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Effectiveness of photobiomodulation and resistive exercise on cartilage tissue in osteoarthritic rats

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ABSTRACT

The aim of the present study was to investigate the association of a resistive training and Photobiomodulation (PBM) on cartilage tissue in an experimental model of knee Osteoarthritis (OA). Forty male Wistar rats (weigh, ± 150g) were distributed into 4 groups. Treatments were performed for 8 weeks (3 sessions per week). The specimens were evaluated by histology, OARSI, morphometric and immunohistochemistry analysis. The results showed that the interventions were able to modulate the degenerative process reacted to OA. Exercised animals (with or without PBM) demonstrated lower values for OARSI and lower expression of IL-1β, caspase-3, MMP-13. Furthermore, animals treated with the associated treatments presented significantly decrease in the density of chondrocytes. Resistive exercise training modulated the morphological alterations and inflammatory process related to the OA progression. However, PBM isolated have not produce extra effects on the variables evaluated

Key words: photobiomodulation; articular cartilage; knee osteoarthritis; physical exercises.

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Introduction

Osteoarthritis (OA) is a progressive chronic joint disease marked by degeneration of the extracellular matrix of articular cartilage and the subchondral bone of a synovial joint, eventually resulting in joint failure.[1] It is estimated that 10% to 30% of elderly refer symptomatic knee OA worldwide.[2] Furthermore, OA is often associated to many symptoms such as joint pain, an impairment in the range of motion and muscle weakness, leading to a significant decrease in quality of life.[3]

OA treatment is based mainly in the use of pharmacological procedures.[4] However, some non-invasive therapeutic approaches such as physical exercise programs have been demonstrating positive effects on managing OA symptoms, with low risk of adverse effects.[5,6] Many authors show that physical exercise programs, especially the ones involving both muscle strengthening, are able of reducing inflammatory cytokines, attenuating the process of muscle proteolysis, consequently improving muscle function and joint disability in OA knees both in experimental models and in human trials.[6-8] It is well known that muscle strengthening exercises (defined by the ability to produce force against an external resistance), is a key component in rehabilitation protocols for OA patients, producing a dynamic compression of the Extracellular Matrix (ECM) of the joint, which stimulate the diffusion of nutrients and oxygen through exudation and reabsorption of synovial fluid.[9,10] Also, the resulting increase of muscle strength improves the stability of the joint, mobility, and physical function, decreasing the level of pain. Studies showed that resistance exercise training programs produced an increase in lower-limb muscle strength, functional capacity and balance in women with knee OA.[10]{Ciolac, 2015, Effects of resistance training in older women with knee osteoarthritis and total knee arthroplasty} These results suggest that resistance exercise training may be an important tool to counteract mobility impairments commonly found in this population. However, the ideal exercise intensity, duration and frequency of sessions need to be determined yet.

Furthermore, Photobiomodulation (PBM) has been used as adjuvant therapy for OA in several contexts, being able of modulating the inflammatory process and decreasing the level of pain in OA patients.[11] Several studies have demonstrated that PBM has decreased the inflammatory cytokines expression and increased antioxidant enzyme levels in an experimental model of inflammation in rats.[11-13] Also, clinical trials have demonstrated that PBM reduced pain, knee swelling and increase the functional performance in knee OA patients.[14,15] In addition, the association of physical exercise and PBM on the management of OA has been studied by some authors.[12,14] In a study performed by our group, the effects of an exercise program (treadmill; 16 m/min; 50 min/day) and PBM has prevented cartilage degeneration and modulating inflammatory process induced by knee OA in rats.[12] Despite the positive evidences, there is a lack of studies highlighting the effects of a resistive exercise program and PBM on knee OA.

In this context, the hypothesis of this study is that the associated therapeutic interventions may favor the metabolism of the cartilage structure in the knees of rats with OA, mainly by the increase in muscle strength and modulation of the inflammatory process, consequently culminating in an improved articular stability and function. The aim of the present work is to investigate the effects of a resistive exercise training and PBM (associated or not) on cartilage tissue in an experimental model of knee OA.

Materials and Methods

Animals and groups

Forty male Wistar rats (*Rattus norvegicus*) (8 weeks and ± 150g) were used in this study. The animals were maintained throughout the experimental procedure in appropriate cages under controlled environmental conditions, receiving common own feed and water ad. libitum. This study was approved by our institution's Animal Care and Ethics Committee (814715/2013).

Animals were randomly distributed into 4 groups (n=10 each group): Osteoarthritis Control (OAC); Osteoarthritis and PBM (OAL); osteoarthritis and exercise animals (OAE); osteoarthritis and exercise and PBM animals (OAEL).

Experimental model of osteoarthritis

All animals were anesthetized (with xilazin (Syntec®, 20 mg/kg, IP) and ketamin (Agener®, at 40 mg/kg, IP) and the surgical procedure was performed (transection of the Anterior Cruciate Ligament (ACLT) of the left hind paw). Left lower limb was shaved and an incision at the articular cartilage region was performed for a medial arthrotomy.

Patella was dislocated and the Anterior Cruciate Ligament (ACL) was isolated and transected. The success of the ACLT was confirmed with Lachman test performed by 2 experts.[16] Postoperative care was performed in all rats and allowed free activities in individual cages.

Resistance exercise training protocol and determination of the maximal load

Exercise training was performed in a training support ladder apparatus (1.1 x 0.18 m, 2cm grid, 80° inclination) with a housing chamber (20 x 20 x 20 cm) at the top of the ladder. Animals performed the climbing in the ladder, with an extra-weight attached in the tail (wrapping the proximal portion of the tail with a self-adhesive foam strip). The protocol of physical exercise followed the methodology used in the study of Patrocinio *et al.*[17]

PBM protocol

The device used was 808 nm gallium-aluminum-arsenide (GaAlAs) diode laser (Photon Laser II, DMC® equipment Ltda, SP, Brazil). Animals were irradiated using the following parameters based on the work of Assis *et al.*: 50 mW power output, 28 sec, 0.028 cm^2, 50 J/cm^2, 1.7 W/cm^2, 1.4 J. PBM irradiation was applied 3 days/week, at 2 points on left knee joint (medial and lateral side of the joint), for 24 sessions. The optical fiber was positioned perpendicularly to the area of irradiation, in the contact skin mode technique. Moreover, the device was calibrated before the experiments. PBM was performed immediately after the resistive exercise protocols in the OAEL.
Twelve weeks after the surgery, all animals were euthanized individually by carbon dioxide asphyxia and left knee joints of each animal were removed for analysis.

Histological analysis

Specimens were fixated in formaldehyde and decalcified in 10% EDTA. Samples were embedded in paraffin blocks and histological sections were obtained (4μm) in the sagittal plane, starting from the medial margin of the joint using a micrometer (Leica RM – 2145, Germany). Samples were stained with hematoxylin and eosin (HE- Merck, Germany) and Toluidine Blue (TB- Merck, Germany). Moreover, 3 sections were obtained for the immunohistochemical analysis.

OARSI analysis

OARSI score, a system with a 24-point scale based on a combination of OA grade (0–6 points) and OA stage (0–4 points), was used to evaluate the OA progression in all the experimental groups (Osteoarthritis Research Society International (OARSI) recommendations and cartilage histopathology grading and staging system).[18]

Morphometric analysis

A computer-based image analysis Axiovision 3.1 Image Analysis (Carl Zeiss, Germany) was used to measure the density of chondrocytes and the cartilage thickness in each area scored. Three areas of 80.000 m^2, at the anterior, central and posterior region of each slide were chosen for counting the number of chondrocytes and the average for the 3 areas was obtained. Thickness was also measured in 3 regions, one central and 2 lateral (300 mm left and right from the first region), from subchondral bone to articular surface.[12]

Immunohistochemistry

The specimens were then incubated with primary antibodies caspase (polyclonal rabitt anti-rat, ab6671, abcam), IL-1β (polyclonal rabitt anti-rat, sc-7884, Sta Cruz biotechnology) at a concentration of 1:50, MMP-13 (polyclonal rabitt anti-rat, ab75606, abcam) at a concentration of 1:100 and Caspase-3 (polyclonalrabitt anti-rat, ab9866, abcam) at a concentration of 1:100. The tissue sections were deparafinized and rehydrated, and incubated with prepared 30% hydrogen peroxide diluted in phosphate buffered saline (PBS) for 30 min. This was followed by application of biotin-labelled secondary antibody (ABC kit, PK-6200, Vector laboratories) at 1:5 dilution for 30 min. Colourimetric detection with a diaminobenzidine substrate and hematoxylin. For a negative control, the primary antibody was omitted and PBS alone applied. Digital images of the 100x magnification were captured by optical microscope. Brown marked cells was considered positive for IL1- β, MMP-13 and caspase-3 expression. The results were evaluated qualitatively (presence of the positive immunomarkers cells).[19]

Statistical analysis

Means ± Standard Error of the Mean (SEM) were used for expressed the data. Shapiro-Wilk's and Levene's test were applied to evaluate the normality and homogeneity of the results, respectively. For the variables that exhibited normal distribution, comparisons between experimental groups were performed by one-way ANOVA, and the Tukey post-test used to compare individual groups. For the variables that exhibited non-normal distribution, Kruskal-Wallis test was used. A *P* value <0.05 was considered significant. All analyzes were performed using a GraphPad Prism 6.0 (GraphPad Software, USA).

Results

Histological descriptive analysis

OAC exhibited intense signs of degradation and fibrillation along the entire articular surface, hypercellularity and disorganization of the chondrocytes (Figure 1A).

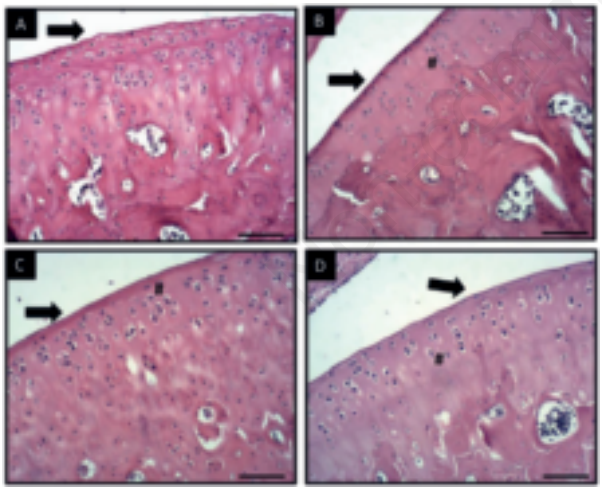

Figure 1. Representative photomicrographs of histological laminas 12 weeks after OA induction. Organization of chondrocytes (arrow); fibrillation and irregularities (arrowhead); joint cartilage (JC), subchondral bone (b). Osteoarthritis control (OAC); Osteoarthritic and laser (OAL); Osteoarthritic and Exercise animals (OAE); Osteoarthritic and Exercise and Laser animals (OAEL). (Stain: H.E.; Scale Bar: 100 μm).

For OAE, OAL and OAEL, the histological findings were similar between the groups, with signs of tissue degradation, fibrillation areas and irregularities along the articular surface. Moreover, chondrocytes could be seen in columns similar to normal tissue (Figure 1B, 1C and 1D).

OARSI scoring system

OARSI score for OAC was significantly higher compared to the OAE (p=0.028) and OAEL (p=0.0005; Figure 2). No other statistical difference was observed.

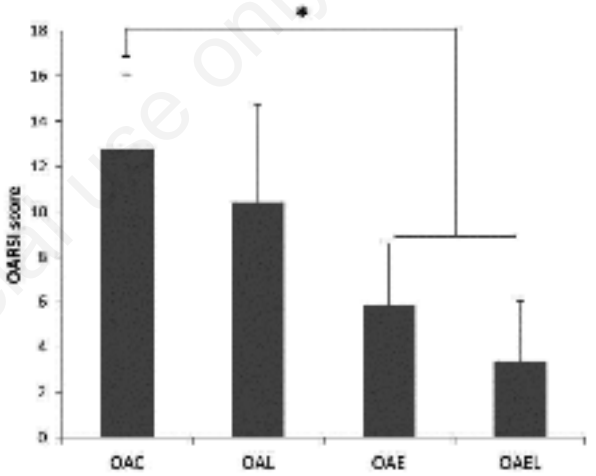

Figure 2. Histopathological evaluation using OARSI score system. Results expressed as mean ± standard error of the mean. Osteoarthritis control (OAC); Osteoarthritic and laser (OAL); Osteoarthritic and Exercise animals (OAE); Osteoarthritic and Exercise and Laser animals (OAEL). (indicated as *p<0.001 *versus* OA).

Density of chondrocytes and thickness

Morphometric evaluation of the density of chondrocytes and thickness can be seen in Figures 3A and 3B. The density of chondrocytes in OAEL was lower compared to OAC (p=0.0011), OAL (p=0.015) and OAE (p=0.0097). No other difference was observed (p > 0.05; Figure 2A). Thickness analysis demonstrated that OAE presented significant higher values compared to OAC (p=0.0007) and

OAL (p=0.0069; Figure 3B). No other significant difference was found between the experimental groups (p>0.05; Figure 3B).

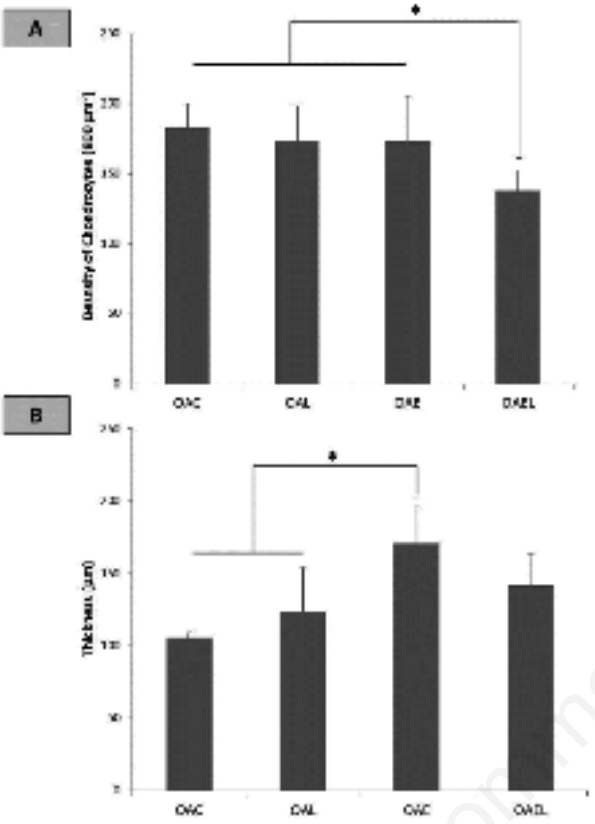

Figure 3. Density of chondrocytes and cartilage thickness (A) Results of the density of chondrocytes (indicated as *p<0.05 *versus* OA); (B) Results of cartilage thickness. Osteoarthritis control (OAC); Osteoarthritic and laser (OAL); Osteoarthritic and Exercise animals (OAE); Osteoarthritic and Exercise and Laser animals (OAEL). (indicated as *p<0.05 *versus* OA). Results expressed as mean ± standard error of the mean.

Immunohistochemistry analysis

Il-1β expression

IL-1β expression was seen in the nucleus of the chondrocytes for all OA groups (Figure 4A, 4B, 4D and 4E). Intense IL-1β expression was noticed in the OAC and OAL (Figure 4A and 4B). In contrast, OAE and OAEL presented moderate IL-1β immunoexpression in the nucleus of the chondrocytes (Figure 4C and 4D).

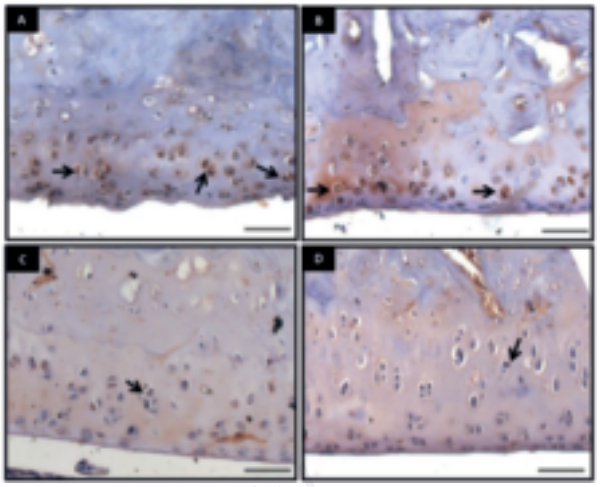

Figure 4. Representative sections of IL-1 immunohistochemistry. Immunolabeled chondrocytes (arrow). A) Osteoarthritis Control (OAC); B) Osteoarthritic and laser (OAL); C) Osteoarthritic and Exercise animals (OAE); D) Osteoarthritic and Exercise and Laser animals (OAEL). (Scale Bar: 50 μm).

Caspase-3 expression

The immunoexpression of Caspase-3 was seen mainly in the chondrocytes for all experimental groups (Figure 5). Furthermore, an intense caspase-3 immunoexpression was

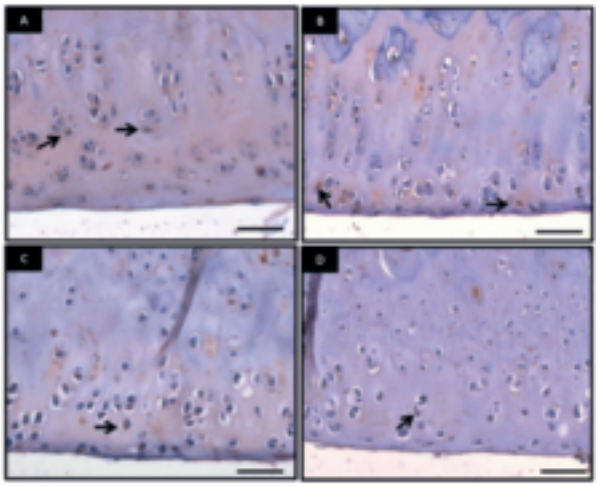

Figure 5. Representative sections of caspase-3 immunohistochemistry. Immunolabeled chondrocytes (arrow). A) Osteoarthritis Control (OAC); B) Osteoarthritic and laser (OAL); C) Osteoarthritic and Exercise animals (OAE); D) Osteoarthritic and Exercise and Laser animals (OAEL). (Scale Bar: 50 μm).

observed in OAC and OAL (Figure 5A and 5B). Interestingly, OAE and OAEL presented moderate expression for this immunomarker (Figure 5C e 5D).

MMP-13 expression

MMP-13 expression was also detected in the nucleus of chondrocytes in all groups (Figure 6). It is possible to observe in figure 6A, an intense MMP-13 immunostainningfor OAC (Figure 6A). Also, a moderate MMP-13 immunoexpression was observed in OAL and OAEL (Figure 6B and 6D). However, OAE presented a lower number of immunomarked chondrocytes (Figure 6C).

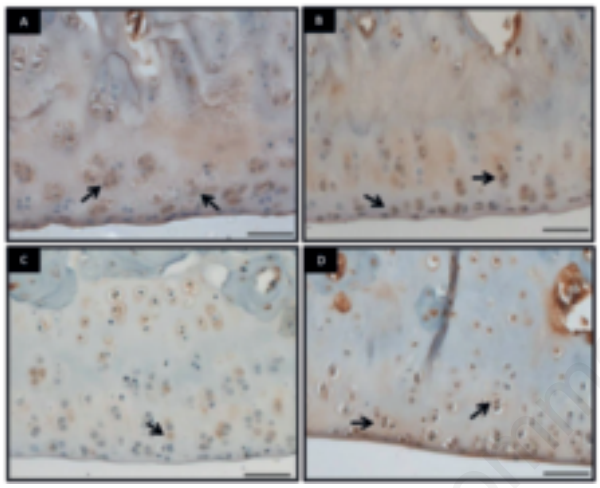

Figure 6. Representative sections of MMP-13 immunohistochemistry. Immunolabeled chondrocytes (arrow). A) Osteoarthritis Control (OAC); B) Osteoarthritic and laser (OAL); C) Osteoarthritic and Exercise animals (OAE); D) Osteoarthritic and Exercise and Laser animals (OAEL). (Scale Bar: 50 µm).

Discussion

The present study investigated the effects of a resistance exercise training and PBM in the cartilage tissue morphology in the knees of OA rats. The histological results revealed that after the experimental period, signs of tissue degradation and fibrillation were observed in the OA untreated animals. Furthermore, OARSI score demonstrated that the physical exercised groups (with or without PBM) presented attenuated signs of tissue degradation. Also, the association of physical training and PBM significantly decreased the density of chondrocytes and in OAE animals an increased thickness was observed. Furthermore, exercise modulated IL-1β, caspase-3 and MMP-13 immunoexpression.

The histological findings presented in this study revealed that the resistance exercise program (with and without PBM) was able to preventing tissue modifications in the OA, maintaining tissue organization and improving OARSI scores, which indicate a positive effect of this approach on tissue metabolism. Physical exercise is one of the most effective management strategies for OA.[20] A series of studies have demonstrated that muscle strengthening through resistive exercise training improves function, decreases the level of pain and reduces disability related to OA.[9] Possibly, the increase of muscle strength and enhanced articular function, associated to the mechanical stimulus produced by physical exercise, determined positive effects on the chondrocyte cell metabolism, culminating in a higher deposition of extracellular matrix and collagen, decreasing the signs of degeneration.[21-23]

Also, it is well known that PBM has stimulatory effects on biological tissues and on the modulation of the inflammatory process.[13,19] Many authors demonstrated that PBM produced positive effects on cartilage metabolism, attenuating the morphological tissues related to OA.[18,24,25] However, in the present study the irradiated animals without physical exercise presented similar results compared to control group in the OARSI, pointing out a possible lack of effect of PBM used isolated in these animals. The hyphotesis that the parameters for PBM used in the present study were not able to offer enough energy to modulate cartilage tissue metabolism, preventing the degeneration or producing an extra stimulatory effect, applied isolated or in combination with the resistance exercise program.

OA progression is based mainly by the imbalance between the cellular anabolism and catabolism, which may affect the capacity of the chondrocyte to proliferate and differentiate.[26,27] A higher number of chondrocytes was observed in the OA, OAE and OAL animals, demonstrating that, both therapeutic interventions, applied alone, were not able to reverting the effects of the degenerative process related to OA. Interestingly, OAEL animals demonstrated a decreased number of chondrocytes, indicating a positive effect of combined treatments on the modulation of cell proliferation. Possibly, the normalization of the fluid flows and the tissue homeostasis produced by the load of the re-

sistance exercise[28] associated to the cell stimulatory effect produced by the exercise training and laser energy may have acted on cell metabolism, avoiding apoptosis and proteoglycan degradation.

In the present study, increased cartilage thickness was observed in the exercised animals. Cartilage thickness is related to the degradation of the proteoglycans in the presence of OA.[29] It seems that resistive exercise training modulated proteoglycans degradation, positively affecting thickness. However, PBM have not had any influence in this variable, which possibly may be explained by the amount of energy offered to the tissue.

During the course of the OA, many inflammatory mediators (such IL-1β and TNF-) are expressed along the disease progression,[30,31] which are responsible for the inhibition of matrix synthesis and cell apoptosis.[32] Moreover, caspases, collagenases and Matrix Metalloproteinase (MMP) also contribute to the degradation of articular cartilage matrix.[33,34] In the present study, increased expression of inflammatory markers was found in the OA and OAL animals, indicating the progression of the disease and the lack of positive effects of PBM. It is known that there is a dose-dependent effect of PBM on tissues and an ideal amount of energy needs to be delivered to obtain the best tissue-response (which is called Biphasic dose-response).[35] The lack of positive effects of PBM in the immunohistochemistry analysis do not corroborate those of other authors who showed an anti-inflammatory effect of PBM on degenerative process.[8,12]

Interestingly, exercised animals presented a modulation of IL-1β, caspase-13 and MMP-13 expression. Many authors state that mechanical stimulus related to physical exercise promotes anti-inflammatory effects in experimental models of OA.[7] Zhang *et al.*[7,17] demonstrated that a physical exercise program produced a decreased expression of inflammatory markers in patients with OA.

Thus, in this study, the resistance exercise training was adequate for improving the parameters evaluated. Possibly, it was able of restoring muscle strength and joint mechanics, with the improvement of physical function in the OA animals.

Study limitations

PBM have not produced stimulatory effects on cartilage. Possibly, these effects were due to the amount of energy offered to the tissue. Moreover, no extra stimulus of PBM on OA exercised rats and the study of the associated treatments needed to be further investigated. It can be hypothesized that the use of different dosages of PBM and physical exercises could be a more effective treatment to stimulate cartilage tissue in the presence of a degenerative process. As this study was limited to relatively short-term evaluation, the investigation of the long-term effects of physical exercise and PBM, using another parameter, remains to be provided.

Conclusions

In conclusion, this study showed that the resistive exercise training modulated the morphological alterations and inflammatory process related to the OA progression. However, PBM isolated have not produce extra effects on the variables evaluated. Further long-term studies should be carried out to provide additional information concerning the effects of both treatments in the late stages of OA, designing future therapeutic programs to reduce functional limitations and improve quality of life in this population.

Contribution

LHGS, LA, ACMR contributed to the conception and design of the study, CRT, LHGS, TIRS, MBS, CCSM, LCLC contributed to the acquisition of data,FV, MST, DAR, NAP, DAR, ACMR contributed to the analysis and interpretation of data. LHGS, LA, DAR, NAP, DAR, ACMR contributed to drafting the article or revising it critically for relevant intellectual content. All authors gave the final approval of the version to be submitted.

Conflict of interest

The authors declare no conflict of inteerst.

Ethics approval

The Research Ethics Committee on Animal of the Federal University of São Carlos (814715/2013) approved this study and all the national guidelines for the use of laboratory animals were observed.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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