitney *U* test was used. **P* < 0.05, vs. control group. The values of A and B are shown as the mean ± standard deviation. The values of C–F are shown as the median (quartile range). CAT: Catalase; PD: Parkinson's disease; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substance.

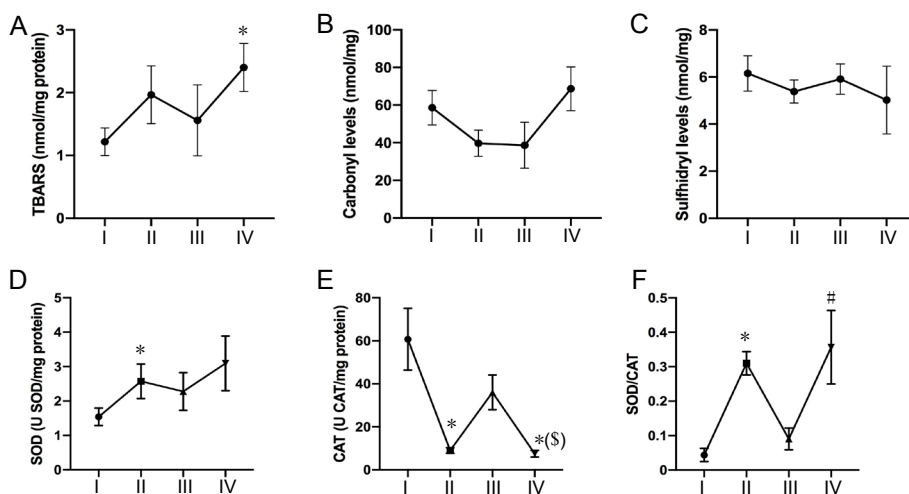


Figure 2 Oxidative stress parameters in PD group at different time points.

Lipid peroxidation-TBARS (A), protein carbonyl level (B), glutathione-sulfhydryl level (C), SOD activity (D), CAT activity (E) and SOD/CAT activity ratio (F). Sample size: 9 patients with Parkinson's disease. Repeated measures analysis of variance with Tukey's *post hoc* test. **P* < 0.05, vs. pre-intervention; \$*P* < 0.05, vs. 48 hours after the first session; #*P* < 0.05, vs. immediately after the first session of aquatic exercise program. The values are shown as the mean ± standard deviation. CAT: Catalase; PD: Parkinson's disease; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substance. I, II, III, IV: Pre-intervention, immediately, 48 hours, and 30 days after the first session of aquatic exercise program, respectively.

Discussion

PD development is characterized by three different biochemical dysfunctions: abnormal protein aggregation, inhibition of mitochondrial complex, and oxidative stress (Jenner, 2003). Several factors lead to the development of PD (Yang et al., 2015), such as tobacco smoking, drinking tea or coffee, use of nonsteroidal antiinflammatory drugs, and physical activity (Barranco Quintana et al., 2009; Ascherio and Schwarzschild, 2016). This study was performed to evaluate the oxidative stress levels in PD patients in response to an aquatic exercise program at different time points. To the best of our knowledge, this is the first study that evaluated the oxidative stress level modulation in a water-based intervention in this population.

In the beginning, we found that PD patients showed lower TBARS levels compared with the healthy controls. However, an imbalance of the antioxidant enzyme activity was found since SOD activity was reduced, and CAT activity was increased, showing a reduced SOD/CAT ratio. This result

might be linked to PD pathophysiology and could contribute to the complications in the disease (Jenner, 2003). In this sense, the neuronal degeneration may result from increased exposure to free radicals coupled with a deficit of antioxidant mechanism, and the antioxidant enzyme activities are negatively correlated with the severity of the disease but independent of age and age of onset (Wei et al., 2018),

According to Romuk et al. (2017), over the past few years, many experimental and clinical studies showed the balance of the oxidation-antioxidant system in neurodegenerative diseases. The results, until now, suggested that the cell aging processes and progressive neurodegeneration are closely associated with oxidative stress (Romuk et al., 2017). Although the body has numerous defense mechanisms against free radicals, it appears that the brain is exposed to increasingly damaging effects of ROS compared with the peripheral organs.

An experimental study showed that lipid peroxidation is different in different brain regions. There was no difference in lipid peroxidation in the cerebral cortex between control

and PD groups; however, lipid peroxidation level in the striatum was higher in the PD group than that in the control group (Romuk et al., 2017). In our study, the PD group showed lower levels of TBARS than the control group. This result is different from the findings from a random-effects meta-analysis that PD patients had significantly higher levels of ferritin, 8-OhdG, nitrite, and MDA compared with the healthy controls (Wei et al., 2018). This difference could be, at least in part, because PD individuals are engaged in regular physical therapy program in our university. Goodwin et al. (2008) showed that under chronic conditions, exercise could reduce oxidative stress damage. We analyzed the short-term and long-term effects of the aquatic exercise protocol and found that lipid peroxidation level increased after 30 days when compared with that measured at the first intervention. However, prior to intervention, TABARS levels in PD patients were lower than those in healthy controls.

At any time points studied, there was no significant difference in carbonyl level between control and PD groups. There are no clinical studies on protein oxidation damage (carbonyl assay). Data obtained from an experimental study showed that treatment with L-dopa significantly increased protein oxidation level compared with the controls (Nikolova et al., 2019). However, antioxidants significantly reduced the increase compared to L-dopa group. These results could attribute to the vital role of antioxidant in the treatment with L-dopa, that is to say, antioxidants can reduce the protein oxidation in patients who need L-dopa treatment.

Different free radicals, including hydrogen peroxide, hydroxyl radical, nitric oxide, and superoxide radical provoke damage to cells, however, the human body has important defenses, including SOD, CAT, glutathione, and uric acid (Wei et al., 2018). The failure of antioxidant defenses could induce damages in all components of the cell, including DNA, lipids, and proteins, eventually leading to cell death, which has been considered to be involved in the development of PD (Wei et al., 2018).

The current study demonstrated that prior to aquatic exercise program, the antioxidant enzyme activities differed between the control and PD groups. Patients with PD showed lower SOD activity and higher CAT activity compared with healthy controls. Therefore, the activity ratio of these two enzymes was also reduced. We also analyzed the short-term and long-term effects of aquatic exercise program and found that aquatic exercise changed these results, i.e., CAT activity increased immediately after the first session of aquatic exercise program and maintained at this level 30 days after the first session of exercise. The ratio of SOD/CAT activities measured immediately after the first session of aquatic exercise was increased compared with that prior to intervention.

Previous studies showed that constant exercise promoted beneficial adaptations, reduced free radical production and increased antioxidant defense (Xu et al., 2010; Monteiro-Junior et al., 2015). Xu et al. (2010) showed that only moderate-intensity vigorous exercise may prevent the occurrence of

PD. However, there is no consensus on this issue. There are also studies reporting that low-to-moderate-intensity exercise could promote the adaptation of antioxidants against the adverse effects of ROS and high-intensity exercise induced deleterious effects (Radak et al., 2005; Monteiro-Junior et al., 2015).

Some limitations of this study must be recognized. First, we used a pre-post intervention design and applied the aquatic exercise to the control group, but we did not affirm that aquatic exercise had a better efficacy than sham therapy. Second, the number of subjects is relatively small, given to the difficulty of recruiting the sample. However, the results inspire us to do other studies with a larger-sized sample, including a control group, which could enable the verification of other issues such as the influence of gender and age on oxidative stress modulation in response to an aquatic exercise protocol in PD patients.

In summary, our results revealed that water-based programs modulated antioxidant enzyme activity, increased SOD activity, reduced CAT activity, and reduced SOD/CAT activity ratio in PD individuals. The modulating effects obtained immediately after the first session of aquatic exercise were better than those measured at other time points studied. Further studies are needed to investigate the exercise intensity and long-term benefits of aquatic exercise therapy in patients with PD.

Author contributions: CD, PP, IRVS, SN, VS and VRE conceived the design of the study and carried out the experiments. ITP, JM, IRVS and DP prepared samples and analyzed results. CD and VRE wrote the manuscript with assistance from all the other authors. All authors approved the final paper.

Conflicts of interest: The authors declare no conflicts of interest.

Financial support: This study was financially supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) for financial support. The funding sources had no role in study conception and design, data analysis or interpretation, paper writing or decision to submit this paper for publication.

Institutional review board statement: The study was approved by the Ethics Committee from Centro Universitário Metodista IPA (approval No. 1.373.911) on August 9, 2019, and performed in accordance with the Declaration of Helsinki.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the forms, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

Reporting statement: This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Biostatistics statement: Statistical methods of this study were reviewed by an expert in biostatistics at Centro Universitário Metodista IPA.

Copyright license agreement: The Copyright License Agreement has been signed by all authors before publication.

Data sharing statement: Datasets analyzed during the current study are available from the corresponding author on reasonable request.

Plagiarism check: Checked twice by iThenticate.

Peer review: Externally peer reviewed.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak,

and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Open peer reviewers: Katharina Schmidt, Johns Hopkins University School of Medicine, USA; Xavier d'Anglemont de Tassigny, Instituto de Biomedicina de Sevilla, Spain.

Additional file: Open peer review reports 1 and 2.

References

- ACSM (2010) ACSM's guidelines for exercise testing and prescription. Baltimore: Lippincott Williams and Wilkins.
- Aebi H (1984) Catalase in vitro. *Methods Enzymol* 105:121-126.
- Ascherio A, Schwarzschild MA (2016) The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol* 15:1257-1272.
- Bannister JV, Calabrese L (1987) Assays for superoxide dismutase. *Methods Biochem Anal* 32:279-312.
- Barranco Quintana JL, Allam MF, Del Castillo AS, Navajas RFC (2009) Parkinson's disease and tea: a quantitative review. *J Am Coll Nutr* 28:1-6.
- Bote ME, García JJ, Hinchado MD, Ortega E (2014) An exploratory study of the effect of regular aquatic exercise on the function of neutrophils from women with fibromyalgia: role of IL-8 and noradrenaline. *Brain Behav Immun* 39:107-112.
- Fisher BE, Wu AD, Salem GJ, Song J, Lin CH, Yip J, Cen S, Gordon J, Jakowec M, Petzinger G (2008) The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease. *Arch Phys Med Rehabil* 89:1221-1229.
- Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL (2008) The effectiveness of exercise interventions for people with Parkinson's disease: A systematic review and meta-analysis. *Mov Disord* 23:631-640.
- Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. *Neurology* 17:427-442.
- Huot P, Levesque M, Parent A (2006) The fate of striatal dopaminergic neurons in Parkinson's disease and Huntington's chorea. *Brain* 130:222-232.
- Jenner P (2003) Oxidative stress in Parkinson's disease. *Ann Neurol* 53:S26-38.
- Jones K, Adams D, Winters-Stone K, Burckhardt CS (2006) A comprehensive review of 46 exercise treatment studies in fibromyalgia (1988-2005). *Health Qual Life Outcomes* 4:67.
- LaHue SC, Comella CL, Tanner CM (2016) The best medicine? The influence of physical activity and inactivity on Parkinson's disease. *Mov Disord* 31:1444-1454.
- Lang AE, Lozano AM (1998) Parkinson's disease. *N Engl J Med* 339:1044-1053.
- Levine RL, Garland D, Oliver CN, Amici A, Climent I, Lenz AG, Ahn BW, Shaltiel S, Stadtman ER (1990) Determination of carbonyl content in oxidatively modified proteins. *Methods Enzymol* 186:464-478.
- McNaught KS, Jenner P (2000) Extracellular accumulation of nitric oxide, hydrogen peroxide, and glutamate in astrocytic cultures following glutathione depletion, complex I inhibition, and/or lipopolysaccharide-induced activation. *Biochem Pharmacol* 60:979-988.
- Monteiro-Junior RS, Cevada T, Oliveira BR, Lattari E, Portugal EM, Carvalho A, Deslandes AC (2015) We need to move more: Neurobiological hypotheses of physical exercise as a treatment for Parkinson's disease. *Med Hypotheses* 85:537-541.
- Nikolova G, Karamalakova Y, Gadjeva V (2019) Reducing oxidative toxicity of L-dopa in combination with two different antioxidants: an essential oil isolated from *Rosa Damascena* Mill., and vitamin C. *Toxicol Rep* 6:267-271.
- Pleash AR, Leavitt BR (2014) Aquatherapy for neurodegenerative disorders. *J Huntingtons Dis* 3:5-11.
- Pochmann D, Peccin PK, da Silva IRV, Dorneles GP, Peres A, Nique S, Striebel V, Elsner VR (2018) Cytokine modulation in response to acute and chronic aquatic therapy intervention in Parkinson disease individuals: A pilot study. *Neurosci Lett* 674:30-35.
- Radak Z, Chung HY, Goto S (2005) Exercise and hormesis: oxidative stress-related adaptation for successful aging. *Biogerontology* 6:71-75.
- Ramaker C, Marinus J, Stiggelbout AM, Van Hilten BJ (2002) Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. *Mov Disord* 17:867-876.
- Romuk E, Szczurek W, Oleś M, Gabrysiak A, Skowron M, Nowak P, Birkner E (2017) The evaluation of the changes in enzymatic antioxidant reserves and lipid peroxidation in chosen parts of the brain in an animal model of Parkinson disease. *Adv Clin Exp Med* 26:953-959.
- Tuon T, Valvassori SS, Lopes-Borges J, Luciano T, Trom CB, Silva LA, Quevedo J, Souza CT, Lira FS, Pinho RA (2012) Physical training exerts neuroprotective effects in the regulation of neurochemical factors in an animal model of Parkinson's disease. *Neuroscience* 227:305-312.
- Volpe D, Giantin MG, Maestri R, Frazzitta G (2014) Comparing the effects of hydrotherapy and land-based therapy on balance in patients with Parkinson's disease: a randomized controlled pilot study. *Clin Rehabil* 28:1210-1217.
- Wei Z, Li X, Li X, Liu Q, Cheng Y (2018) Oxidative stress in Parkinson's disease: a systematic review and meta-analysis. *Front Mol Neurosci* 11:236.
- Wills ED (1966) Mechanisms of lipid peroxide formation in animal tissues. *Biochem J* 99:667-676.
- Xu Q, Park Y, Huang X, Hollenbeck A, Blair A, Schatzkin A, Chen H (2010) Physical activities and future risk of Parkinson's disease. *Neurology* 75:341-348.
- Yang F, Trolle Lagerros Y, Bellocchio R, Adami HO, Fang F, Pedersen NL, Wirdefeldt K (2015) Physical activity and risk of Parkinson's disease in the Swedish National March Cohort. *Brain* 138(Pt 2):269-275.

P-Reviewers: Schmidt K, de Tassigny XD; *C-Editor:* Zhao M; *S-Editor:* Li CH; *L-Editor:* Song LP; *T-Editor:* Jia Y