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Low-Level Laser Therapy for Rheumatoid Arthritis: A Review of Experimental Approaches

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Abstract

Introduction: Rheumatoid arthritis (RA) is an inflammatory and autoimmune disorder that is characterized by joint inflammation, pain, physical disability, and morning stiffness. In the present study, the effect of low-level laser therapy (LLLT) on RA was reviewed.

Methods: "Low-level laser therapy", "rheumatoid arthritis disease", and "photobiomodulation" keywords were searched in Google Scholar, PubMed, and Medline.

Results: A literature survey led to a discussion about the immunology of the RA, laser therapy, mechanism of LLLT action, and anti-inflammatory and immunomodulatory properties of LLLT.

Conclusion: It was concluded that LLLT could improve RA patients' quality of life, reduce pain, and enhance physical movement.

Keywords: Low-level laser therapy; Photobiomodulation; Rheumatoid arthritis; Autoimmune disease; Inflammation.

Introduction

Rheumatoid arthritis (RA) is one of the common chronic autoimmune diseases with unknown etiology that involve joints. RA has become a major challenge for public health due to cartilage and bone damage, functional disability, socioeconomic high costs, and early death in patients. Multiple genetic variants and environmental factors are involved in RA.[1,2] Human leukocyte antigen (HLA)–DRB1 locus is identified in patients with RA and has a strong association with the disease. Smoking, lifestyle, and viral infections also play a role in gene-environment interactions in RA disease.[3]

RA is characterized by joint inflammation and swelling, synovial inflammation, autoantibody production, joint and bone deformity, and functional disability.[3] RA also represents pulmonary, cardiovascular and skeletal manifestations.[1] Immune responses play a crucial role in the pathogenesis of RA. Innate and adaptive immune cells along with the presence of the auto-antibodies cause joint inflammation.[4] Inflammatory immune cells including dendritic cells, macrophages, lymphocyte subsets (especially TH17 cells), and B cells infiltrate into the synovial structure and cause more inflammation and tissue destruction.[5]

Cytokines and chemokines also play a major role in the inflammation process and inflammation. Tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), interleukin 17 (IL-17), interleukin 22 (IL-22), and granulocyte-monocyte colony-stimulating factor (GM-CSF) are present in the inflamed synovial tissue. Immune cells beside the inflammatory cytokines induce osteoclastogenesis which causes intensive chondrocyte catabolism and joint destruction.[6]

Current treatment strategies have focused on inducing remission, inhibiting joint and bone destruction, and increasing the quality of life of the patients.[7] Conventional treatments include non-steroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying anti-rheumatic drugs such as methotrexate, Janus kinase (JAK) inhibitors or TNF-α inhibitors.[8,9]

Low-level laser therapy (LLLT) is a safe, simple, and non-invasive treatment approach that has been considered an adjuvant therapy for various diseases including multiple sclerosis, autoimmune thyroiditis, join disorders, wound healing, Alzheimer's disease, and also RA due to its photobiomodulating effects, pain

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reduction and direct interference with inflammatory responses.[10,11] LLLT also has regenerative properties and could stimulate tissue repair by involving various cellular and molecular mechanisms such as adenosine triphosphate (ATP) production, nitric oxide formation, and oxidative stress modulation.[11,12]

In the present review, we discussed the effect of LLLT as an adjuvant treatment on joint disorder and RA in order to improve the quality of life of RA patients.

Methods

To find the relative sources, we performed a comprehensive search in Google Scholar, PubMed, and Medline databases, with keywords "low-level laser therapy", "rheumatoid arthritis disease", and "photobiomodulation" in the English language. After screening the explored titles, we determined and studied the comprehensive abstracts. Finally, 71 articles were used to construct the review structure.

Results

Immunology of Rheumatoid Arthritis

As mentioned before, RA is a chronic and progressive disorder that involves articular and extra-articular regions.[13] RA causes severe cartilage damage and destruction, extensive physical disability, and a decrease in patients' quality of life. Various complex cellular and molecular mechanisms are associated with the disease pathogenesis. However, inflammation and immune responses play a major role in the pathogenesis of RA.[14]

Immune responses are triggered with either autologous or exogenous antigens. Antigen-presenting cells such as dendritic cells, macrophages secret inflammatory cytokines (TNF-α, IL-6, IL-1, IL-12). These cells activating adaptive immune system through the proliferation of the effector T cells.[6,15,16] TH1 and TH17 cells are the most T cell clones which are involved in the interferon-γ, IL-17 and IL-22 cytokine production.[17,18] B cells also play an important part in the pathogenesis of RA through rheumatoid factor and anti-cyclic citrullinated peptide autoantibodies production[19,20] (Figure 1).

Production of the inflammatory cytokines leads to RANK ligand (RANK-L) activation.[21] RANK-L activation results in osteoclast formation which is the main mediator of joint damage and destruction.[22,23]

Laser Therapy

Light amplification by the stimulated emission of the radiation (Laser) beam is a visible monochromatic light which has a distinctive wavelength and is a source of light energy.[24] According to the various therapeutic approaches, different types of lasers have been used, including the carbon dioxide laser, erbium laser, and diode laser.[25] The intensiveness of the energy of the laser beam is enough to induce several cellular and molecular processes.[26] Laser photons are absorbed into the cells and target cellular organelles, and they stimulate biological events. Interestingly, a low wavelength leads to the highest photon absorption.[27]

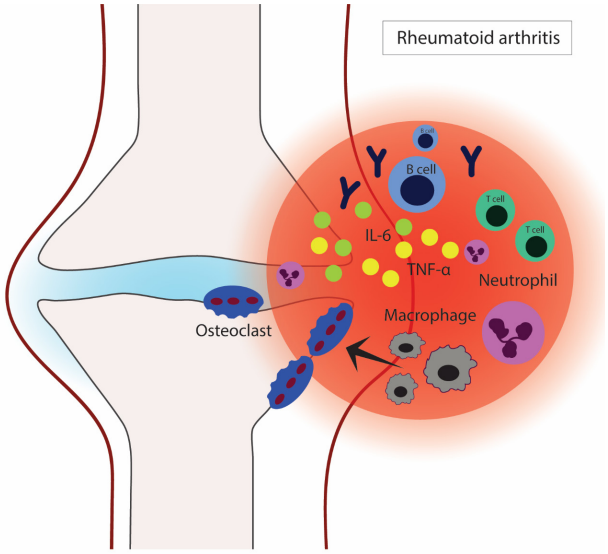

Figure 1. Immunopathogenesis of Rheumatoid Arthritis. Inflammatory responses and immune cell functions lead to osteoclast activation and joint destruction

Low-intensity lasers are a kind of laser device which affects the cellular mechanisms in a non-thermal and non-invasive manner.[28] LLLT must include some criteria such as: wavelength range (300-10 600 nm), 0.001- 0.1 W power output, and 0.01-10 W/cm^2 intensity.[29] At the power of 3–8 J/cm^2 laser photons could strongly penetrate into different tissues and modulate various mechanisms including tissue repair and regeneration.[30,31]

Recently, LLLT, also known as photobiomodulation, has gained lots of attention as an adjuvant treatment in clinical studies such as pain reduction, dentistry, surgery, and physical medicine.[32,33] LLLT has also been applied as a therapeutic approach in the treatment of inflammatory and autoimmune disorders such as multiple sclerosis (MS), RA, stroke, bone fractions, and autoimmune thyroiditis.[34-38]

LLLT Mechanism of Action

LLLT photons are absorbed in the cells through the mitochondria organelle. Mitochondria cytochromes use these photons in order to synthesize ATP. ATP production as the main source of cell energy induces cellular events such as DNA synthesis and replication, cell proliferation, cell differentiation, and protein synthesis.[30]

Moreover, LLLT regulates cell metabolism through the induction of two key players of the respiratory chain, NADH-dehydrogenase and cytochrome c oxidase. As a result, cell growth is stimulated.[39]

Studies showed that LLLT regulated the cell cycle, cell proliferation and apoptosis. In this regard, LLLT

induced cell proliferation and inhibited cell apoptosis by modifying gene expression.[40,41] LLLT could dampen the BCL2-Associated X protein (BAX) pro-apoptotic gene and stimulate e B-cell lymphoma 2 (Bcl-2) which is an anti-apoptotic gene.[42]

Studies indicated that LLLT induced tissue remodeling and regeneration. It could increase fibroblast, endothelial and keratinocytes growth, and it enhanced collagen release which is important for the wound healing process.[28] LLLT could also stimulate angiogenesis, and it improved blood flow in the tissue. In this manner, LLLT decreased acidosis and caused pain relief.[28]

Anti-inflammatory and Immunomodulatory Properties of LLLT

LLLT could modulate inflammation in cells and tissues. Studies indicated that LLLT had anti-inflammatory effects similar to nonsteroidal anti-inflammatory drugs.[43] In injured and inflamed tissue, LLLT suppressed the arachidonic acid cascade which led to the inhibition of prostaglandin E2 (PGE2) production. LLLT also inhibited cyclooxygenase 2 mRNA expression and production.[44]

LLLT could increase reactive oxygen species (ROS) in normal cells; however, it acts vice versa in inflammatory situations and inhibits ROS production and oxidative stress in injured cells. It also decreases H2O2 production and superoxide dismutase.[45]

It was shown that LLLT inhibited the expression of a variety of inflammatory cytokines and chemokines that play a crucial role in the inflammatory process and cause tissue damage. LLLT suppressed IL-1, IL-6, TNF-α, and IL-18 cytokines.[44,46] Photobiomodulation also reduced the chemokines like CXCL11 and RANTES. LLLT inhibited nuclear factor kappa B (NF-κB) transcription factor as a major inflammatory signaling pathway.[47] On the other hand, LLLT induced IL-10 anti-inflammatory cytokine expression.[48]

Studies showed that LLLT could decrease immune cell infiltration into the injured site.[49] It was shown that neutrophil infiltration significantly decreased after LLLT in animal models. LLLT also inhibited macrophage migration in the inflamed joint. LLLT also affected the mast cell which is an important inflammatory mediator and causes pain. LLLT inhibited mast cell degranulation and decreased histamine release.[50]

LLLT could alter the phenotype and characteristics of the monocytes and macrophages. LLLT induced anti-inflammatory M2 macrophages. Low-level laser irradiation increases the expression of the M2 macrophage markers such as CD206 and TIMP1.[51,52]

Effects of LLLT on Joint Disorders and RA

LLLT has great potential as a therapeutic approach in joint disorders including osteoarthritis (OA) and RA. Studies indicated that LLLT inhibited the expression of inflammatory cytokines and mediators in OA patients. Animal studies indicated that LLLT decreased IL-1β and IL-6 mRNA expression in the articular synovial lavage of the OA animal models.[53] Synovial joints of the treated animals showed less immune cell infiltration, such as neutrophils and macrophages, and fewer morphological changes compared to the untreated group. It was supposed that LLLT was a useful treatment modality for the synovitis associated with OA[54] (Table 1).

Other studies showed that photobiomodulation had a great impact on decreasing knee joint swelling and PGE2 expression inhibition. In higher doses of LLLT, vascular extravasation markedly decreased.[37] It was also demonstrated that LLLT irradiation on the joint capsule had beneficial effects on reducing pain and improved the quality of life of the patients with chronic joint disorders.[55] A clinical trial on 61 patients with temporomandibular joint disorders treated with LLLT showed that this approach could significantly reduce the chronic pain of the patients and was a useful treatment modality.[56,57]

Besides the anti-inflammatory effects of LLLT, low-level laser irradiation stimulates joint repairment.[58] LLLT induced fibroblast proliferation and caused new blood vessel generation which is providing oxygen and nutrients for the tissue healing process.[59,60] A study indicated that laser irradiation had chondrocyte protective effects on the knee joints in rat models. LLLT improved knee tissue structures and increased the number of chondrocytes. Laser irradiation also decreased the expression of caspase-3 and matrix metalloproteinase (MMP-13) and IL-1 cytokine in the experimental animal groups.[61]

An investigation into an RA animal model showed that laser irradiation (wavelength of 780 nm and power output of 22 mW) had anti-inflammatory effects and could inhibit lymphocyte infiltration into the injured sites. Histological findings showed that treated groups had less exudate than control groups. Interestingly, tissue necrosis decreased in the treated groups and the levels of tissue necrosis were reduced significantly in the early-treated animal groups compared to the late-treated groups.[62] Other studies also indicated that LLLT reduced joint edema and joint disability.[63]

Meta-analysis on clinical trial investigations into RA patients demonstrated that LLLT in wavelengths from 632 nm to 1064 nm had significantly beneficial effects on pain reduction and could improve joint flexibility compared to the control groups. LLLT also improved the morning stiffness of RA patients.[64]

An LLLT study on the hands of 82 RA patients showed that laser irradiation (wavelength of 785 nm, dose of 3 J/cm^2, and power of 70 mW) improved the quality of life of the treated patients. Hand function improved in the RA patients and they experienced less pain than placebo groups. However, there were no differences in morning stiffness in the treated and controlled groups.[65]

Table 1. The Beneficial Effects of LLLT on Rheumatoid Arthritis and Osteoarthritis

Study	Groups	Duration	Results
RA animal model	1) Treated groups with different wavelengths (λ=635, 785, 808 and 905 nm) 2) Control group	15 min	Fewer inflammatory cells in the synovial joints of mice irradiated with 635 nm
Rat RA animal model	1) Control group 2) Inflammation control group 3) 50-mW LLLT group 4) 100-mW LLLT group	24 hours	The 50-mW laser was more efficient than 100 mW in reducing cellular inflammation and decreased the expression of IL-1β and IL-6.
Patients with temporomandibular joint disorders	1) 61 patients treated with 10 J/cm² or 15 J/cm², 2) control group of 19 patients	10 sessions in 1 month	10 J/cm² or 15 J/cm² was more effective in reducing pain
experimental model of osteoarthritis	1) Group 1 was treated with (660 nm, 100 mW) 2) Group2 was treated with (808 nm, 100 mW)	40 seconds in 14 days	wavelength of 808 nm stimulated angiogenesis and reduced the formation of fibrosis
RA induced animal model	1) Control group 2) RA induction group 3) Treated group in early RA stage 4) Treated group in late RA stage	Once per day in 14 days	LLLT modulated inflammatory response in the early and late stages of RA
82 RA patients	1) Placebo group 2) Experimental group (785 nm, dose of 3 J/cm²)	twice a week for a period of 2 months (16 sessions)	Improvement in pain in both hands
100 patients with knee arthritis	1) Standard physical therapy 2) LLLT treatment (810-nm wavelength)	3 sessions of treatment per week for 12 weeks	Patients clearly benefited from LLLT treatment (reducing pain)

Six trials on RA patients showed that LLLT caused physical rehabilitation and helped the patients to exercise with less pain. LLLT also enhanced morning stiffness in 32 patients. However, it was reported that the beneficial effects of the LLLT were maintained for a short time (about 3 months).[66]

Interestingly, a clinical trial with a 6-year follow-up on 100 patients indicated that LLLT plus conventional treatment could delay joint replacement surgery compared with the control group. This study showed that LLLT could be used in combination with current treatments for RA patients[67] (Figure 2).

Taken together, although it was proved that LLLT had beneficial effects on joint disorders and RA, some studies reported less significant effects of LLLT on morning stiffness, joint tenderness, and joint pain. It seems that the irradiation protocol, sample collection, and disease stage influenced the effectiveness of LLLT.[68]

Discussion

LLLT has many beneficial properties including simple use, being a non-invasive and non-thermal approach, and having no or fewer side effects compared to the pharmacological treatment approaches. Investigations showed that LLLT could be a therapeutic approach for RA patients. However, we should consider LLLT as an alternative and complementary therapy.[69,70]

Since LLLT has dose-dependent anti-inflammatory effects, more LLLT investigations are needed to explore the exact mechanisms of action, dose and irradiation protocols in different clinical situations. In this regard, more clinical implications should be considered in order to obtain precise, valid and quantitative data.[48,50] Due to variations in laser sources, radiation patterns, and dose response of patients, it seems that laser application in medicine has opened a new window which will provide a hopeful opinion to treat different types of diseases in the near future. It is also important to unify treatment protocols for different diseases based on rational parameters.[71]

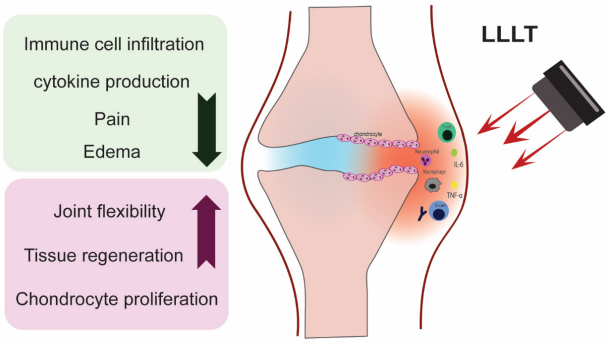

Figure 2. The Effect of LLLT on Rheumatoid Arthritis. LLLT causes tissue regeneration and reduces inflammatory responses

Conclusion

Evidences revealed that LLLT is a suitable method for treating RA and can be considered a potential method with higher efficacy and capacity to progress.

Conflict of Interests

The authors declared no conflict of interest.

Ethical Considerations

Not applicable.

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