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REVIEW ARTICLE

The low level laser therapy (LLLT) operating in 660 nm reduce gene expression of inflammatory mediators in the experimental model of collagenase-induced rat tendinitis

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Abstract Tendinopathy is a common disease with a variety of treatments and therapies. Laser therapy appears as an alternative treatment. Here, we investigate the effects of laser irradiation in an experimental model of tendinitis induced by collagenase injection on rats' Achilles tendon, verifying its action in important inflammatory markers. Male Wistar rats were used and divided into five groups: control saline (C), non-treated tendinitis (NT) and tendinitis treated with sodium diclofenac (D) or laser (1 J) and (3 J). The tendinitis was induced by collagenase (100 μg/tendon) on the Achilles tendon, which was removed for further analyses. The gene expression for COX-2; TNF-α; IL-6; and IL-10 (RT-PCR) was measured. The laser irradiation (660 nm, 100 mW, 3 J) used in the treatment of the tendinitis induced by collagenase in Achilles tendon in rats was effective in the reduction of important pro-inflammatory markers such as IL-6 and TNF-α, becoming a promising tool for the treatment of tendon diseases.

Keywords Tendinitis · LLLT · Laser therapy · Inflammation · Tendon · Rats

Introduction

Tendinopathies are musculoskeletal disorders, which modify the tendon health, attaining a substantial portion of the population in developed countries, mainly people above 50 years old, athletes or computer overusing, and increasing the tendon injuries in both athletic and occupational settings [1–3]. This fact results in a significant increase of resources expended by

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the employer relating to the sick leave and the need for relocation and qualifying new employees [4].

The high incidence of tendon diseases has become a social problem wherein medical therapies and interventions for rehabilitation are limited [5]. Therefore, its prevention, the identification of associated causes, and also the promotion of safe return for working activities became the subject of several studies in public health [6].

There are a number of etiologic factors that can be attributed as tendinitis inductors. The most common cause is the overexertion of tendons extension promoting distension of collagen fibers leading to partial ruptures, developing an intense and painful inflammatory reaction [7]. The cyclooxygenase II (COX-2), for example, is an integral enzyme which is induced during this inflammatory process influencing the formation of important inflammatory cytokines, including the interleukins (IL-1, IL-6, and IL-10) and tumor necrosis factor (TNF-α). These cytokines have a major role in the modulation of tendon inflammation [8]. IL-6, e.g., is a cytokine with a central role in inflammation after injurious processes [9]. In acute inflammation of tendon, it is commonly observed a significant increase of both granulocytes and neutrophil in synovial sheath, usually triggered by increasing IL-1 and IL-6. The presence of these cytokines is directly related to the progression of tendinitis in a painful process after tendon rupture [10–12].

In contrast, IL-10 is known for its anti-inflammatory activity. IL-10 inhibits both the expression of the interleukins (IL-6 and IL-8) and the migration of inflammatory cells at the lesion site including macrophages and monocytes [13, 14].

TNF-α is a pleiotropic cytokine related to cell survival and proliferation but also to cell death in the apoptotic process expressed by tenocytes in inflammatory conditions [15]. TNF-α may be the key cytokine in the origin of several musculoskeletal diseases such as rheumatoid arthritis, osteoarthritis, and tendinitis [12]; however, its role in tendon disease has not been well determined. It is known that its expression is increased in tendons such as traumatic situations or after surgery where there is a harmful process [15, 16].

In this context, the treatment of tendinitis aims to reduce inflammation because its persistence can increase the pro-inflammatory mediators extending the inflammatory phases favoring the scar tissue outbreaks altering the characteristics of original tendon [17, 18].

The most common treatment is still conservative and recommended by most authors as the initial strategy. In this context, the nonsteroidal anti-inflammatory drugs (NSAIDs), even being a controversial treatment, are the commonest drugs used as part of initial treatment, especially in reducing pain [19, 20]. However, there are a few scientific evidences in order to support its use, paving the way for non-pharmacological therapeutic alternatives capable to reduce the inflammatory process in tendon tissue focusing on the control of wound healing process by modulating the levels of anti- and pro-inflammatory cytokines [8, 9, 13, 20, 21].

In recent years, several studies have been performed in different situations, leading laser therapy to be considered as a promising alternative therapy for numerous diseases, acting in the early stages of inflammation by inhibiting the onset of chemotactic factors altering the presence of anti- and pro-inflammatory mediators [22–25].

For instance, it was demonstrated that therapy with low-power laser 660 nm has important action in both proliferation tendineae when the migration of cells [26, 27]. Further work showed that the angiogenic effect of red laser in injured tendons can change the proportion of collagen I and III. This fact is important to mechanical properties of tendon, favoring tissue repair [28, 29]. In acute inflammatory process, laser therapy (660 nm) can reduce IL-6 modulated by IL-10 increase [8, 13]. However, it is important to notice that very few studies are addressed the molecular effects in gene expression over the lasers action in the acute inflammatory process, especially in tendons [30].

This work aims to study the effect of low level laser 660 nm, 100 mW in acute inflammation of tendon, investigating the changes in the expression of enzymes and inflammatory mediators such as COX-2, IL-6, IL-10, and TNF-α.

Material and methods

All of the experimental procedures were submitted and approved by the Ethical Committee of the University of Sao Paulo. Thirty male Wistar rats weighing 250±20 g were randomly divided and housed five per cage before the experimental procedure. Food and water were provided ad libitum throughout the experiment. Rats were anesthetized with xylazine and ketamine injection (90 and 10 mg/kg, respectively) before collagenase injection. All the necessary preoperative procedures were performed in order to prevent discomfort and to avoid any infection. Skin was surgically prepared and collagenase was injected in the right leg (100 μg/tendon) percutaneously into the Achilles tendon, approximately 2 mm proximal to the osteotendinous junction under anesthesia using a 30 G needle [23, 31]. The same volume of PBS without collagenase was injected using the same procedure in a control group (C). Thirty minutes after collagenase injection, one group (called D) was treated using sodium diclofenac (Voltaren injectable®; Novartis 2.5 mg/kg) injected in the gluteus muscle. Two other groups were treated by laser 1 h after collagenase injection. A single LLLT was performed with an infrared laser unit (Thera Lase, DMC, Brazil). The laser unit emitted a continuous optical radiation under a wavelength of 660 nm, with a power of 100 mW in a core spot size area of 0.028 cm^2. Laser irradiation was performed in skin contact at the site of collagenase injection with doses of 1 and

3 J, corresponding to irradiation times of 10 and 30 s, respectively. The laser energy doses were chosen according to the previous studies [23, 31]. The two groups were called L1J and L3J, for 1 and 3 J, respectively. The last group (called TEN) was not subjected to any treatment of tendinitis. Six animals of each group were sacrificed with an overdose of xylazine and ketamine injection (270 and 30 mg/kg, respectively), 2 h after tendinitis induction for biochemical analysis. After the removal of skin and connective tissue, Achilles tendons were dissected, frozen in liquid nitrogen, and stored at −80 °C for further analysis.

RNA isolation and real-time PCR analysis The Achilles tendons were dissected, frozen in liquid nitrogen, and stored at −80 °C. Total RNA was isolated in the Trizol reagent, according to the manufacturer's instruction. DNase I was employed to digest DNA in order to obtain RNA purification and the integrity of RNA was verified by agarose gel electrophoresis. Total RNA (2 μg) was used for first-strand cDNA synthesis (reverse transcriptase [RT]) using SuperScript II. In addition, RNaseOUT was also added to protect the RNA during this process. Three pooled RNA aliquots were routinely sham reverse transcribed (i.e., RT omitted) to insure the absence of DNA contaminants. Diluted RT samples (1:10) were submitted to real-time PCR amplification using Platinum Sybr QPCR Supermix-UDG and specific oligonucleotides for COX-2 (forward: AGATCAGAAGCGAGGACCTG; reverse: CCATCCTGGAAAAGTCGAAG), IL-6 (forward: TGACCCAACCACAAATGC; reverse: CGAGCTCTGA AACAAAGGAT), IL-10 (forward: CATGGGTGTTGG GAAGAGAA; reverse: GCTTTCGAGACTGGAAGT GG), and TNF-α (forward: GGTGATCGGTCCCAAC AAGGA; reverse: CACGCTGGCTCAGCCACT). Beta-actin was used as an internal control (forward: AAGATT TGGCACCACACTTTCTACA; reverse: CGGTGAGC AGCACAGGGT). The conditions for PCR were as follows: 50 °C for 2 min; 95 °C for 2 min, followed by 30 cycles of 95 °C for 15 s; 60 °C for 1 min; and 72 °C for 15 s. Ct values were recorded for each gene, and the results of genes of interest were normalized to results obtained with the internal control gene. ddCT were calculated and the results are expressed as fold increase. All oligonucleotides and reagents utilized in this protocol were purchased from Invitrogen Co.

Statistical analysis Data are expressed as mean and standard error (±) of the mean (SEM) and were analyzed using Student′s *t* test to evaluate the statistical significance of the null hypothesis versus CTL and/or TEN. All data were statistically evaluated by the analysis of variance (ANOVA), followed by the Tukey's test. Values with $P<0.05$ were considered to be statistically significant.

Results

Figure 1a shows the COX-2gene expression, 2 h after induction of tendinitis. We can observe that tendinitis (NT=6.64) and the other three groups (D=8.2, 1 J=5.83, and 3 J=4.88) presented a significant increase in COX-2 gene expression when compared to the control group (C=1.04) after tendinitis induction.

In Fig. 1b, we can observe the IL6 gene expression at 2 h after induction of tendinitis. We could observe that there was an increase in gene expression of IL-6 in tendinitis untreated group (NT=314) compared with the control group (C=10.25). Tendinitis groups treated with sodium diclofenac (D=900.92) and irradiated (1 J=691.92) failed to reduce the IL-6 expression, when compared with the control group, showing increased expression compared to NT group. However, the group irradiated with the energy of 3 J (3 J=170.61) presented a significant inhibition of IL6 gene expression (54 %) when compared to non-treated group.

Figure 1c shows the IL-10 gene expression, 2 h after induction of tendinitis in Achilles tendons of rats. We can observe the increase of IL-10 expression in all groups where the tendinitis was induced compared to control group. The group treated with sodium diclofenac (D=32.25) and the irradiated group (1 J=31.26) showed increased expression of the same gene, when compared with untreated group (NT=15.18).

Figure 1d shows the TNF-α gene expression, 2 h after tendinitis induction. We can observe that the untreated group showed a significant increase in TNF-α gene expression (NT=35.53) when compared to the control group (C=1.44). It was also observed that both groups treated with sodium diclofenac (D=29.98) and laser 1 J (1 J=32.18) failed to reduce the expression of TNF-α. Only the group treated with laser irradiation at the energy of 3 J (3 J=18.18) was able to significantly reduce the TNF-α expression when compared to NT group.

Discussion

Low-level laser therapy has been studied since the 1960s being considered as a therapeutic alternative with good perspectives for use especially in musculoskeletal and inflammatory disorders. In our study, we investigated the effects of low-level laser therapy on important inflammatory mediators, involved in acute inflammation of the tendon.

Recent studies have focused on the discovery of new therapies able to promote cytokines inhibition, such as IL-1β, TNF-α as well as metalloproteinases in tendon diseases [32]. Thus, tendinitis appears as the target of concern, both in the sports medicine and in labor.

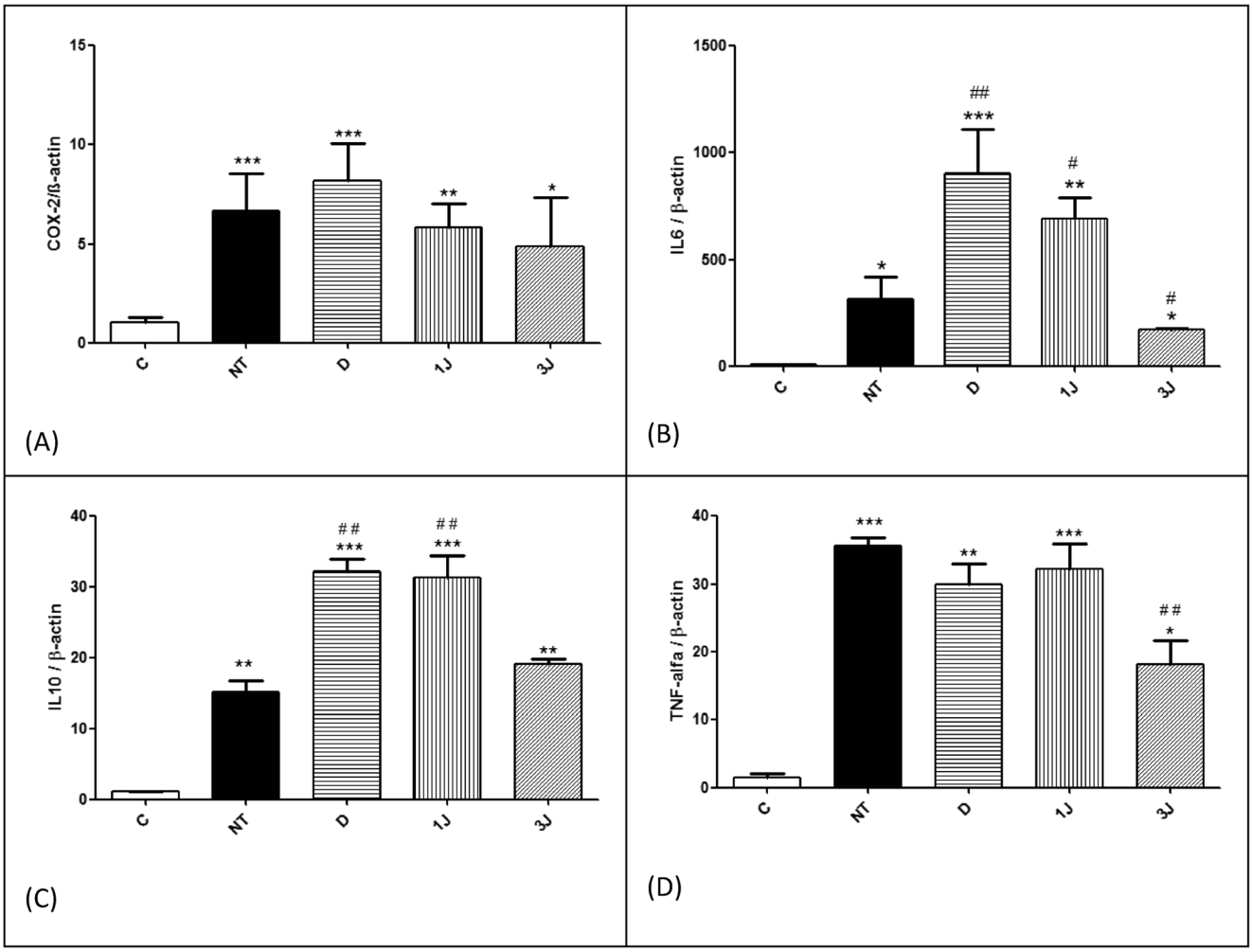

Fig. 1 mRNA gene expression of COX-2 (**a**), IL-6 (**b**), IL-10 (**c**), and TNF-α (**d**). The samples were collected 2 h after the collagenase-induced tendinitis. Groups, *C* Control; *NT* Tendinitis non-treated; *D* Treated with sodium diclofenac; and 1 J and 3 J are irradiated groups by laser 660 nm, 100 mW. The values are represented by the mean values and error bars are SDs, $n=6$ animals per group. *$p<0.05$; **$p<0.01$; and ***$p<0.001$ versus control. #$p<0.05$; ##$p<0.01$ versus NT (non-treated)

Here, we employed the nonsteroidal anti-inflammatory drug sodium diclofenac as a pharmacological reference therapy to be compared to laser irradiation in tendon inflammation induced by collagenase. The experimental model used was the tendinitis induced in Achilles tendon of rats by collagenase injection. This experimental model of tendon inflammation is well known in the study of tendinitis in which edema and acute destruction of the extracellular matrix are similar to those found in natural tendon injury, being considered an excellent model, which allows to investigate molecular and histological changes [33].

The development of inflammation during the injury is a beneficial event that aims to restore tissue homeostasis. In this process, the formation of chemical mediators with pro- or anti-inflammatory action is produced from cyclooxygenase pathways that also increase in inflammatory processes.

In tendinitis model, due to low vascularity or to transitions between tendinitis and tendinosis periods, this tissue has not always inflammatory infiltrate. However, COX-2 increase was observed in both cases which indicate in some extent, tissue degeneration as a result of the inflammatory process [34].

Previous study from our group was the first to determine the time course of COX-2 gene expression and the peak time after 2 h of tendinitis induction [23]. From these data, we choose the period of 2 h, the same used previously, to study the effects of laser irradiation, this time operating in 660 nm, in the experimental model of collagenase-induced rat tendinitis.

In the present study, it was observed that COX-2 gene expression increased in non-treated group (NT). In the same way, non-treated group presented significant increases in the other pro-inflammatory cytokines, IL-6, and TNF-α.

The treated group with sodium diclofenac (D) also presented increase in COX-2 and TNF-α expression, similar to NT group and more IL-6 expression compare to NT. On the other

hand, the irradiated groups, especially 3 J, showed a slight decrease in COX-2 (26 %), IL-6 (45 %), and TNF-α (48 %) compared to NT.

Cyclooxygenase-2 increased can directly interfere in the formation of specific inflammatory mediators, such as interleukins and tumor necrosis factor, by changing the tissue repair process. TNF-α is another factor that can modulate this process. Their levels are generally increased in the presence of musculoskeletal diseases like tendinitis and could be important in degenerative process of the tissue by inducing an increase in inflammatory cells [12]. Thus, the increase of TNF-α gene expression after tendinitis induced may represent an increase in the inflammatory process triggering other important inflammatory mediators, such as matrix metalloproteinases [33, 35].

Changes in tendon repair can lead to scar formation with different characteristics of the original tissue. The scar initially provides the physical continuity of the tissue, but the proliferation of adjacent tissue can be undesirable and hinder the sliding mechanism tendon [8]. One way to reduce these changes would be control the healing process, modulating the inflammation by cytokines levels, involved in the repair, such as IL-6, IL-10, and TNF-α, observed in this work and associated with disease progression. IL-10, for instance, has functional activities such as suppression of pro-inflammatory events by inhibition of inflammatory cytokines such as IL-1, IL-6, and TNF-α and also inhibits some MMPs that could hamper tissue repair [9].

In this work, the expressions of pro-inflammatory cytokines (IL-6 and TNF-α) were increased not only in the NT group, but also in diclofenac group (D) and even in the irradiated group (1 J). Only the irradiated group (3 J) was able to reduce the expression of these pro-inflammatory cytokines. On the other hand, the expression of anti-inflammatory cytokines (IL-10) was increased in all groups where tendinitis was induced, probably a natural action of the body to reduce inflammation, but in the treated groups D, 1 J, and 3 J, this increase was even higher.

It is well known that the IL-10, along with other cytokines, shares many functional activities, such as the suppression of pro-inflammatory events. Thus, IL-10 may inhibit inflammation by the inhibition of IL-1, IL-6, and TNF-α. [8]. Opposite, in tendinopathies, was observed in IL-10 reduction [36]. Several studies show the importance of balance between pro-inflammatory (IL-6) and anti-inflammatory (IL-10) cytokines, in the control of inflammatory process [37–39]. For instance, Tnf-α strongly activates the expression of other cytokines like IL6 and IL-10. However, the role of IL6 and IL-10 still remains unclear [40].

Thus, the relationship between the amounts of IL-6 and IL-10 show a positive anti-inflammatory response, mainly in the irradiated group 3 J.

These results together suggest that in the non-treated group (NT) the inflammation remained high and probably the highest level of tissue injury, on account of increase of TNF-α to be associated with increased of matrix metalloproteinase enzymes.

Previous results demonstrated that treatment with sodium diclofenac reduces prostaglandin E2 synthesis and NK1 neuropeptides expression, receptors likely to pain [41]. However, our results showed that sodium diclofenac treatment failed to reduce the expression of cytokines (IL6 and TNF-α). Diclofenac treatment failure may be related to specific tendon characteristics that are poorly vascularized.

The sum of these factors is a strong indication that low level laser therapy in 660 nm, 100 mW, and 3 J can be effective in reducing the acute inflammatory process induced by collagenase in Achilles tendons of rats. However, further analysis is needed to determine this laser modulation operating in 660 nm on matrix metalloproteinases in tendon tissues during the inflammatory process. The investigation of biochemical factors as protein expression of inflammatory mediators, enzyme dosage, and morphological and functional factors such as histological and mechanical properties analyzes are important to understanding of this inflammatory event and the action mechanism involved at cellular and structural changes in tendinitis.

Conclusion

We can conclude that the model of tendinitis by collagenase-induced in rats increased the expression of COX-2, IL-6, IL-10, and TNF-α. Treatment with sodium diclofenac and laser 1 J was not effective in reducing inflammatory mediators. The low level laser therapy (660 nm, 100 mW) at 3 J of energy was effective in reducing the inflammation in this model.

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