

# Levels of brain-derived neurotrophic factor in patients with fibromyalgia and chronic low back pain: Results of an aquatic physical therapy protocol

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## Abstract

**Objectives:** This work aims to assess changes in brain-derived neurotrophic factor (BDNF) levels in women after the practice of a specific short duration 10-session aquatic physical therapy protocol in patients with fibromyalgia (FB).

**Methods:** Case-control study. Thirteen women diagnosed with FB and 11 controls with the same age group, 35–55 years. Patients were evaluated according to the visual analog scale of pain and the fibromyalgia impact questionnaire (FIQ). All were subjected to a short protocol totaling 10 sessions of 40 min twice a week for five weeks. Heart rate and pain were monitored. BDNF levels were measured using enzyme immunoassay.

**Results:** A statistically significant increase in BDNF values was noted in patients with FB between the pre- and post-10th session assessments (mean of 35.52–41.96;  $p = 0.041$ ).

**Conclusion:** BDNF values may present fluctuations during a short duration moderate aerobic exercise protocol, when measured and analyzed in a longitudinal design. Further studies with a more frequent BDNF evaluation could help in understanding its behavior more accurately and are warranted.

**Key words:** hydrotherapy, fibromyalgia, intervention, exercise and pain

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## Introduction

Fibromyalgia (FB) is a rheumatic syndrome of unknown etiology characterized by widespread and chronic musculoskeletal pain in at least 11 points of the body for at least three months (Letieri et al. 2013). This disease affects 1%–3% of the world's population, 10.5% of the general population, and 8% of the Brazilian population. It has a higher incidence in women 22 to 55 years old, accounting for 70%–90% of the cases (Heymann et al. 2010; Letieri et al. 2013). It is often associated with

generalized fatigue, sleep disturbances, morning stiffness, dyspnea, mood changes, and often evolving to depressive disorders. This is a disorder that causes decreased modulation of pain mechanisms (nociception) leading to an increase in pain sensitivity (Rivera et al. 2006; Santos et al. 2006). This disease is closely related to the central nervous system. The etiology varies in individuals, and may be due to several factors such as neurogenic inflammation, inflammatory response to an allergen, bacterial or viral infections, chemical exposures, or emotional stress. Due to these factors, some inflammatory mediators and proteins may show abnormalities in patients' serum levels (David and Lloyd 2001; Salvador et al. 2005).

The brain-derived neurotrophic factor (BDNF) is a protein that modulates the synaptic plasticity of the central and peripheral nervous systems and neurotransmitters, which regulates neuronal excitability and hyperalgesias (Lindsay et al. 1994; Lewin and Barde 1996; Escobar et al. 2003; Luo et al. 2016). In recent years, a BDNF precursor called proBDNF was described as a biologically active molecule. Both the mature and precursor forms of BDNF are now implicated in several nervous system functions such as neuronal survival and apoptosis. Moreover, these proteins are involved in long-term depression and neuronal cell death (Costa et al. 2017). In FB, a disorder of nociceptive impulses, processing occurs and BDNF may be abnormal, as it contributes to the modulation of these inputs (Ranzolin et al. 2016). In addition, chronic diseases can cause depression, and some studies suggest that this protein has antidepressant effects and that its abnormalities may be related to the pathogenesis of major depression (Karege et al. 2002; Haas et al. 2010). Some factors can change the blood levels of this protein, and aerobic exercise can affect it. However, the intensity and ideal volume of aerobic exercise that needs to be performed for changes to be detected is unknown (Winkelmann et al. 2012). Recently, the role of BDNF in pain states has received more attention as a neuromediator of hyperalgesia and spinal central sensitization (Haas et al. 2010).

Given that exercise in water heated to 33.5 °C promotes increased cardiac output, blood metabolism, and the production of certain neurotransmitters like catecholamines and beta-endorphins, we hypothesized potential modifications to BDNF levels after the application of a controlled protocol of water exercises in people with FB (Assis et al. 2006). Thus, given the potential for significant changes to a patient's quality of life, better pain control, and a decrease in expenses due to a reduction in drug costs, the main objective of our study was to determine if BDNF levels changed after the practice of a specific aquatic physical therapy protocol during which pain and heart rate parameters were controlled.

## Patients and methods

### Study design and participants

Sixteen women 35 to 55 years old diagnosed with FB and attending the physiotherapy clinic at the Universidade Catolica de Pelotas (UCPEL) were included in this study. Data collection and participant recruitment occurred from November to December 2012. This case-control study, which had a determined sample with a confidence level of 5% ( $\alpha = 0.05$ ), 80% power ( $\beta = 0.20$ ), an estimated variance in the population of 3.28, and an expected difference between the means of the groups at the end of the study of 1.50 points on the pain scale. The calculations determined a minimum of nine people in each group. Adding 50% to losses and refusals, the expected number will be 14 people in each group, totaling 42 people in the sample.

After providing voluntary and signed consent to participate in the study, all FB group patients were evaluated to confirm FB diagnosis. A rheumatologist from the UCPEL ambulatory care service

performed the assessment following the American College of Rheumatology criteria 1990 (Wolfe et al. 1990).

Of the 16 patients, 13 were diagnosed with FB. Control group participants were recruited based on the following criteria: in the same age group as the case group participants, receiving treatment at the same hospital, and diagnosed as not suffering from FB after a clinical evaluation. The control group was required to have chronic pain identified as low back pain. As a clinical feature and to be characterized as having a chronic condition, all participants were required to have experienced at least one year of pain symptoms. All participants underwent to the same evaluations and exercise protocol regardless of whether they were in the case group or the control group.

Patients with cognitive impairment, neurological problems, and those not adapted to the liquid medium were excluded. The study was approved by the Ethics Committee of the Universidade Catolica de Pelotas, IRB No. 06040212.0.0000.5339.

### Study protocol and blood sample collection

In the first session, questionnaires were applied to describe the socio-demographic profile of the participants according to the Brazilian Association of Research Companies (ABEP) and fibromyalgia impact questionnaire (FIQ). The FIQ is a questionnaire consisting of 19 questions, organized into 10 items, where health aspects FB affects most are assessed and measured as follows: functional capacity, professional situation, psychological symptoms, and physical symptoms (Marques et al. 2006). The score ranges from 0 to 100 where individuals with FB often reach a score of approximately 50 points, and those severely affected can reach up to 70 or more points.

The ABEP uses the CCEB (economic classification criterion in Brazil) as a tool to verify the economic class. It is built using a survey where household characteristics (presence and amount of some household items of comfort and household head degree of education) are asked to differentiate the population. This criterion assigns points to each household characteristic and performs the sum of these points. Finally, a relationship between test scores is performed and an economic classification is defined as A1, A2, B1, B2, C1, C2, D, and E (Bennett 2002).

### Aquatic physical therapy protocol

The aquatic physical therapy protocol occurred in 10 sessions, twice a week for five weeks. The therapy pool had a varying depth from 1.40 to 1.80 m, with a temperature of 33 °C. The protocols applied in the FB and control groups were identical and consisted of 10 min walking back and forth in the pool; 15 min of stationary running with flexion and extension of the arms, maintaining 60%–65% of maximum heart rate ( $HR_{max}$ ); 15 min of interval training with exercises in a 40 cm step (up and down four steps); and running in deep water (running in depth) attaining 75%–80% ( $HR_{max}$ ) while being held with a lower back vest. In addition, the following exercises were each performed for 1.5 min: (1) abduction and adduction of the hip while standing, closed loop with upper limbs pointing forward of the static body and on the water surface; (2) hip flexion and slow knee extension like a kicking knee, and alternating legs; (3) fast gait with hip and knee flexion; (4) water punches with quick abdomen contractions; (5) cross-country ski in a closed kinetic chain with upper arm flexion and extension; and (6) stationary race. The session finished with 10 min of slow walking in the pool and snaked passive relaxation (supine position with proper vest and leggings stabilization). For  $HR_{max}$  control, an initial measurement at rest ( $HR_{max} = 220 - \text{age}$ ) was performed, and monitoring during the exercise execution was done using a frequency meter waterproof Oregon Scientific (Portland, Oregon, USA), NOHR102 model. The protocol sessions were performed under the supervision of six trained physiotherapists, who were also in the pool (Sañudo et al. 2010). After the questionnaires

were applied to both study groups, a blood sample (10 mL) was collected and stored in an anticoagulant tube with vacuum. These samples were centrifuged at 2000g for 15 min and the plasma was stored at 18 °C until analysis. Pain assessment was made using the visual analog scale (0 = no pain, 10 = a lot of pain), which was applied at all sessions before and after treatment (Coughill and Gracely 1996).

## BDNF measurements

BDNF levels were measured using enzyme immunoassay with a commercially available kit (Chemikine by Chemicon, Temecula, California, USA). Patients were asked not to eat 2 h before the blood collection sessions. Blood was collected 10 min before patients entered the pool and immediately after the end of the session. Blood sampling was performed in the morning, before and after the aquatic physical therapy protocol was delivered, and in the first and last sessions.

## Statistical analysis

Data analysis was performed using the Wilcoxon and Kruskal–Wallis tests, accepting the level of significance of  $p < 0.05$ , and the statistical package used was Stata 10.0 (StataCorp 2007).

## Results

After exclusion and inclusion criteria assessment, 13 FB patients were recruited to participate in the case group and 11 patients (without FB) in the control group. The sample ages in both groups ranged from 35 to 55, demonstrating uniformity in the sample (Table 1). No differences in BDNF values were found when both FB and control groups were compared in the first pre- and post-qualifying session and at the 10th session (Table 1). Table 2 shows the BDNF levels in the first and last sessions. When analyzing a total sample (FB and control groups), there was apparently a trend to increase BDNF after a first hydrotherapy session (Table 3). Analyzing the values before and after the first and 10th BDNF sessions, a significant increase in BDNF values was noted in patients with FB between the pre- and post-assessments after the 10th session (mean of 35.52–41.96;  $p = 0.041$ ) (Table 4). Table 5 shows the BDNF values according to age, pain level, and quality of life (as measured by the FIQ in the total sample before and after hydrotherapy. Results revealed that there is no significant relationship between the protein and the studied variables. When comparing the BDNF concentrations before the sessions (1 and 10), it is seen that BDNF pre-intervention values decreased from session 1 to session 10. However, this reduction was only significant in the FB group (Table 5,  $p = 0.002$ ).

## Discussion

The BDNF protein participates in the modulation of nociceptive inputs and presents with high blood plasma levels in chronic diseases such as FB (Haas et al. 2010). This protein appears to increase as a defense mechanism in painful and stressful situations (Nugraha et al. 2012; Leech and Hornby 2017). The first evidence in serum emerged a decade ago (Karege et al. 2002). It is postulated that low levels of BDNF are associated with psychological stress through dysfunction of the hypothalamic–pituitary–adrenal axis, thus playing an important role in the pathogenesis of depression and cognition disorders. In relation to FB, the expression of BDNF is known for its importance in synaptic plasticity, and its action as a neuromodulator in the dorsal horn of the spinal cord has been proposed in various models of pain, including peripheral inflammation, axotomy, nerve damage, and neuropathic pain (Haas et al. 2010). Moreover, increased serum BDNF levels mediate the disinhibition of motor cortex excitability as well as the function of descending inhibitory pain modulation system, independent of the physiopathology mechanism involved in musculoskeletal pain syndromes (Caumo et al. 2016).

**Table 1.** Demographic and clinical characteristics of controls and subjects with fibromyalgia.

	Control ( <i>n</i> = 11)			Fibromyalgia ( <i>n</i> = 13)			<i>p</i>
	Value (mean ± SD)	<i>n</i>	%	Value (mean ± SD)	<i>n</i>	%	
Age (years)	45.33 ± 4.09	—	—	46.41 ± 4.41	—	—	0.613
<b>Ethnicity</b>							0.640
Caucasian	—	8	72.7	—	10	83.3	
Not Caucasian	—	3	27.3	—	2	16.7	
<b>Schooling</b>							0.689
Fundamental incomplete	—	0	—	—	1	12.5	
Complete primary	—	3	42.8	—	3	37.5	
Full gymnasium	—	2	28.6	—	3	37.5	
Full school	—	2	28.6	—	1	12.5	
<b>Socioeconomic levels (ABEP)</b>							0.820
A + B	—	4	36.4	—	3	23.1	
C	—	7	63.6	—	9	69.2	
D + E	—	0	—	—	1	7.7	
<b>Smoker</b>							0.810
No	—	7	63.6	—	9	75.0	
Yes	—	1	9.1	—	3	25.0	
Ex-smoker	—	3	27.3	—	0	—	
<b>Pain level</b>							
Visual analog scale	6.02 ± 2.38	—	—	6.17 ± 1.59	—	—	0.794
<b>Self-perception of health</b>							0.754
Good or very good	—	2	18.2	—	1	10.0	
Fair	—	6	54.6	—	7	70.0	
Bad or very bad	—	3	27.2	—	2	20.0	

**Note:** The totals of the *n* values for each characteristic do not necessarily equal the sample *n* value because of missing data. SD, standard deviation; ABEP, Brazilian Association of Research Companies.

**Table 2.** Brain-derived neurotrophic factor values before and after hydrotherapy for the total sample (*n* = 24).

	Mean (ng/mL)	Standard error
Pre-hydrotherapy session 1	43.54	15.02
Post-hydrotherapy session 1	46.69	15.78
Pre-hydrotherapy session 10	38.19	14.21
Post-hydrotherapy session 10	43.72	13.17

**Table 3.** Comparison of brain-derived neurotrophic factor values for cases and controls before and after hydrotherapy ( $n = 24$ ).

	Controls ( $n = 11$ )		Cases ( $n = 13$ )		$p^a$
	Mean (ng/mL)	Standard error	Mean (ng/mL)	Standard error	
Pre-hydrotherapy session 1	40.25	4.93	46.57	3.73	0.389
Post-hydrotherapy session 1	49.54	4.11	43.89	5.09	0.498
Pre-hydrotherapy session 10	41.08	4.64	35.52	3.79	0.267
Post-hydrotherapy session 10	45.64	3.38	41.96	4.33	0.242

<sup>a</sup>Wilcoxon rank-sum test.

**Table 4.** Brain-derived neurotrophic factor levels for cases and controls before and after hydrotherapy sessions 1 and 10.

	Hydrotherapy session 1					Hydrotherapy session 10				
	Pre		Post		$p^a$	Pre		Post		$p^a$
	Mean (ng/mL)	Standard error	Mean (ng/mL)	Standard error		Mean (ng/mL)	Standard error	Mean (ng/mL)	Standard error	
Cases	46.57	3.73	43.89	5.09	0.637	35.52	3.79	41.96	4.33	0.041
Controls	40.25	4.93	49.54	4.11	0.182	41.08	4.64	45.64	3.38	0.789

<sup>a</sup>Wilcoxon signed-rank test.

**Table 5.** Brain-derived neurotrophic factor (BDNF) values according to age, pain level, and quality of life (as measured by the fibromyalgia impact questionnaire (FIQ)) in the total sample before and after hydrotherapy ( $n = 24$ ).

	Pre-hydrotherapy <sup>a</sup>			Post-hydrotherapy <sup>b</sup>		
	Mean (ng/mL)	Standard error	$p$	Mean (ng/mL)	Standard error	$p$
<b>Age (years)</b>			0.535 <sup>c</sup>			0.495 <sup>c</sup>
Less than 50 ( $n = 13$ )	41.86	3.55		44.27	3.13	
50 or more ( $n = 10$ )	45.73	5.69		43.02	5.04	
<b>Pain level</b>			0.261 <sup>d</sup>			0.851 <sup>d</sup>
Mild ( $n = 3$ )	34.13	16.22		41.04	11.0	
Moderate ( $n = 5$ )	42.94	14.96		48.80	17.50	
Intense ( $n = 16$ )	47.97	14.89		44.71	5.35	
<b>FIQ</b>			0.535 <sup>c</sup>			0.220 <sup>c</sup>
Less than 60 ( $n = 9$ )	45.46	4.50		46.57	3.71	
60 or more ( $n = 15$ )	41.05	4.35		38.38	3.19	

**Note:** The  $n$  values for “Age” total 23 rather than 24 because of missing data in the fibromyalgia group.

<sup>a</sup>BDNF values before starting physiotherapy.

<sup>b</sup>BDNF values after the last physiotherapy session.

<sup>c</sup>Wilcoxon signed-rank test.

<sup>d</sup>Kruskal–Wallis test.

In this study, we did not see an increase in BDNF levels as expected. However, the control group showed lower BDNF levels in the last session when compared with the FB group. This result is interesting because previous studies have shown that patients with FB have higher levels of BDNF. FB is a musculoskeletal disorder with significant changes in nociceptive regulation, which leads to changes in the processing of painful stimuli. Therefore, as BDNF modulates hyperalgesia, it is plausible to see increased levels in FB patients. Age, pain, and quality of life through were analyzed using the FIQ, and no significant associations of BDNF with these variables were found in the FB group, which is consistent with [Karege et al. \(2002\)](#). We also analyzed time of the disease, antidepressant use, and sex, showing that they were not related to BDNF. Although the two groups in the study were patients with chronic pain, the purpose of the study was to evaluate the effect of hydrotherapy on FB. However, the levels of BDNF did not significantly change after hydrotherapy sessions.

Low to moderate intensity aerobic exercises are ideal for the treatment of FB ([Nugraha et al. 2012](#)) because they help with promoting increased muscle energy capacity, avoiding fatigue, and improving cardiovascular capacity. [Sañudo et al.'s \(2010\)](#) study supported a protocol of aerobic exercises with long-term heart rate control to achieve an improvement in pain scores, FIQ scores, and depression symptoms. We offered a short-term aquatic physical therapy protocol for FB cases and controls, controlling for heart rate to be maintained in the aerobic moderate zone. Participants had pain reduction in all pain categories, as well as improved FIQ scores in the FB cases, which is consistent with [Sañudo et al. \(2010\)](#). An eight-month study of aerobic exercises performed in hot water and controlled heart rates of participants showed improvement in pain and FIQ scores, and respiratory parameters were obtained, which has been seen in other studies ([Jentoft et al. 2001](#)). In people submerged in water up to the thorax level, a warm water temperature and body reaction forces cause significant physiological changes in the cardiovascular and endocrine systems, leading to an increase in the plasma levels of the beta-endorphins, therefore promoting analgesia.

In the physiological sense, the levels of BDNF studied in this research showed a variation when analyzed before and after the first hydrotherapy session, with decreasing concentrations in cases with an average going from 46.57 to 43.89 ng/mL; however this was not statistically significant. Evidence has proven that the effects of exercise on brain function are mediated by growth factors such as BDNF ([Costa et al. 2017](#)), and strength exercises are not able to modify BDNF values ([Correia et al. 2010](#)). In this research study, BDNF values were measured before and after the first and 10th intervention sessions and, contrary to expectations, there was an increase in the BDNF value from 35.52 to 41.96 ng/mL in the FB group. This finding can be explained by the sample anticipatory stress that showed anxiety due to completion of the intervention. Emotional factors such as anxiety and stress could increase these values. However, the first and 10th pre-session values and the first and 10th post-session values showed statistically significant decreases in BDNF levels in both FB cases and controls. The first and 10th pre-session values in the case group ranged from 46.57 to 35.52 ng/mL,  $p = 0.002$ . No comparative data assessing the cumulative result of exercise evaluated longitudinally were found in the literature. We believe that the intervention contributed to analgesia promotion for the FB cases group; it would be ideal to answer this for BDNF values analyzed during the entire intervention. Among the limitations of the study are having such an early analysis and that middle and end of interventions could be presented differently. These aspects need to be further investigated. BDNF values may present fluctuations during a short-duration moderate aerobic exercise protocol when measured and analyzed in a longitudinal design.

## Conclusion

We evaluated the effects of a hydrotherapy protocol on the levels of BDNF patients with FB and chronic low back pain. It was not possible to verify significant changes after treatment.



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## Author contributions

DGM, CXF, AJR, and JPO conceived and designed the study. DGM, CDW, CXF, JLC, AJR, and JPO performed the experiments/collected the data. DGM, CDW, JLC, AJR, and JPO analyzed and interpreted the data. DGM, CDW, AJR, and JPO contributed resources. DGM, CDW, CXF, JLC, AJR, and JPO drafted or revised the manuscript.

## Competing interests

The authors have declared that no competing interests exist.

## Data accessibility statement

All relevant data are within the paper.

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