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Effects of photobiomodulation and a physical exercise program on the expression of inflammatory and cartilage degradation biomarkers and functional capacity in women with knee osteoarthritis: a randomized blinded study

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Abstract

Background: The knee osteoarthritis (OA) is a joint disease characterized by degradation of articular cartilage that leads to chronic inflammation. Exercise programs and photobiomodulation (PBM) are capable of modulating the inflammatory process of minimizing functional disability related to knee OA. However, their association on the concentration of biomarkers related to OA development has not been studied yet. The aim of the present study is to investigate the effects of PBM (via cluster) with a physical exercise program in functional capacity, serum inflammatory and cartilage degradation biomarkers in patients with knee OA.

Methods: Forty-two patients were randomly allocated in 3 groups: ESP: exercise + sham PBM; EAP: exercise + PBM and CG: control group. Six patients were excluded before finished the experimental period. The analyzed outcomes in baseline and 8-week were: the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) and the evaluation of serum biomarkers concentration (IL-1β, IL-6, IL-8, IL-10 e TNF-α, and CTX-II).

Results: An increase in the functional capacity was observed in the WOMAC total score for both treated groups ($p < 0.001$) and ESP presents a lower value compared to CG ($p < 0.05$) the 8-week post-treatment. In addition, there was a significant increase in IL-10 concentration of EAP ($p < 0.05$) and higher value compared to CG ($p < 0.001$) the 8-week post-treatment. Moreover, an increase in IL-1β concentration was observed for CG ($p < 0.05$). No other difference was observed comparing the other groups.

Conclusion: Our data suggest that the physical exercise therapy could be a strategy for increasing functional capacity and in association with PBM for increasing IL-10 levels in OA knee individuals.

Trial registration: ReBEC (RBR-7t6nzr).

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Keywords: Knee osteoarthritis, Inflammation, Cytokines, Biomarkers, Photobiomodulation

Introduction

Osteoarthritis (OA) leads to degradation of articular cartilage, formation of osteophytes, decrease of joint space and degeneration of subchondral bone and is characterized as a chronic joint disease [1]. These morphological alterations culminate in an increasing of the level of articular pain, loss of function, decrease in the range of motion and muscle weakness, impairing the quality of life of the patients [2].

The pathogenesis of OA has relation with the increase of expression of specific cytokines and immune system and, which contribute to cartilage degradation [3, 4]. It has been demonstrated that patients with OA showed high levels of proinflammatory cytokines, which disturb the catabolism and anabolism processes, being responsible by inflammation and consequence articular cartilage degeneration [5]. In this context, the most important cytokines involved in this process are Tumor Necrosis Factor alpha (TNF-α), interleukin-1β (IL-1β) and interleukin -6 (IL-6) [6]. As result of degradation of cartilage, a release of protein specific tissue fragments (neo-epitopes) in cleavage of type II collagen by matrix metalloproteinases (MMPs) can be observe, especially with analyze of biomarker as C-telopeptide of type II collagen (CTX-II) [7]. Based on this, the inhibition of interleukins (ILs) activity and analysis of CTX-II as a biomarker of progression of cartilage lesion are related to radiological grades of cartilage degradation and may help to improved strategies to treat OA [8].

In this context, for OA, one of the most common treatments is based on pharmacological intervention, mainly nonsteroidal and steroidal anti-inflammatory drugs (NSAIDs) [9]. However, the continuous use of NSAIDs can lead to severe adverse effects, like gastrointestinal problems, and limited efficacy [10]. In an attempt to attenuate these problems, alternative treatments have been studied including physical exercise programs, presenting positive effects on pain control, joint dysfunction and disability in patients with OA [11]. Furthermore, Castrogiovanni et al. [12] demonstrated that the moderate physical activity (MPA) significantly increased on the expression of anti-inflammatory [interleukin-4 (IL-4) and interleukin-10 (IL-10)] biomarkers in the synovium of an OA-induced rat model. The exercise protocol has been shown to have an anti-inflammatory effect, reducing levels of biomarkers like IL-6 and TNFα and suggesting that cytokine reduction can be an effective contribution for modulating pain due to OA [13].

Another promising therapeutic intervention that has been showing positive effects on degradation of cartilage tissue in the presence of OA is the low-level laser therapy (LLLT) or more recently, photobiomodulation (PBM) [14, 15]. It is well known that PBM produces stimulatory effect on healing and has the ability of modulating the inflammatory process in different tissues, including cartilage [5, 16]. Chondroprotective effects, inhibition of cartilage degradation, decreases in the expression of chemotactic factors and inflammatory cytokines and increase antioxidant enzyme levels have been observed in several experimental model of OA in rats after PBM [17, 18]. Also, clinical trials have demonstrated that PBM is able of reducing pain, articular stiffness, knee swelling, increasing the functional performance in knee OA patients [10, 19]. Alghadir, et al. [20] showed that PBM (850 nm, 50mW, 6 J/point), applied in eight points on knee during 4 weeks/ two times per week, improved the functional capacity evaluated by Western Ontario and McMaster Universities Arthritis Index (WOMAC) in patients with knee OA (grade II or III).

Furthermore, some authors have been investigating the association of physical exercise and PBM on the management of OA symptoms [21, 22]. De Paula Gomes et al. [21] observed that PBM nine diode cluster device (one 905 nm super-pulsed diode laser with, four 875 nm light-emitting diode (LED) and four 640 nm LED) associated to a physical exercise program had positive effects on reducing pain intensity in individuals with knee OA. Similar findings were observed by Alayat et al., [23] and de Matos Brunelli Braghin et al., [24].

Although all the positive effects of physical exercise programs for treatment of OA, its association with PBM via a cluster device on the expression of ILs and biomarkers related to cartilage degradation in patients with OA has not been studied yet. In this context, based on the need of determining a more appropriate therapeutic intervention to treat patients with OA, the present study aimed to investigate the effects of the incorporation of PBM (via cluster) into a physical exercise program in serum inflammatory biomarkers (IL-1β, IL-6, IL-8, IL-10 e TNF-α), cartilage degradation biomarker (CTX-II) and functional capacity (WOMAC) in patients with knee OA.

Materials and methods

Study design and setting

This is a single-blind (participants) randomized controlled trial. Ethical approval (Ethics in Human Research Committee of the Federal University of São

Paulo- approval number 1.368.478) and written informed consent (patients signed) were obtained. The study was conducted at the Laboratory of Manual and Physical Resources and Balance Space – Fitness and Health from April 2018 to February 2020 and was logged with the Brazilian Clinical Trials Registry (RBR-7t6nzr). All participants were recruited via advertisements in local newspapers and social media.

Patients

As eligibility criteria, patients had aged between 55 and 70 years, present symptomatic OA in the previous 6 months, a diagnosis of unilateral or bilateral knee OA according to the American College of Rheumatology and a radiographic confirmation of OA (grades 2 or 3 of the Kellgren-Lawrence classification) [25]. The diagnosis of knee OA was determined through an examination and the written opinion of a specialist in rheumatic diseases. Also, patients should present BMI between 22 to 35 kg/m^2, criteria established by Pan American Health Organization [26], more than 2 points on the Numeric Rating Pain Scale and should be classified as active and irregularly active (physical activity with a frequency of at least 3 times a week or a minimum of 150 min per week, according to Criteria established by American College of Sports Medicine measures by the International Physical Activity Questionnaire – Short Version (IPAQ).

Patients were excluded if they have: fibromyalgia and/or any kind of orthopedic or rheumatic diseases that may prevent the physical exercise; surgery of the knee within the past 6 months or joint replacement. Also, patients with diagnoses of lung diseases, cardiologic alterations, uncontrolled hypertension, diabetes and had any contraindications to PBM as cancer. During the study, patients who missed two consecutive training sessions or more than 3 sessions along the treatment and who discontinued the pharmacological treatment for OA started before the study were excluded.

Randomization

All patients met all inclusion criteria to participate in the study and signed a consent form. 42 patients were randomly allocated in ESP, EAP or CG groups, as observed below:

ESP: exercise + sham PBM, patients of this group performed the physical exercise program associated to PBM sham irradiation;
EAP: exercise + active PBM, patients of this group performed the physical exercise program associated to active PBM irradiation.
CG: control group, patients of this group were not submitted to any kind of therapeutical intervention.

A researcher, who was not involved in the experiment, conducted the randomization process by a simple drawing through a computer program that created a random table of numbers and put these numbers (1, 2 and 3) on opaque envelopes corresponding the group (ESP, EAP and CG), respectively.

Evaluation and reevaluation were performed by a researcher blinded to the experimental groups. Patients were also blinded to the mode of PBM application (sham or active).

Sample size

The sample size calculation was performed using the GPower 3.0.10 program with parameters: effects size of 0.25 [27], power observed of 0.75 and $\alpha = 5\%$, considering ANOVA model for three groups. The required sample would be 12 patients for each treatment group ESP, EAP or CG with a total of 36 patients. Each treatment group was started with 14 patients for possible dropout.

Experimental procedures

After the initial evaluation, the following experimental procedures were made 48 h before and 48 h after interventions: blood collection and functional capacity analysis (WOMAC). Participants of the control group were oriented to maintain the same habits and do not start any new treatment for the period of 8 weeks.

Assessments

WOMAC questionnaire

The functional capacity of lower limb and knee joint could be evaluated by using Western Ontario and McMaster Universities Osteoarthritis (WOMAC). The WOMAC is a self-administered reliable and valid questionnaire for patients with hip and knee OA and used for assessment of pain, stiffness joints, and physical activity of patients with hip and knee OA [28, 29]. The total score range of 0–96 and increased scores indicate a higher level of disability and lower level of quality of life.

Blood collection and serum biomarkers measurement

One biomedical collected 8 ml of peripheral blood samples from each patient before and after intervention period. After collected, the samples were centrifuged to prepare the plasma and stored at -80 °C in cryogenic tubes until in measurement. All the samples were sent to a certificate laboratory for analyses. The enzyme-linked immunosorbent assays (ELISA) kits were used to analyze the levels of CTX-II (MyBioSource), IL-1β and IL-10 (Enzo Life Sciences, Inc.) and IL-6, IL-8 e TNF-α (Fine Test®) following the procedures recommended by the manufacturer with automated pipetting.

Interventions

Both groups, ESP and EAP, received the intervention excepted CG (waitlist).

Physical exercise program

The physical exercise protocol used was adapted from the study by Silva et al. [30] and Foley et al., [31]. A protocol with warming (5 min on treadmill), 6 strength exercises (Hip abductors and adductors chair, SLR – *seated leg raise,* Glute Bridge (Hip lift), Knee flexors and extensors chair) and stretching of major muscle groups was used for this purpose. The patients were subjected to a physical exercise protocol twice a week (Monday and Wednesday) for 8 consecutive weeks performed individually and supervised by a physical therapist. The application of the physical exercise protocol occurred according to 1-RM (repetition maximum) was determined each 2 weeks for prescription and load progression of the exercises. The exercise consisted 3 sets of 8 repetitions each, with 60% of 1-RM and a rest interval of 2–3 min between sets based on American Geriatrics Society [32] for patients with OA.

PBM via cluster

A cluster with 7 diodes and an infrared wavelength (808 nm) was used in continuous mode, a 0.05cm^2 spot size, 100mW power output, 2 W/cm^2 power density, 91 J/cm^2 energy density, and energy of 4 J per point/56 J per knee, 40 s per application based on recommendations of the World Association of Laser Therapy [33]. The cluster dimension is 150 mm(L) × 100 mm(W) × 55 mm(H), with 1 cm of distance between infrared diodes. After each training session for ESP and EAP, respectively, sham or active PBM was applied on medial and lateral region of knee affected for unilateral OA and applied on medial and lateral region of most affected knee for bilateral OA (with knee positioned at 45 degrees of flexion) (Fig. 1). A researcher responsible to conduct the intervention turned on the device of PBM irradiation and immediately turned off the equipment to apply the sham PBM.

Statistical analysis

To analyze the variables age, height, body mass, BMI, IL-1β, IL-6, IL-8, IL-10, TNF-α, CTX-II and WOMAC at groups and evaluations, were performed the analysis of variance (ANOVA *one-way* and *two-way test*) followed by Fisher's post hoc test to identify the possible differences among groups. The adopted significant value was α < 5%. Data were expressed as mean ± standard deviation (SD).

Fig. 1 PBMT irradiation points

The difference between groups was performed per-protocol analysis**.**

Results

Six patients (one from ESP, one from EAP and four from CG) were excluded from the study due to the absence in 2 consecutive treatment sessions. Table 1 displays the baseline values of the outcome measures, anthropometric and demographic characteristics of the participants per group. Significant difference among ESP ($p = 0.024$), EAP ($p = 0.009$) and CG were identified for age. The EAP group showed higher values of BMI compared to CG ($p = 0.04$). The percentage of the weight range for each group was 15.4% normal weight, 69.2% overweight and 15.4% obesity for ESP; 30.8% normal weigh, 38.4% overweight and 30.8% obesity for EAP and 50% normal weigh, 40% overweight and 10% obesity for CG.

Figure 2 shows the baseline and 8-week values of WOMAC total score. The results demonstrated that there was significant difference between ESP, in the baseline compared to ESP in the 8-week ($p = 0.00006$), between EAP in the baseline and EAP in the 8-week ($p = 0.00002$) and between ESP and CG in the 8-week ($p = 0.011$).

The results of WOMAC pain, stiffness and function subscales are demonstrated in Table 2. There was significant decrease in all domains for ESP and EAP compared baseline with 8-week evaluation ($p < 0,05$) and significant decrease in WOMAC stiffness subscale for CG ($p = 0.01$). Thus, in baseline values, significant difference was found

Table 1 Mean and SD of baseline values, anthropometric and demographic characteristics

Variables	ESP (n = 13)			EAP (n = 13)			CG (n = 10)		
	Mean		SD	Mean		SD	Mean		SD
Age (years)	62.29	±	4.39 *	61.57	±	4.42 *	66.5	±	4.06
Height (m)	1.60	±	0.04	1.60	±	0.07	1.60	±	0.06
Body mass (kg)	77.06	±	10.34	78.6	±	12.67	69.9	±	7.29
BMI (kg/m^2)	30.11	±	3.64	30.49	±	4.35 *	27.24	±	2.99
Unilateral and Bilateral OA (%)	23% uni 77% bi			23% uni 77% bi			50% uni 50% bi		
WOMAC pain	7.43	±	3.48	10.36	±	2.76 $^{\&}$	9.1	±	4.33
WOMAC stiffness	3.21	±	2.51	2.57	±	1.55	3.2	±	2.34
WOMAC function	23	±	11.36	30.5	±	7.79 $^{\&, *}$	21.3	±	9.25
WOMAC total	33.64	±	15.92	43.43	±	9.89	33.6	±	9.86
IL-10 (pg/ml)	8.52	±	2.09	8	±	2.48	7.21	±	1.39
IL-1β (pg/ml)	5.02	±	0.52	5.47	±	1.16	4.98	±	0.64
CTX-II (ng/ml)	4.24	±	0.78	4.10	±	1.10	4.45	±	0.48
IL-6 (pg/ml)	5.66	±	0.35	5.61	±	0.68	5.34	±	0.13
IL-8 (pg/ml)	11.28	±	2.54	11.25	±	1.77	11.26	±	1.81
TNF-α (pg/ml)	26.94	±	14.88	26.38	±	20.01	19.68	±	1.19

ESP: exercise and sham PBM group; EAP: exercise and active PBM group; CG: control group; BMI: body mass index; kg: kilograms; m: meter; uni: unilateral; bi: bilateral. IL-10: interleukin-10; IL-1β: interleukin-1β; CTX-II: C-telopeptide of type II collagen; IL-8: interleukin-8; TNF-α: Tumor Necrosis Factor alpha; WOMAC: Western Ontario and McMaster Universities Osteoarthritis

* statistical difference from CG

& statistical difference from ESP

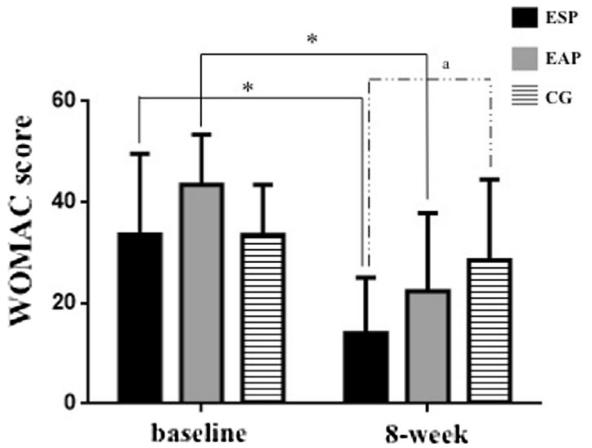

Fig. 2 Values of WOMAC in the baseline and in the 8-week for all the experimental groups. WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; ESP: exercise and sham PBM group; EAP: exercise and active PBM group; CG: control group. *statistical significance between in the baseline and in the 8-week. [a]Statistical significance from ESP group in the same condition

between the EAP and ESP in WOMAC pain (p = 0.04) and function (p = 0,0001) subscales, and between EAP and CG in WOMAC function subscale (p = 0.02). Significant difference was found between the ESP and CG in WOMAC pain (p = 0.02) and function (p = 0.01) subscales 8-week.

Figure 3 shows the baseline and 8-week values of the IL-10. It is possible to observe a statistical significant difference between the values found for EAP in the baseline compared to the 8-week (p = 0.047). Also, a significant difference was found between the values of EAP and CG after the experimental period (p = 0.0009).

For IL-1β expression, there was a significant increase and difference between the values found in the baseline and in the 8-week for CG (p = 0.016) (Fig. 4).

Table 3 shows the values found in the baseline and in the 8-week of the pro-inflammatory cytokines (IL-6, IL-8, TNF-α) and cartilage degradation biomarkers (CTX-II). For these variables, no significant difference was observed.

Discussion

The results of this study demonstrated that the physical exercise program was able of increasing the functional capacity in the patients and, the associated treatments increased IL-10 expression compared to CG after the experimental period. In addition, IL-1β expression was higher for CG comparing the values in the baseline and 8-week and no difference for the others biomarkers were observed.

Table 2 Means and SD of Western Ontario and McMaster Universities Osteoarthritis Questionnaire

Variables	ESP (n = 13)						EAP (n = 13)						CG (n = 10)					
	Baseline			8-week			Baseline			8-week			Baseline			8-week		
	Mean		SD	Mean		SD	Mean		SD	Mean		SD	Mean		SD	Mean		SD
WOMAC pain	7.43	±	3.48	3.36	±	2.87 *	10.36	±	2.76 [a]	4.79	±	4.51 *	9.1	±	4.33	7	±	4.27 [a]
WOMAC stiffness	3.21	±	2.51	1.21	±	1.48 *	2.57	±	1.55	1.43	±	1.28 *	3.2	±	2.35	1.7	±	1.7 *
WOMAC function	23	±	11.36	9.5	±	7.38 *	30.5	±	7.79 [a]	16.14	±	10.7 *	21.3	±	9.25 [b]	19.8	±	11.45 [a]
WOMAC total score	33.64	±	15.92	14.07	±	10.99*	43.43	±	9.89	22.36	±	15.49*	33.60	±	9.86	28.50	±	15.95 [a]

ESP exercise and sham PBM group, EAP exercise and active PBM group, CG control group, WOMAC: Western Ontario and McMaster Universities Osteoarthritis

[*] statistical significance between in the baseline and in the 8-week

[a] statistical significance from ESP group in the same condition

[b] statistical significance from EAP group in the same condition

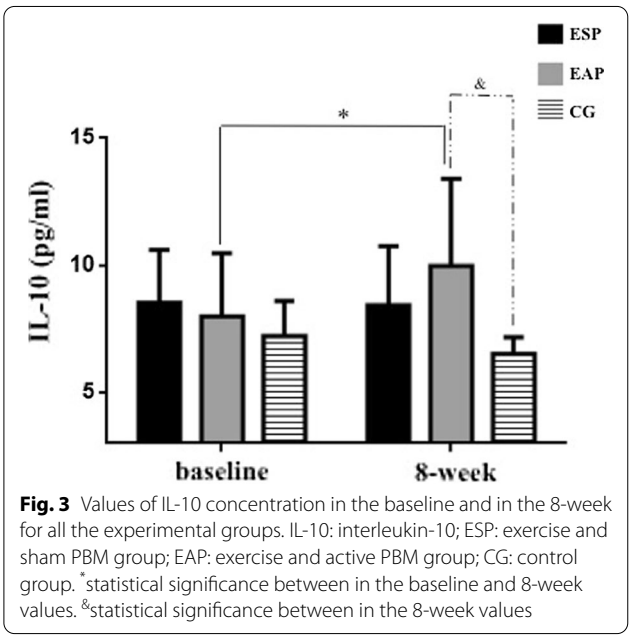

Fig. 3 Values of IL-10 concentration in the baseline and in the 8-week for all the experimental groups. IL-10: interleukin-10; ESP: exercise and sham PBM group; EAP: exercise and active PBM group; CG: control group. [*]statistical significance between in the baseline and 8-week values. [&]statistical significance between in the 8-week values

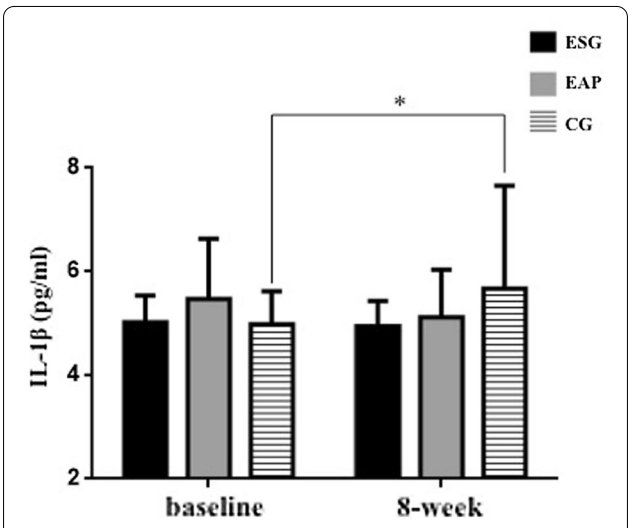

Fig. 4 Values of IL-1β concentration baseline and 8-week for all the experimental groups. IL-1ß: interleukin-1ß; ESP: exercise and sham PBM group; EAP: exercise and active PBM group; CG: control group. [*]Statistical significance between in the baseline and 8-week intervention values

Knee OA is clinically associated with pain and loss of functional capacity, reaching 25% of the population over the age of 60 years [34]. As described above, the lower WOMAC score demonstrated by the physical exercised patients (irradiated or not with PBM) is possibly related to the increase in muscle strength after the exercise program, improving the joint stability and the level of pain, and consequently, leading to the improvement of the functional capacity. Interestingly, PBM did not produce any extra positive effect in the exercised patients. Data from the literature do not corroborate the findings of the present study demonstrating a superior effect measured by WOMAC in exercised and irradiated patients with OA [35–37]. Kheshie et al. [36] also observed a decrease in WOMAC subscales in patients with OA treated with physical exercises and PBM. One hypothesis that can be raised is that the PBM parameters used in this study were not sufficient to produce an additional effect in the exercised patients.

Furthermore, it is well known that IL-10 has an important anti-inflammatory role in OA, presenting a chondroprotective effect and, inhibiting chondrocyte apoptosis [38]. Our results showed that the active PBM associated with physical exercises significantly increased IL-10 expression after the experimental period of treatment. Assis et al., [17] also observed an increase of IL-10 expression in an experimental study, submitting rats with OA to a program of aerobic exercises and PBM irradiation. All the positive effects may be related to the effects

Table 3 Means and SD of IL-10, IL-1b, IL-6, IL-8, TNF-α and CTX-II

Variables	ESP (n = 13)				EAP (n = 13)				CG (n = 10)			
	Baseline		8-week		Baseline		8-week		Baseline		8-week	
	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD	
IL-10 (pg/ml)	8.52 ± 2.09		8.44 ± 2.33		8.00 ± 2.48		9.98 ± 3.42*&		7.21 ± 1.39		6.54 ± 0.63	
IL-1b (pg/ml)	5.02 ± 0.52		4.94 ± 0.49		5.47 ± 1.16		5.11 ± 0.92		4.98 ± 0.64		5.67 ± 1.99*	
CTX II (ng/ml)	4.24 ± 0.78		4.38 ± 0.63		4.10 ± 1.10		4.26 ± 0.65		4.45 ± 0.48		4.07 ± 0.98	
IL-6 (pg/ml)	5.66 ± 0.35		5.57 ± 0.24		5.61 ± 0.68		5.65 ± 0.86		5.34 ± 0.13		5.37 ± 0.22	
IL-8 (pg/ml)	11.28 ± 2.54		11.76 ± 2.97		11.25 ± 1.77		11.40 ± 1.73		11.26 ± 1.81		11.89 ± 1.85	
TNF-α (pg/ml)	26.94 ± 14.88		26.24 ± 12.11		26.38 ± 20.01		23.00 ± 8.59		19.68 ± 1.19		19.42 ± 1.09	

* statistical significance between in the baseline and 8-week values

& statistical significance between in the 8-week values compare to CG group

ESP: exercise and sham PBM group; EAP: exercise and active PBM group; CG: control group

of physical exercises and PBM on inflammatory markers. Physical exercises (and the related muscle contraction) produce a mechanotransduction stimulus, which maintain homeostasis of articular cartilage and contribute to attenuate OA physiological events [39]. As a consequence, physical exercise programs have anabolic, anti-inflammatory and antioxidant effects in OA patients [40]. Moreover, many studies have demonstrated the anti-inflammatory effects of PBM [41, 42]. PBM is able to modulate mRNA gene expression of IL-10 in acute and chronic inflammatory phase and decreases the expression of this cytokine and consequently modulates the inflammatory process of OA [43]. Taking together, the combined treatments presented a positive effect on IL-10 expression, which could represent a modulation of the inflammatory process.

IL-1β is considered one of the main cytokines in OA development and the literature points out that the reduction of IL-1β production is an indication of the attenuation of cartilage degenerative process related to OA [44]. CG demonstrated a significant increase of IL-1β expression after the experimental period. Similarly, an experimental study using rats with OA also observed a higher IL-1β expression in the control animals compared to the treated ones CG [45]. In this context, it can be suggested that the treatments were able to positively kept stable the IL-1β expression.

IL-6, a pro-inflammatory cytokine has a catabolic activity in the pathogenesis of OA. In the present study, no significant difference in IL-6 expression was observed in both experimental periods for any group. Conversely, Aguiar et al., [13] found a significant reduction in IL-6 levels in patients with knee OA, after a treatment of flexibility training and muscle strengthening, 3 times a week for 12 weeks. Furthermore, a systematic review concluded that PBM has no effect on the expression of the inflammatory cytokine IL-6 in OA animals [46]. However, experimental studies indicate that PBM is capable of modulating inflammatory mediators such as IL-6 in rats using an experimental model of joint inflammation [47]. The controversial results may be related to PBM parameters or the frequency if the treatment.

Furthermore, both treatments did not have any effect on IL-8 and TNF-α cytokines concentration. IL-8 is a chemokine produced by various inflammatory cells such as neutrophils, basophils, macrophages and T cells [48]. TNF-α, a pro-inflammatory cytokine seems to be related to IL-1β (pro-inflammatory cytokine) because are secreted by the same cells of the joint, in addition the increased presence of TNF-α stimulates the synthesis of IL-6 and IL-8 [49]. These results corroborates with Helmark et al., [50] who also observed that a resistance exercise training (25 sets of 10 repetitions at 60% of 1-RM) have not decreased the levels of IL-8 and IL-6 of patients with knee OA. Aguiar et al., [13] have not observed changes in TNF-α expression after 12 weeks of physical training using 60–80% of the maximum load of individuals with knee OA. In addition, a study applied PBM immediately after total knee arthroplasty and observed a decrease of IL-8 expression [49]. Moreover, a systematic review and meta-analysis points out that the PBM is capable of reduce considerably TNF-α expression in models of joint inflammation [47]. The results of the present study for IL-8 and TNF-α cytokines can be justified by type and modality of the load used in physical exercises once it is suggested that maximum training load seems to modulate the levels of these cytokine [51].

CTX-II is a biomarker released due to the degeneration of cartilage related to catabolic activity that leads to loss of type II collagen concentration, which is the most abundant protein of the cartilage matrix and proteoglycan matrix of cartilage [52]. There was no statistically

significant difference in CTX-II levels in this study. These findings do not corroborate those of with Nambi et al. [1], which demonstrated that a protocol of PBM (905 nm, super pulsed, 1.5 J per point, 12 J per knee) and exercise in patients with knee OA during 4 weeks (twice a week) were able of inhibiting CTX-II, MMP-3 (stromelysin), MMP-8 (collagenase-2), and MMP-13 (collagenase-3) expression. However, the study mentioned analyse the levels of CTX-II fragments from urinary fraction and our study evaluated from the serum fraction of peripheral blood samples and this difference in analyse can justify the results of the present study.

In addition, it may be suggested that PBM application, through a cluster device constitutes an advantage for treating patients with knee OA, allowing the irradiation of a larger area and optimizing the treatment [21]. Although some positive effects of the treatments in the patients in this study, some limitations can be raised as a minor number of patients in sample size. It would be extremely important to assess the presence of inflammatory markers in the synovial fluid, which would increase the accuracy of their analysis, as well as the possibility of correlating them with symptomatic variables. Also, there is an absence of a follow-up in order to provide information about the maintenance of results over time in these patients.

Conclusion

The results of this study demonstrated that the physical exercise program in association with PBM was capable of increasing IL-10 levels, and the physical exercise program improved the function capacity. However, PBM did not promote an additional effect to the positive effects of exercise in improving pro-inflammatory and cartilage degradation biomarkers, and functional capacity in women with knee OA. Thus, more studies need to be carried out, using other parameters, since the literature demonstrates heterogeneity in the parameters of treatment with PBM when associated with physical exercise, for the consolidation of an intervention protocol for patients with knee OA.

Clinical messages

- Patients who underwent physical exercise program in association with PBM for 8 weeks showed improvement in IL-10 levels after treatment and when compared to the control group who did not any intervention;
- The function capacity was improved in patients undergoing a physical exercise program;
- Only the control group had the pro-inflammatory marker (IL-1β) increased;
- Physical exercise program and its association with PBM had no effect on others pro-inflammatory and cartilage degradation biomarkers.

Abbreviations

OA: Osteoarthritis; TNF-α: Tumor Necrosis Factor alpha; IL-1β: Interleukin-1β; IL-6: Interleukin -6; MMPs: Matrix metalloproteinases; CTX-II: C-telopeptide of type II collagen; NSAIDs: Nonsteroidal and steroidal anti-inflammatory drugs; MPA: Moderate physical activity; ILs: Interleukins; LLLT: Low-level laser therapy; PBM: Photobiomodulation; WOMAC: Western Ontario and McMaster Universities Arthritis Index; LED: Light-emitting diode; ESP: Exercise sham photobiomodulation group; EAP: Exercise active photobiomodulation group; CG: Control group; ANOVA: Analysis of variance; ELISA: Enzyme-linked immunosorbent assays; SLR: Seated leg raise; RM: Repetition maximum.

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Authors' contributions

PGV, HTT and ACR–Conceptualization, methodology, data collection, writing-original draft preparation and editing; RMDSC and LAG–methodology, statistic work, writing-reviewing and editing. CFDS—biomedicine responsible for blood sample collection from volunteers. The author(s) read and approved the final manuscript.

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Availability of data and materials

Study data can be made available upon reasonable request to the principal investigator.

Declarations

Ethics approval and consent to participate

All procedures were approved by the Ethics Committee of University (Approval Number 1368478) and, registered in www.clinicaltrials.gov, RBR-7t6nzr. All participants gave their informed consent before participation.

Consent for publication

Not applicable.

Competing interests

The author(s) declare(s) that there is no conflict of interest.

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