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Aquatic exercise and Far Infrared (FIR) modulates pain and blood cytokines in fibromyalgia patients: A double-blind, randomized, placebo-controlled pilot study

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ABSTRACT

Fibromyalgia (FM) has an inflammatory component, as elevated serum levels of inflammatory biomarkers are associated with its diagnosis. Treatments decreased pain, body temperature, improved quality of life and reduced serum levels of IL-6 in both groups; however, these beneficial effects were more pronounced in aquatic exercise (AE) + Far-Infrared (FIR) group. The findings of the present study suggest that the association of AE to FIR increases the benefits of aquatic exercise in patients with FM.

1. Introduction

Fibromyalgia (FM) is a painful syndrome that affects mainly women between the ages of 20 and 55 years (Heidari et al., 2017). The most prominent symptoms include fatigue, muscle stiffness, sleep disturbances, muscle pain, as well as memory and cognitive impairment. Pain has been identified as one of the most characteristic symptoms in FM (García et al., 2016), with significant impact upon quality of life and functional capacity (Matsushita et al., 2008). FM treatment is a complicated and a controversial process, but a wide range of pharmacological (Flitzcharles et al., 2013), cognitive behavioral and exercise-based interventions (Jiménez et al., 2013) have been indicated in recent evidence-based guidelines (Häuser et al., 2017).

Although FM is originally described as a non-inflammatory chronic pain syndrome, recent studies support an inflammatory hypothesis. This hypothesis (Omoigui, 2007) implies the involvement of inflammatory cytokines and states that the source of all pain is inflammation, therefore the body's response is inflammatory in nature. In fact, studies have found that individuals with FM present high levels of tumor necrosis factor (TNF) (Wang et al., 2008; Bazzichi et al., 2007; Wang et al., 2004), Interleukin (IL) 8 (Wang et al., 2008; Bazzichi et al., 2007) and IL-6 (Mendieta et al., 2016; Malhotra et al., 2012). TNF could be directly related to pain, since it may promote the sensitization of nociceptors which leads to chronic pain (Tsilioni et al., 2016) and muscle fatigue (Dina et al., 2011). A direct correlation of the disease severity with serum levels of IL-8 and IL-6 when compared to healthy individuals has also been demonstrated (Mendieta et al., 2016). It is well known that IL-6 induces events similar to the clinical symptoms of FM such as hyperalgesia, fatigue, pain, and anxiety (Rodriguez-Pinto et al., 2014) whereas IL-8 has a more direct correlation to sleep and pain (Bote et al., 2013). On the other hand, anti-inflammatory cytokines such as IL-10 might reduce pain (Omoigui, 2007).

Although the pathophysiology of FM is not completely understood, and its treatment is ineffective, non-pharmacological approaches such as physical exercise, have shown to increase the patient's quality of life, physical fitness and muscular strength. All these effects (Pedersen and

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Table 1
Description of exercises performed during the intervention period.

Exercise blocks	Exercise descriptions
(a) Stretching exercises (5–7 min)	- Stretching of the hamstring muscles - Stretching of the triceps surae and iliopsoas muscles - Stretching of upper extremities - Stretching of the trunk
(b) Aerobic warm-up in the water (5–7 min)	- Forward walking with alternated movement of the upper and lower extremities - Walk raising the knee - Lateral walking - Backward walking
(c) Passive stretching (5 min)	- Stretching of the hamstring muscles - Stretching of the triceps surae and iliopsoas muscles - Stretching of upper extremities - Stretching of the trunk
(d) Aerobic aquatic fast (15 min)	- Running in water: With water at waist level, patients will run along the bottom of the pool, changing trajectory
(e) Strength exercises (15 min)	- Can-Can kicks: Submerged to chest depth, patients will kick the water with alterating legs - Hydro-Jumps: With feet on the pool's floor, patients will jump, bending their knees at the highest point in their jump - Pedaling: With a pool noodle under the neck, patients will move their legs in the motion of pedaling a bicycle while moving along the pool - Rocking Horse: With one foot before the other, patients will alternate jumps with the front and back leg - Relay Race: the winner will be the group that returns the baton to the first participant in the shortest time - Strengthening Gastrocnemius, quadriceps, ischiotibial, adductors, quadratus lumborum, deltoid, triceps brachii, superior trapezius
(f) Cool down (10 min)	- Breathing and passive stretching exercises - An Ai-Chi sequence with music. The Ai-Chi done in the following order: “Folding”, “Soothing”, “Gathering”, “Freeing”, “Shifting” and “Accepting”

Saltin, 2006) could potentially be achieved with warm water and low impact exercise, as is the case of aquatic therapy (Mannerkorpi and Iversen, 2003), with effects directly related to increased pain threshold. In fact, aquatic exercising is among the most common non-pharmacological therapies for the treatment of FM (Ambrose and Golightly, 2015). Additionally, the combination of exercise therapy with warm water has been shown to reduce pain in this population (Jiménez et al., 2013), with greater benefits than exercise alone (Ambrose and Golightly, 2015), and with longer effects on pain management (Flitzcharles et al., 2013; Jiménez et al., 2013). Thus, the association of aquatic exercise (AE), with temperature-increasing therapies such as Far-Infrared (FIR) therapy is justified.

FIR therapy is known to produce analgesia through thermal as well as non-thermal mechanisms (Vatansever and Hamblin, 2012). Recently, Far-Infrared Emitting Ceramics (cFIRs) have attracted attention for their therapeutic effects, especially for pain management (York and Gordon, 2009). Additionally, evidence suggests that cFIRs may increase resistance to fatigue and decrease energy expenditure even during steady-state exercise (Hausswirth et al., 2011). Inoué and Kabaya (1989) observed that the use of clothes imprinted with cFIRs improve quality of sleep, as well as reduce shoulder and leg pain. Nevertheless, despite the well-known analgesic and anti-inflammatory effects of cFIRs, the precise mechanisms underlying these effects are not fully elucidated.

Given the known benefits of AE (Sevimli et al., 2015) in warm water, and the analgesic properties of cFIRs, we hypothesized that the combination of these therapies could substantially reduce pain in patients with FM. Thus, the aim of this study was to evaluate the effect of the association of AE with cFIRs upon biochemical markers of pain and inflammation (TNF, IL-6 and IL-10), as well as pain thresholds and quality of life in FM female patients.

2. Material and methods

2.1. Participants

Participants with the following criteria were excluded: presence of active or previous neoplastic conditions, infection or continued use of oral or local corticosteroids or anti-cytokine therapy that could influence cytokines serum levels. Inclusion criteria were: medical diagnosis of FM, female sex, aged between 30 and 69 years of age, and meeting FM criteria determined by the American College of Rheumatology. All participants were advised not to engage in any other regular physical activity outside the study AE program.

Twenty-eight participants were randomly allocated (randomized by the Research Randomizer, version 4.0, available at http://www.randomizer.org/) into two groups: (1) AE + cFIR in which participants were asked to wear T-shirts imprinted with a FIR emitting ceramics during 6 weeks (n = 14); and (2) AE + placebo (n = 14) NO-cFIR, formed by participants that were asked to wear placebo T-shirts, i.e., that were not imprinted with cFIRs. Both groups underwent an AE program described below.

There were seven office visits throughout this period. Both patients and investigator were blinded to group assignment. Participants with poor adherence to the program (defined as missing > 2 consecutive sessions or > 20% of all sessions) were excluded from the study.

2.2. Procedures

This study was approved by the Research Ethics Committee of UNISUL, under the Protocol number 29240014.5.0000.5369, according to the guidelines laid out in the Declaration of Helsinki. Each participant gave written consent prior to the start of the study, which was registered into the ensaiosclinicos.gov.br (Brazilian Registry of Clinical Trials [ReBEC]) (RBR-7q4sdy register number). Female patients with medical FM diagnosis (ages from 30 to 69) were selected from the Physiotherapy Clinic of the University of Southern Santa Catarina (UNISUL), Brazil. All participants met the 2010 American College of Rheumatology classification criteria for fibromyalgia.

2.3. Aquatic exercise program

The AE program consisted of 18-50 min sessions conducted 3 times a week over a period of 6 weeks in a heated (32 ± 2 °C) pool (12 m × 6 m × 120 cm). The participants were supervised by trained physiotherapists and randomly assigned to each group. The exercises used for both groups included stretching and strengthening of the major muscle groups of the lower and upper extremities and trunk (Table 1).

All participants completed the program with a minimum attendance of 90%. Self-assessed Heat Rate (HR) was also performed at the end of

each part of the protocol during the exercise program. The program was designed in accordance with the training standards of the American College of Sports Medicine (ACSM) recommendations (Riebe et al., 2015) as described below:

a) stretching exercises (5–7 min); (b) aerobic warm-up, with slow walking and easier movements in different directions (5–7 min); (c) static stretching of the main muscle groups – elbow, trunk, and knee extensors and flexors (5 min); (d) aerobic aquatic fast walking and more difficult movements such as running and jumping (15 min); (e) strength exercises involving the main muscle groups of the upper limbs (with and without overload) – anterior and posterior chest muscles, elbow extensors and flexors, forearm supinator and pronator muscles (15 min); and (f) cool down – breathing and passive stretching exercises (10 min). Parts a, b, c, and f were performed at low intensity (40–50% maximal heart rate). Part (d) was performed at low-to-moderate intensity (50–60% maximal heart rate, HR) at the beginning of the program, and with increased intensity at the end of the program (65–75% maximal heart rate). This intensity is recommended for this type of study (Maquet et al., 2007; Jones et al., 2002).

2.4. cFIRs and placebo t-shirts

The cFIRs formulation used in this study was composed of micro particles of ceramic materials such as aluminum oxide and silicon dioxide which were mixed with a textile ink (Silkscreen Plastisol, Imagine Color, Brazil) and silkscreened onto a 92% polyester and 8% spandex fabric throughout the internal surface of the shirts (graphical abstract). Placebo t-shirts were silkscreened with 100% plastisol. cFIRs absolute emissivity of 93% in the wavelength of 9–11 μm was measured with a Scientech (Boulder, CO, USA) Astral S-series AC2500S calorimeter.

All participants were advised to wear the T-shirts for 6–8 h a night (during sleep). A questionnaire was applied three times a week on the days of the aquatic exercises sessions to control the use of the shirts by the participants.

2.5. Measurements

2.5.1. Primary outcome measures

2.5.1.1. Visual analogue scale (VAS) for pain and the short form McGill pain questionnaire (SF-MPQ). The primary outcome measure was pain assessed using the VAS for Pain and the SF-MPQ. VAS is a simple and often used method to evaluate variations in pain intensity. It was validated in the setting of chronic pain by various authors (Silva and Deliberato, 2009). VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end (0 = no pain, 10 = worst pain). The patient marks the position on the line they feel represents their current state. VAS score is determined by measuring in millimeters from the left-hand end of the line to the point marked by the patient. The level of pain of the participants was evaluated before interventions (pre), once a week, and after 6 weeks (post). The SF-MPQ consists of 15 descriptors (11 sensory; 4 affective) which are rated on an intensity scale as 0 = none, 1 = mild, 2 = moderate or 3 = severe. Three pain scores are derived from the sum of the intensity rank values of the words chosen for sensory, affective and total descriptors. The SF-MPQ also includes the Present Pain Intensity (PPI) index of the standard MPQ and a VAS. The present study used the validated Portuguese version of the SF-MPQ (Pimenta and Teixeira, 1996). The participants were evaluated before interventions (pre), and after 6 weeks (post).

2.5.2. Secondary outcome measures

2.5.2.1. Fibromyalgia impact questionnaire (FIQ). To assess the impact of fibromyalgia, the Brazilian version of the FIQ (Marques et al., 2006) was used. This scale commonly performed on patients with FM is regarded to be reliable and valid. The FIQ contains 10 items: physical function (10 sub items), feel good (1 item), missed work (1 item), do job (1 item), pain (1 item), fatigue (1 item), rested (1 item), stiffness (1 item), anxiety (1 item), and depression (1 item). The participants were evaluated before interventions (pre), and after 6 weeks (post).

2.5.2.2. Infrared thermography analysis. An infrared camera, ThermaCAM® E320 (FLIR Systems Inc., Wilsonville, Oregon, USA) resolution of 320 × 240 pixels in the spectral range of far-infrared (7.5–13 μm) with 0.1 °C sensitivity, was placed on a tripod to record thermal images. The sensor converts the infrared energy radiated by the skin into a thermogram that represents the exact temperature of its surface. The recorded thermograms were processed and analyzed by the QuickReport v.1.2 SP2 software (FLIR, USA). The thermal distribution on the skin surface is shown in a color palette next to the thermograms. The hottest parts are displayed in white, the average temperature in red and yellow, while blue represents the coldest surfaces (Tirloni et al., 2017).

The camera was positioned 2 m away from the participants and 0.9 m off the floor, temperature (≈22 °C) and humidity (≈50%) of the room were recorded for analysis of the images, and a 0.98 emissivity (body human) was adopted. Participants were acclimatized to the room at least 20 min before the thermogram pictures were recorded.

Thermograms of anterior and posterior views of the participants were obtained with focus on the trunk and upper limbs, where the t-shirts exerted greater contact with the patient's skin. For the analyzes, the mean skin temperature of the anterior cervical, costochondral, epicondyles, trapezius and supraspinatus regions were obtained (Table 2).

2.5.2.3. Serum level of cytokines. Biochemical markers were assessed first before starting the protocol and then after 6 weeks. Peripheral blood (5 mL) was collected by venipuncture from the radio humeral venous plexus. Sampling was carried out between 8.00 and 9.00 am, before (pre) and at the end of the program (6 weeks, post), 1 day after finishing the last session of the exercise program (to avoid the effect of acute exercise) (Brüggemann et al., 2017). Samples were maintained for 15–20 min at room temperature, and then centrifuged in “serum tubes” at 3500 rpm for 10 min, and finally aliquoted and stored at −80 °C until assay.

We measured the circulatory concentrations of IL-6, IL10 and TNF. Circulating concentrations for total serum of interleukins were determined using commercially available DuoSet Sandwich Enzyme-Linked Immunosorbent Assay (ELISA) kits (DuoSet, R&D Systems, Minneapolis, MN, USA). The concentrations of cytokines were estimated by interpolation from a standard curve by colorimetric measurements in an ELISA plate reader (Perlong DNM-9602, Nanjing Perlove Medical Equipment Co, Nanjing, China). All results were expressed in pg/ml. Samples and provided standards were analyzed in duplicate according to manufacturers' instructions. Interassay coefficients of variance (CV) ranged from 4.8% and 5.7%, respectively. The ranges of detection were (pg/mL): IL-6: 3.1 - 300; IL-10: 31.3-2000; and TNF: 15.6-1000 (Brüggemann et al., 2017). These ranges were within those reported by the manufacturer.

Table 2
Characterization of the study sample.

Variables	AE + Placebo group (n = 14)	AE + cFIR group (n = 14)	P
Age (y)	50.4 ± 7.9	52.8 ± 10	.509
Body mass (kg)	65.4 ± 10.5	72 ± 11.3	.146
Height (cm)	157.7 ± 4.5	157 ± 7.5	.801
BMI (kg/m^2)	26.5 ± 10.5	28.8 ± 3.9	.174
Occupation situation	7 Inactive 1 Part-time 6 Full-time	6 Inactive 0 Part-time 6 Full-time	

2.6. Statistical analysis

The results were analyzed with the Graph Pad Prism program (version 6.0 - La Jolla, California, USA). Initially, the Shapiro-Wilk normality test was applied to evaluate the normality of the data. The results are expressed as means and standard deviation (SD) and/or median and interquartile range (IQR) for continuous variables. In the comparisons between pre and post values, repeated-measures (RM) one-way analysis of variance (ANOVA), with the Greenhouse-Geisser correction followed by Tukey post hoc test, RM two-way ANOVA followed by Bonferroni post hoc test or the Wilcoxon test for the non-parametric data. When comparing AE + placebo vs AE + cFIR groups in a single condition (pre or post) the Mann-Whitney test for the non-parametric data. Values of $P < .05$ were considered as statistically significant.

3. Results

In this study 85 female patients with fibromyalgia diagnosis were selected; 57 met the exclusion criteria; therefore, 28 patients were selected and randomly allocated into one of the two groups: AE + placebo ($n = 14$) or AE + cFIR ($n = 14$) as demonstrated in Fig. 1.

The mean (SD) age of the participants was 50.4 (7.9) for AE + placebo, and 52.8 (10) for AE + cFIR. The body mass in the AE + placebo was 65.4 (10.5) and 72 (11.3) in the AE + cFIR. Height and body mass index (BMI) were 157.7 (4.5) cm and 26.5 (10.5) kg/m^2 for the AE + placebo, and 157 (7.5) cm and 28.8 (3.9) ± kg/m^2 for the AE + cFIR. Only 1 participant in the AE + placebo smoked regularly, representing (3.57%) of the total sample. There was no statistically significant difference between the groups (Table 2). Regarding the occupation of the participants, approximately 50% had a steady job.

The results presented in Fig. 2 show that VAS scores do not statistically differ in between pre- and post-intervention periods of the same group or intergroup as demonstrated by the mean weekly evaluations (Fig. 2A). Interestingly, AUC analysis demonstrates that VAS significantly improved only in the AE + cFIR group (Fig. 2B). In the post intervention evaluation, AE + cFIR scores decreased significantly ($P < .0007$), with a lower VAS in comparison to AE + placebo (Fig. 2B).

Pain scores measured with the McGill-SF questionnaire did not differ between the two groups in the sensory descriptor (Fig. 3A and B). Nevertheless, in the affective descriptor (pain descriptor) a significant decrease ($P < .05$) was detected in the AE + cFIR group (Fig. 3C) but not in the pain index descriptor (Fig. 3D). In the total descriptor both groups showed a significant improvement ($P < .05$) of the scores throughout the study (Fig. 3E and F).

FIQ results are summarized in Table 3. Pre and post-treatment scores for each criteria are shown. Pain, stiffness, anxiety, depression and overall domain significantly improved after treatment in the AE + cFIR group, whereas only "work missed" significantly improved in the AE + placebo group. No statistically significant differences were found between groups.

The results presented in Fig. 4A–C show that in the anterior cervical (AE + placebo $P < .0006$ vs AE + cFIR $P < .01$), epicondyles (AE + placebo $P < .006$ vs AE + cFIR $P < .009$) and trapezius (AE + placebo $P < .02$ vs AE + cFIR $P < .03$) regions the temperature decreased in both groups. Interestingly, temperature in the costochondral region significant decreased ($P < .05$) only in the AE + cFIR group (Fig. 4A–C). Temperature in the supraspinatus region did not differ between the groups (AE + placebo $P < .34$ vs AE + cFIR $P < .15$).

TNF, IL-6 and IL-10 results are showed in Fig. 5. Both groups showed significant reduction in IL-6 levels in intra-group analysis ($P = .04$ and $P = .04$, AE + placebo and AE + cFIR respectively). No differences were found in TNF and IL-10 levels (neither intra nor intergroup analyses).

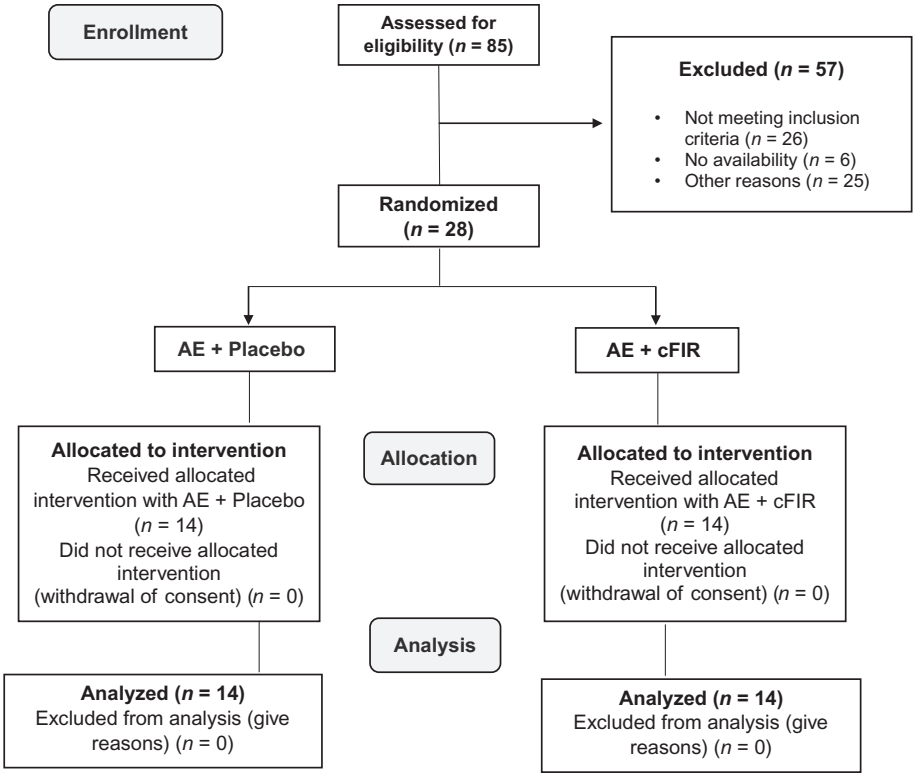


Fig. 1. AE + Placebo group formed by participants that took part in the 6-week aquatic exercise program and were asked to wear placebo T-shirts (no cFIRs coating). AE + cFIR group – participants that took part in the 6-week aquatic exercise program and were asked to wear cFIRs coated T-shirts. WC: withdrawal of Consent.

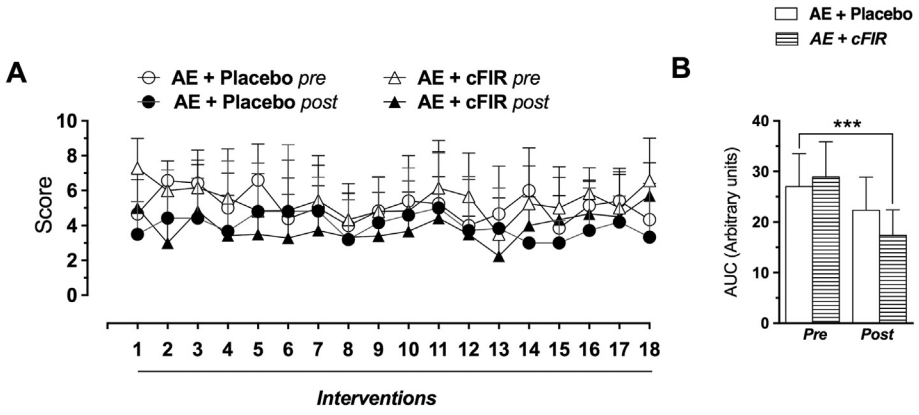


Fig. 2. Effects of the association of aquatic exercise training program with Far Infrared (FIR) on pain assessed through the visual analogue scale. Fig. 2A shows the daily evaluations before and after each intervention in the pool. Repeated-measures two-way analysis of variance followed by Bonferroni post hoc test. In panel 1B the result is expressed by the area under the curve. Repeated-measures (RM) one-way analysis of variance (ANOVA), with the Greenhouse-Geisser correction followed by Tukey post hoc test $^{***}P < .001$. AE + Placebo group was formed by participants that took part in the 6-week aquatic exercise program and were asked to wear placebo T-shirts (no cFIR coating). AE + cFIR group – participants that took part in the 6-week aquatic exercise program and were asked to wear cFIR coated T-shirts. AUC: area under the curve.

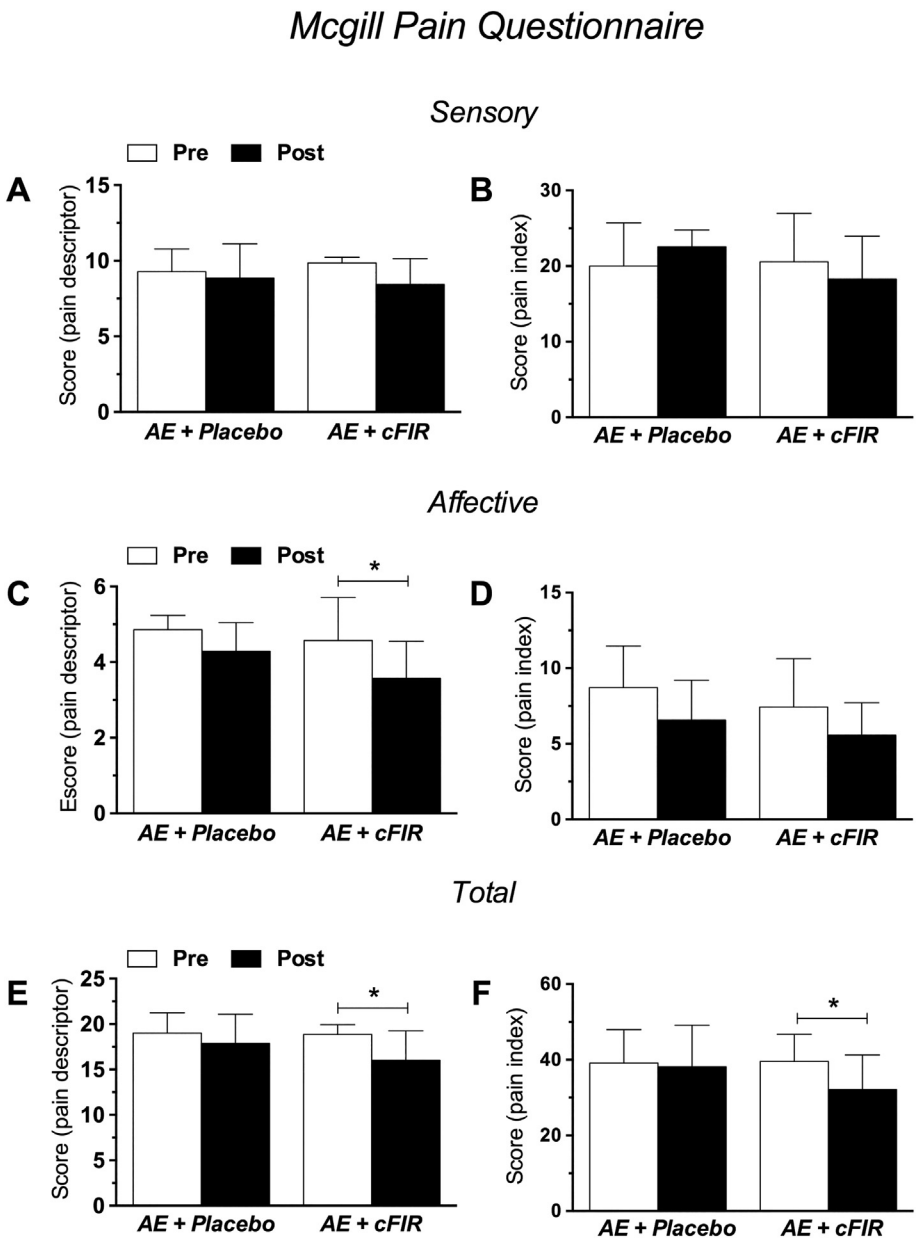
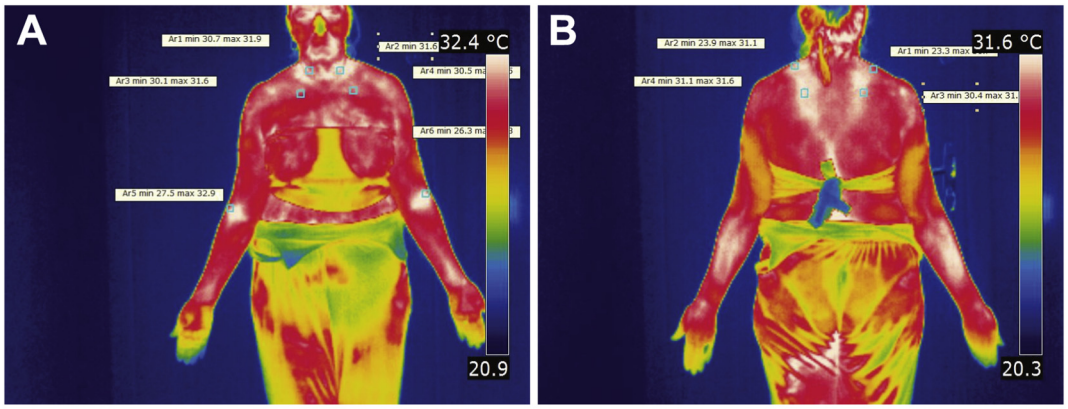


Fig. 3. Effects of the association of aquatic exercise training program with Far Infrared (FIR) on pain assessed through the Mcgill Pain Questionnaire. Sensory Score pain descriptor (panel A) index (panel B). Affective pain descriptor (panel C) index (panel D). Total score pain descriptor (panel E) index (panel F). In panels A-F, either the Wilcoxon or Mann-Whitney tests were used (pre and post comparisons, respectively). $^{*}P < .05$. AE + Placebo group was formed by participants that took part in the 6-week aquatic exercise program and were asked to wear placebo T-shirts (no cFIR coating). AE + cFIR group - participants that took part in the 6-week aquatic exercise program and were asked to wear cFIR coated T-shirts.

Table 3
Effects of the association of aquatic exercise training program with Far Infrared (FIR) upon the Impact Questionnaire on Fibromyalgia. Results expressed in Mean ± standard deviation (SD) pre and post-interventions.

Domains	Placebo group				cFIR group			
	Pre	vs	Post	*P* value	Pre	vs	Post	*P* value
Physical impairment	5.9 ± 4.1	vs	5.0 ± 1.4	.664	4.0 ± 2.3	vs	4.4 ± 1.9	.402
Feel good	3.2 ± 2.4	vs	3.0 ± 2.4	.803	4.8 ± 1.9	vs	3.4 ± 1.8	.128
Work missed	12.0 ± 3,6	vs	6.9 ± 4.9	.003**	10.6 ± 4.7	vs	9.1 ± 5.5	.349
Difficult to work	7.1 ± 3.1	vs	6.2 ± 3.1	.170	8.6 ± 1.5	vs	7.0 ± 2.7	.218
Pain	7.5 ± 2.5	vs	6.2 ± 3.1	.166	9.2 ± 0.9	vs	7.0 ± 2.7	.013*
Fatigue	7.7 ± 3.1	vs	7.0 ± 2.7	.120	8.1 ± 2.8	vs	7.7 ± 2.1	.446
Rested	6.8 ± 3.2	vs	6.2 ± 3.1	.282	7.5 ± 2.8	vs	6.8 ± 3.4	.473
Stiffness	7.4 ± 3.1	vs	6.8 ± 2.9	.303	8.3 ± 2.1	vs	5.2 ± 3.6	.012*
Anxiety	8.2 ± 2.8	vs	7.0 ± 2.8	.139	8.3 ± 2.7	vs	6.0 ± 3.2	.009**
Depression	7.2 ± 3.3	vs	5.7 ± 3.7	.074	8.3 ± 2.8	vs	6.0 ± 3.3	.035*
Overall count	70.34 ± 19.22	vs	58.3 ± 24.7	.064	71.2 ± 15.3	vs	60.7 ± 16.7	.012*

* $P < .05$.
** $P < .01$.



C

Regions	*AE + Placebo group*					*AE + cFIR group*				
	T-Pre	vs	*T*-Post	Delta *T*	*p* value	*T*-Pre	vs	*T*-Post	Delta *T*	*p* value
Anterior cervical	32.19 ± 0.53	vs	31.46 ± 0.77	-0,73	*0.0006**	32.0 ± 0.67	vs	31.36 ± 0.81	-0.64	*0.0151**
Costochondral	31.46 ± 0.78)	vs	31.20 ± 0.76	-0,25	*0.158*	31.35 ± 1.0	vs	30.87 ± 0.50	-0.48	*0.051**
Epicondyles	31.38 ± 0.75)	vs	30.59 ± 1.2	-0,79	*0.0062**	31.67 ± 0.70	vs	31.10 ± 0.67	-0.57	*0.0094**
Trapezius	30.98 ± 0.92)	vs	30.24 ± 1.05	-0,75	*0.0278**	30.95 ± 1.1	vs	30.09 ± 0.67	-0.85	*0.0302**
Supraspinatus	31.25 ± 0.75)	vs	30.94 ± 0.84	-0,31	*0.3487*	31.28 ± 0.96	vs	30.86 ± 0.79	-0.42	*0.1586*

Fig. 4. AE + Placebo group formed by participants that took part in the 6-week aquatic exercise program and were asked to wear placebo T-shirts (no cFIR coating). AE + cFIR group – participants that took part in the 6-week aquatic exercise program and were asked to wear cFIR coated T-shirts. Values are means (SD) or numbers (%), Delta T (difference between post and pre), *$P < .05$. °C: thermometric scale (degrees Celsius). In panels A-F, either the Wilcoxon or Mann-Whitney tests were used (pre and post comparisons, respectively).

4. Discussion

To the best of our knowledge, this is the first study to evaluate the association of AE with FIR reflected by cFIRs upon pain, body temperature, serum cytokines and quality of life of FM patients. Our results suggest a reduction in pain, IL-6 levels and body temperature, as well as an increase in the quality of life of these individuals. These findings are clinically relevant and highlight the benefits of combining two adjuvant therapies in the treatment of FM. In fact, evidence-based guidelines emphasize the need for multimodal treatments in fibromyalgia cases (Häuser et al., 2017).

The present study was designed based on the recent hypotheses that FM etiology included an inflammatory aspect accompanied by changes in the neuro-immuno-endocrine system (Okifuji and Hare, 2013). Current evidence has shown that there is an increase in the levels of proinflammatory cytokines (IL-1RA, IL-6 and IL-8) and chemokines in patients with fibromyalgia, which suggests an important role of inflammation in the pathogenesis of this syndrome (Rodriguez-Pinto et al., 2014). Based on the anti-inflammatory effects of exercise and FIR, the association of these therapies may be a good strategy to follow, in

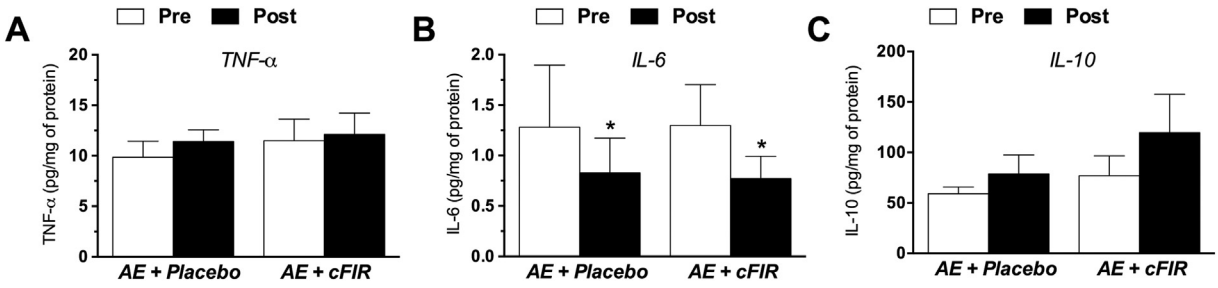


Fig. 5. Effects of the association of aquatic exercise training program with Far Infrared (FIR) on serum levels of cytokines. Levels of TNF (pg/mg, panel A), IL-6 (pg/mg, panel B) and IL-10 (pg/mg, panel C). In panels A-F, either the Wilcoxon or Mann-Whitney tests were used (pre and post comparisons, respectively). AE + Placebo group was formed by participants that took part in the 6-week aquatic exercise program and were asked to wear placebo T-shirts (no cFIR coating). AE + cFIR group – participants that took part in the 6-week aquatic exercise program and were asked to wear cFIR coated T-shirts. *$P < .05$ significant results.

the management of inflammatory diseases, including FM.

Even though there is no fail proof treatment for patients with fibromyalgia, non-pharmacological therapies such as physical exercise in warm water provide pain relief (Kas, 2016). Additionally, adjuvant therapies such as FIR therapy may contribute to the management of pain, as in the case of cFIR imprinted clothes. A systematic review has highlighted the analgesic effect of FIR under different pain conditions (Jorge et al., 2017). In addition, clinical studies have demonstrated that FIR induces improved function and pain reduction in patients with arthritis and Raynaud's syndrome (Ko and Berbrayer, 2002); helps manage the discomfort of primary dysmenorrhea (Lee et al., 2011); and induces analgesia when used for the treatment of chronic foot pain due to diabetic neuropathy (York and Gordon, 2009). Furthermore, we have recently shown the effects of cFIR on biochemical and neuromuscular markers in futsal players wearing cFIRs clothes (Nunes et al., 2018).

Another interesting finding of the present study was the effect of AE and the association with FIR upon body temperature on areas related to FM tender points. A study evaluated tender points in the upper limbs of patients with FM and identified a non-specific hyperthermic pattern in these individuals when compared to patients with other chronic pathologies (Biasi et al., 1994). Brusselmans et al. (2015) performed a study that evaluated thermal dysfunction in 23 women with FM, and demonstrated that there is a thermal adaptive response of individuals with FM when compared to control. On the other hand, Radhakrishna and Burnham (2001) analyzed the temperature of the tender points of sixteen women with fibromyalgia with an infrared hand-held thermometer and concluded that skin temperature cannot be used to diagnose and monitor the progress of the treatment because skin temperature at the sensitive points did not directly correlate with pressure sensitivity. In the present study, we found that although AE induced a temperature decrease in such areas, a more pronounced effect was obtained in association with FIR.

It has been shown that in FM patients increased levels of IL-6 stimulate the production of prostaglandins, which leads to the sensitization of muscle nociceptors inducing the release of substance P (Mendieta et al., 2016), resulting in hyperalgesia, and fatigue (Bote et al., 2013). In the present study, there was a decrease in IL-6 levels in both groups after the interventions. In this regard, a previous study with 14 FM female patients has shown no difference in serum levels of cytokines such as IL-6 after a 4-month aquatic exercise protocol (3× a week for 60 min) (Ortega et al., 2009). In addition, several studies have demonstrated the immunological imbalance in FM female patients (Wang et al., 2008; Wang et al., 2004), mainly in cytokines such as TNF and IL-1 (Rodriguez-Pinto et al., 2014). Such an imbalance could contribute to different responses, making it difficult to use cytokines as a biomarker for diagnosis. The decrease of the inflammatory biomarkers induced by the treatments (i.e. IL-6) could, at least partially, have contributed to the improvement in the Visual Analogue Scale (VAS), the short form McGill Pain Questionnaire (SF-MPQ) and FM-related quality of life aspects determined by the FIQ. However, as we found no difference in IL-6 levels between groups, we cannot attribute this effect to FIR. On the other hand, a reduction in the affective component of pain in the SF-MPQ in the AE + FIR group suggests that FIR has contributed to a selective inhibition (modulation) of C-fibers in pain excitatory afferent pathways (Duncan, 1989).

In the present study we observed an increase in the benefits produced by AE when associated with the use of FIR-impregnated T-shirts. Several mechanisms may be underlying the effects of the combined treatments. For example, overnight use of cFIR shirts could extend the thermal effect produced by AE (Inoué and Kabaya, 1989). Alternatively, the non-thermal effects of FIR in modulating neuronal activity could contribute to the effects of AE potentiating analgesia (Sommer et al., 2008). One limitation of this study was the small number of volunteers (reduced sample size), which could decrease statistical power. A longitudinal approach could perhaps better identify the factors that affect the quality of life and physical functioning of these patients, and follow-up questionnaires and evaluations could better assess the medium and long-term effects of the interventions. In conclusion, the results presented herein suggest that the association of FIR increases the benefits of AE training programs in patients with FM.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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