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Research article

Photobiomodulation with low-level laser (λ = 808nm) to treat experimental rheumatoid arthritis: A morphological study, collagen fiber analysis and IL-6 protein expression

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Abstract: Rheumatoid arthritis is a chronic systemic autoimmune disease that affects the synovial joints. Low-level laser photobiomodulation (LLLT) has microcirculatory, analgesic, and anti-inflammatory effects. In this paper, the percentage of collagen fibrils and IL-6 protein expression in the synovia were measured to evaluate the effects of photobiomodulation (PBM) with LLLT (λ = 808 nm) on the morphology. Eighteen female Wistar rats were assigned into three groups: Control, Sham, and PBM. To induce arthritis, animals from the Sham and PBM groups received one intraarticular dose of zymosan (200 µg) under anesthesia. Twenty-four hours after induction, an LLLT treatment (λ = 808 nm, 25 mW nominal power, fluence of 20J/cm^2, beam area of 0.02 mm^2, time of 33 s, total energy of 0.825 J) was applied. Seven days after induction, samples from the animals' knees were subjected to histological and morphometric analyses, and the percentage of collagen fibers in the synovial area (% total area) with and without polarized light and IL-6 protein expression were measured by immunohistochemistry. Statistical analyses were performed an ANOVA and Tukey's post-test with $p < 0.05$ to compare the experimental groups using. Inflammation of the synovial region showed significant differences between Sham vs. Control, $p < 0.0001$, and PBM vs. Sham, $p < 0.001$. The areas of collagen fibers (total percentage) showed differences between Sham vs. Control, $p < 0.0001$, and Sham vs. PBM, $p =$

0.0149. IL-6 showed differences between Sham vs. Control and PBM vs. Sham, $p < 0.001$. Treatment with PBM using LLLT showed decreased synovial inflammation, collagen fiber formation, fibrosis, and IL-6 protein expression, and consequently decreased joint degradation.

Keywords: arthritis; photobiomodulation; low-level laser; inflammation; morphology

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune and inflammatory disease. Symptoms include, pain, swelling, heat, morning fatigue, and stiffness. Synovial membrane damage impacts joint inflammation bone and cartilage destruction, which can cause progressive damage and loss of function [1].

RA is a disease that has a worldwide prevalence of 0.5–1%. It can occur in any race and ethnic group; however, it mostly affects North Americans and the population of Northern Europe. Women are three times more likely to develop RA throughout their lives compared to men, and the age range is from 35 to 50 years [2]. Treatments for RA consist of drug combinations, physical exercises, disease understanding, and diet, which collectively aim to achieve complete remission or at least significantly reduce the incidence of joint damage, disability, and systemic manifestations [3,4].

Photobiomodulation (PBM) with a low-level laser (LLL) (i.e., LLLT) is a non-invasive and sterile treatment which provides inflammation control and pain reduction. PBM has photochemical, photophysical, and photobiological therapeutic effects capable of altering the cellular behavior, thus improving tissue repair [5,6].

LLLs have proprieties to improve cellular oxygenation through the production of ATP associated with neo angiogenesis by increasing microcirculation and accelerating the repair of injured tissues [7,8]. In addition, treatment with LLLT shows analgesic and anti-inflammatory effects [9].

Most studies have used multiple sessions of PBM with laser therapy, unlike our study, which uses a single dose laser to promote PBM [5–9]. Another important point is an early collagen fiber analysis, which is not commonly used but has been shown to be an important biomarker for the disease prognosis [4].

The aim of this study is to evaluate the effects of PBM with single dose of LLL ($\lambda = 808$ nm) on the morphology and percentage of collagen fibers in the synovial region of Wistar rats in an experimental model of RA.

2. Materials and methods

2.1. *Ethical aspects*

This study was performed with approval by the Animal Ethics Care Committee–CEUA of Hermínio Ometto Foundation, protocol number 025/2021. All the experiments were conducted using the ARRIVE guidelines, which are recommended by the National Council for the Control of Animal Experimentation (CONCEA) of the Brazilian Ministry of Science, Technology and Innovation.

2.2. Experimental groups and arthritis induction

Thirty-six female Wistar rats (60 days old, 180 ± 20 g) were kept in light-dark cycles of 12 hours each, with food and water *ad libitum* throughout all experimental periods. There were randomly assigned into three groups (n = 12): Control (without arthritis), Sham (arthritis induced with Zymosan), and PBM (arthritis induced with Zymosan and treated with PBM). At time zero, after the administration of Ketamine (30 mg/kg) and Xylazine (10 mg/kg), animals of the Sham and PBM groups underwent intra-articular injections of Zymosan (200 μg) in the right knee of the hind limb [10].

2.3. PBM with low-level laser

Twenty-four hours after the induction of arthritis by Zymosan, animals of the PBM group were anesthetized with Ketamine [30 mg/kg]-Xylazine [10 mg/kg] and received treatment with PBM by a LLL with a Gallium Aluminum Arsenide device (GaAlAs, Magnus Plus model, DMC Equipamentos, São Carlos, Brazil), with the following parameters: λ = 808nm, nominal power = 25 mW, fluence = 20 J/cm^2, area = 0.02mm^2, time = 33 s, E = 0.825 J (per point/total), and punctual application in the right patellar region by a single dose application (Table 1) [10]. The Control and Sham groups received treatments with the laser turned off, thereby simulating time and stress that can be caused.

Table 1. Different parameters used in PBM group.

Group	λ (nm)	Diode	ED (J/cm^2)	P (mW)	E (J)	TE (J)	A (cm^2)	T (s)
PBM	808	GaAlAs	20	25	0,825	0,825	0,02	33

2.4. Euthanasia and sample collection

The euthanasia of the animals occurred after seven days with an anesthetic plan (3:1) of Ketamine (90 mg/kg) and Xylazine (30 mg/kg); additionally, cervical dislocation was used as a second physical method for euthanasia after confirming the absence of ocular and plantar reflexes. Samples were collected from the right knee, at the hip-femoral level, and from the joints of the hind limbs for morphometric analyses and the percentage of collagen fibers [11].

2.5. Histological Processing

Samples of the animals' knees were kept in Millonig buffer and were processed using a standard histological protocol (decalcification, dehydration, clearing, paraffinization, and embedding of histological pieces). Morphometric analyses of the inflammatory areas of the synovium (Hematoxylin and Eosin) and the percentage of collagen fibers in the area (% total area [10^4 μm] - Picro-Sirius red) with and without polarized light were performed [10,12].

2.6. Morphometric analysis

Histological sections were prepared with 5 μM thickness and the slides were stained with Hematoxylin-Eosin (HE). For the morphological evaluation, measurements of the inflammatory areas of the synovial membrane (μm^2) were obtained from the data of three digital images from each of the three documented sessions (n = 9 images/animal) of the central region of the knee joint of each animal from the different experimental groups. The evaluation of the collagen fibers percentage (% of total

area) was forwarded from the collection of six digital images from each of the three sessions (n = 18 images/animal) documented from the center of the knee joint of each animal from the different experimental groups. The photo documentation was performed using a Leica DFC300 FX microscope, and the images were analyzed using the ImageJ program (NIH/USA, free program).

2.7. Immunohistochemistry assay

Protein expression by immunohistochemistry was analyzed using the immunohistochemistry technique previously described by Bomfim et al[12]. Briefly, the sections were processed, labeled with the primary antibody (IL-6, 1:500, Sigma Aldrich), and detected utilizing the Peroxidase Detection Systems secondary antibody kit. The immunoreactivity was quantified by evaluating the intensity of the color formed by the immunohistochemical reaction with the DAB stain, counting the cells in five fields per slide, and analyzing images using the Image J program.

2.8. Statistical analysis

Statistical analyses were performed with GraphPad Prism 5.0, and the analysis of variance (ANOVA) and Tukey's post-tests were applied with $p < 0.05$ to analyze the measurement of synovial inflammation and the percentage of collagen fibers between the experimental groups.

3. Results

3.1. Morphological analysis

Inflammation of the synovial region (Figure 1) in mean ± SD showed significant differences between the Sham (Figure 1B) 187.8 ± 56.95 *vs* Control (Figure 1A) 9.55 ± 1.675 with $p < 0.0001$ and Sham (Figure 1B) *vs* PBM (Figure 1C) 15.15 ± 3.554 (See Figure 2A).

3.2. Percentage of collagen fibers and IL-6 expression

The areas of collagen fibers (Figure 2B) (total percentage) in showed differences (mean ± SD) between the Sham (Figure 3C and D) 60.07 ± 1. 604 *vs* Control 22.13 ± 2,120 (Figure 3A and B) with $p < 0.0001$, and the Sham (Figure 3C and D) *vs* PBM 54.40 ± 1.778 with $p = 0.0149$ (Figure 3E and F). The number of positive cells for IL-6 protein expression (Figure 4A) showed significant differences between the Control (1.600 ± 0.910) *vs* Sham (6.867 ± 2.446) with $p<0.0001$ and Sham *vs* PBM (1.333 ± 0.516) with $p<0.0001$ (Figure 4B).

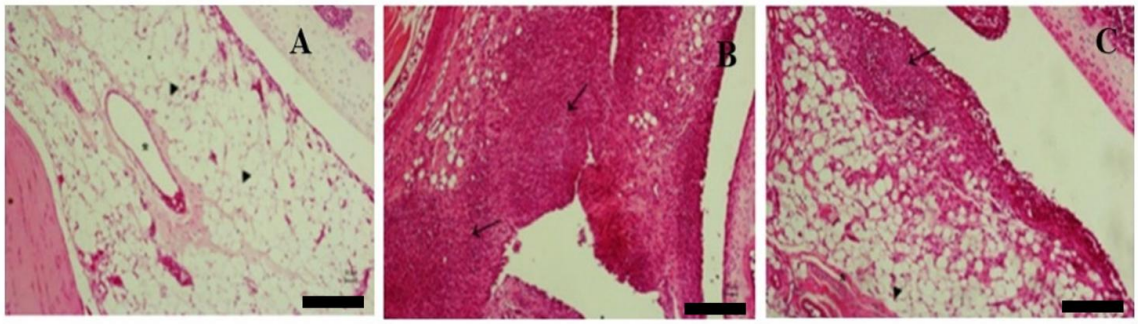

Figure 1. Morphological analysis of the inflammatory areas in the control (A), Sham (B), and PBM (C) groups after 7 days. In the Sham group, there was a large noticeable inflammatory infiltrate when compared to the Control group. The PBM group, which was treated with a low-intensity laser, showed an improvement in the inflammatory infiltrate within the synovial region. Control: Arrows–normal appearance. Sham: Arrows–inflammatory infiltrate. PBM Upper arrow: limited inflammatory infiltrate in the region of the synovial membrane and Lower arrow: improvement in the inflammatory infiltrate. (Bar = 100 μm).

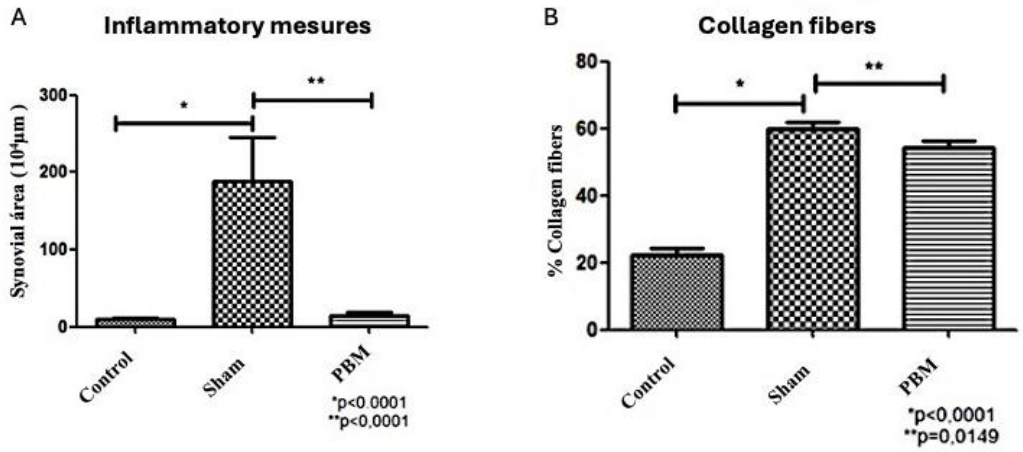

Figure 2. Inflammatory measurements of the synovial region. There are significant differences between the Sham group and the Control group and between the Sham group and the PBM group (A). Percentage of collagen fibers in the synovial region. There were significant differences between the Sham and Control groups and between the PBM and Sham groups (B).

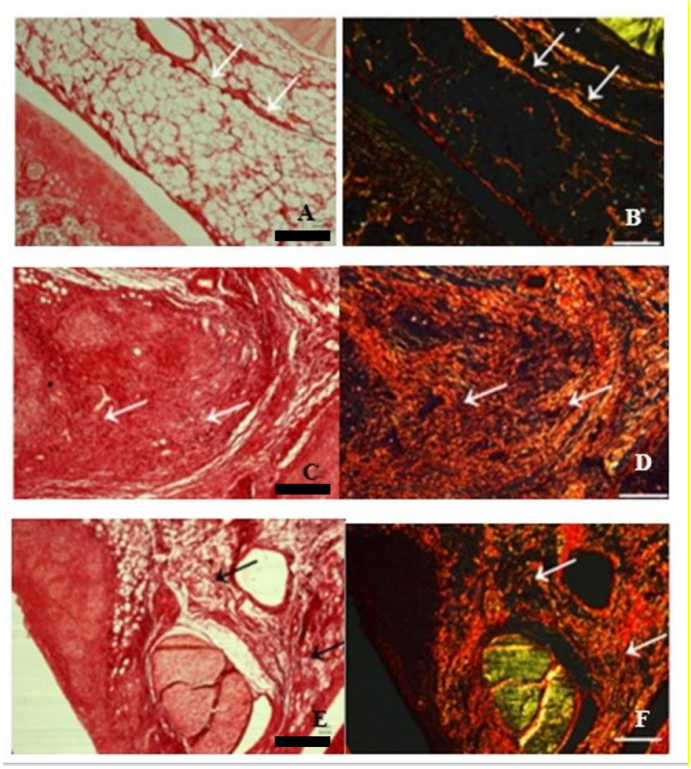

Figure 3. Percentage of collagen fibers in the area (% in area-10^4 μm^2) (Picro-Sirius Red) with and without polarized light performed on the Control (A and B), Sham (C and D), and PBM (E and F) animal groups over a 7-day period. The Control group showed a normal appearance. The Sham group showed an increase in the percentage of collagen fibers, thus indicating a possible onset of fibrosis. In the PBM group, there was a decrease in the collagen fiber formation. Control group: Arrows - normal appearance of the synovial region. Sham Group: Arrows–severe growth of collagen fibers. PBM group: Arrows—indicate an improvement in the appearance of the synovium, close to normal. (Bar = 100 μm).

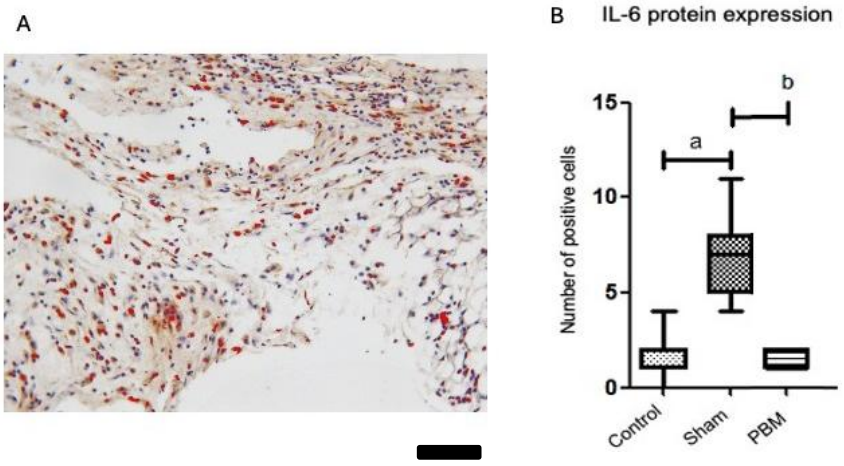

Figure 4. A: Representative figure of the cell counting of positive cells after immunohistochemistry for IL-6 (Bar = 100 μm). B: Statistical analyses of the experimental groups for IL-6 protein expression (a/b p <0 .001).

4. Discussion

This study aimed to evaluate the effects of PBM with a LLL (λ = 808nm) by analyzing the morphology and percentage of collagen fibers in the synovial region of joints as a treatment after inducing RA in female animals, an experimental design that is related to the higher incidence of RA in the female population [13].

In our experimental model of RA, acute inflammation was performed after induction by Zymosan, whose application leads to the release of pro-inflammatory cytokines such as TNF-α, IL-18, IL-1β, and IL-6, synovial joint hypertrophy, and recruitment neutrophils. These inflammatory conditions are similarly seen in the acute phase of RA and osteoarthritis [14].

The stress caused by RA can lead to mitochondrial dysfunction, and this organelle is a target for therapy with laser PBM, since the directed light induces a therapeutic photochemical effect that improves the mitochondrial function and antioxidant defenses, thus treating the lesion at the site specific.

In addition, they affect metabolism, signaling, cell growth factors, and inflammatory processes [15].

The components of PBM with a LLL, such as the intensity, time, duration, and wavelength, try to maximize the benefits of the treatment, inducing cell proliferation and increasing cell differentiation, which helps in healing and the normalization of cell functions; in our study, this was observed in the group after laser radiation [16]. After light absorption, ATP activation occurs by the cytochrome c oxidase pathway, which is associated with microcirculation and a greater nutritional support. PBM improves blood circulation, enhances collagen synthesis, promotes tissue regeneration and the stimulation of specific and non-specific immunity, and promotes analgesic effects such as the relief of physical pain or symptoms [17].

Morphological evaluations are important to understand cell flux and the mechanisms to improve repair. One of the parameters is to observe the inflammatory infiltrates in areas affected by the disease, since RA is known to be a chronic, autoimmune disease, and is characterized by the accumulation of an inflammatory infiltrate in the synovial membrane, which significantly reduces the quality of the cartilage through tissue disorganization of the joints, thus leading to synovitis and progressive joint destruction [18].

In the control group, there was no presence of inflammatory infiltrates; on the other hand, in the Sham group, we observed the presence of an intense inflammation area. In the PBM group, which was treated with a LLL, there was a reduction in the inflammatory infiltrate, which was restricted to the synovial membrane.

In a study that evaluated the effects of LLLT on joint homeostasis, there was a decrease in the inflammatory process in the synovial region, with a moderate inflammatory infiltrate only in the synovial membrane [11].

These data are in line with our findings in the morphological analysis: in the PBM group, the infiltrate was limited to the membrane only. In groups treated with LLLT, there were a reduction in synovial inflammation when analyzing the morphological and percentage of collagen fibers. The mechanism associated a LLL on the injured tissue is related to its ability to inhibit chemotactic factors in the early stages of inflammation, to interfere with the effects of chemical mediators induced by inflammation, and to inhibit the synthesis of prostaglandins; all of these effects were also found in Wistar rats [19].

The clinical potential of a laser (λ = 904nm/single dose of 1 J/cm^2) for the treatment of arthritis

in the experimental model is based on reducing pain and protecting the morphology of the joint region, thus preventing joint degeneration [20]. These effects were evidenced in our animals treated, where edema and local repair presented significant differences in the morphological aspects when compared to the Sham group.

PBM therapy has effects based on the absorption of light by tissues, specifically by the mitochondria, thus resulting in an improvement of ATP, the modulation of intracellular oxidative stress, an induction of transcription factors, cell mitosis, and a higher extracellular matrix (ECM) synthesis. This stimulation of angiogenesis affects the inflammatory process and causes an increase in microcirculation [21]. In our study, a decrease in synovial inflammation was observed and the morphology was preserved. In addition, there was the formation of new blood vessels when both treatments were proposed.

In a study with RA-modeled rats that were treated with single dose of a LLL, RA reflected in the morphological and morphometric changes in the anterior tibial muscle of Wistar rats, such as the presence of an inflammatory infiltrate, which may be due to the higher index of adhesion molecules in the vascular endothelium, thus facilitating the process of the migration of inflammatory cells to the site [22]; these results corroborate our findings. Additionally, in the Sham group, the morphology analyses demonstrated a large cluster of cells at the site due to the inflammatory response.

Joint cartilage is mainly composed of type II collagen, which is a target of degradation during RA, mainly mediated by metalloproteinases, and responsible for the destruction of the connective tissue, thus causing a lack of collagen [23]. Due to this destruction of collagen II, it can be replaced by type I collagen fibrocartilage, thus initiating the fibrosis process. When evaluating the Sham group, we observed an increase in collagen fibers by picro-sirius red, which indicates a possible establishment of connective tissue as part of a fibroid healing process.

IL-6 protein expression decreases in the PBM groups; what was expected once IL-6 is involved in cartilage destruction and synovial inflammation associated with RA [24,25], and PBM was shown to be as effective as some drugs, such as tocilizumab and sarilumab, which also showed a decrease in the IL-6 concentration in clinical trials [26–28].

IL-6 and other interleukins such as IL-1β are key in driving inflammation and joint damage. Treatments which target IL-6 have proven to be very useful for those patients who do not respond to conventional therapies or even less standard ones. This information is important and show the relevance to study the regulation of IL-6 protein expression, similar to what was observed in the PBM group when the number of positive cells were close to control group [29].

This study sought to elucidate the effects of PBM treatment with a LLL (λ = 808nm) on the morphology, thereby emphasizing areas containing inflammatory infiltrates and the percentage of collagen fibers, with the beginning of the fibrosis process in the synovial region and how IL-6 can contribute to a decrease in synovial inflammation.

It is important to observe that a decrease in synovial inflammation contribute to an improved bone quality and a decrease in the destruction of femur and tibia. Additionally, its benefits are related to PBM that has a capacity through biochemical and biostimulant effects to improve the repair and bone formation and modify the bone protein expression [30,31].

Highlighting limitations of our study, it was observed that PBM can differ between human and experimental models in the energy dose; additionally, there is a lack of studies with a single dose of PBM with a LLL therapy. Future prospects may include applications of a single dose of PBM with a LLL in patients with RA and other joint and bone pathologies.

5. Conclusions

PBM treatment with a single dose LLL showed lower synovial inflammation and a decrease in the formation of collagen fibers, which are related to a decrease in the formation of fibrosis areas and a decreased joint degradation in the experimental period studied.

Author contributions

Conceptualization: Gaspar de Jesus Lopes-Filho, Fernando Russo Costa do Bomfim; Data curation: Luiz Felipe Barreta, Danielly Mandato Oliveira, Bruna Silva Gomes, Sabrina Zanchetta Lanza, Marcelo Augusto Marretto Esquisatto; Formal analysis: Marcelo Augusto Marretto Esquisatto, Gaspar de Jesus Lopes-Filho, Fernando Russo Costa do Bomfim; Investigation: Luiz Felipe Barreta, Danielly Mandato Oliveira, Bruna Silva Gomes, Sabrina Zanchetta Lanza and Fernando Russo Costa do Bomfim. Methodology: Luiz Felipe Barreta, Danielly Mandato Oliveira, Bruna Silva Gomes, Sabrina Zanchetta Lanza and Fernando Russo Costa do Bomfim; Supervision: Overseeing and guiding the research project; Validation: Gaspar de Jesus Lopes-Filho, Fernando Russo Costa do Bomfim; Project administration: Gaspar de Jesus Lopes-Filho, Fernando Russo Costa do Bomfim

Use of Generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflicts of interest

All authors declared no conflict of interest.

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