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Low-level laser therapy as a supporting resource in the treatment of rheumatoid arthritis – integrative review

La terapia con láser de baja potencia como recurso de apoyo en el tratamiento de la artritis reumatoide – revisión integrativa
A terapia com laser de baixa potência como recurso coadjuvante no tratamento da artrite reumatóide – revisão integrativa

ABSTRACT

Objective: To analyze the evidence of low-level laser treatment applied to patients with rheumatoid arthritis. **Methods:** This study is an integrative literature review using scientific articles indexed in the Pubmed and Virtual Health Library (VHL) databases through descriptors related to rheumatoid arthritis and low-level laser, according to the health descriptors. The screening was carried out in July 2020. **Results:** The articles obtained were published between the years 2010 to 2020, 266 articles were found, after the exclusion of articles that did not meet the inclusion criteria and four duplicates were selected. Low-level laser therapy was considered a viable and promising therapeutic resource for patients with rheumatoid arthritis. Due to the small number of publications on the subject, the need for more research directed to the applicability of laser in rheumatic diseases is notable.

DESCRIPTORS: Laser biostimulation; Rheumatoid arthritis; Low power laser; Low intensity light therapy.

RESUMEN

Objetivo: Analizar la evidencia del tratamiento con láser de baja intensidad aplicado a pacientes con artritis reumatoide. **Métodos:** Este estudio es una revisión integradora de la literatura utilizando artículos científicos indexados en las bases de datos de Pubmed y Biblioteca Virtual en Salud (BVS) a través de descriptores relacionados con la artritis reumatoide y láser de baja intensidad, según los descriptores de salud. El cribado se realizó en julio de 2020. **Resultados:** Los artículos obtenidos fueron publicados entre los años 2010 a 2020, se encontraron 266 artículos, luego de la exclusión de los artículos que no cumplieron con los criterios de inclusión y se seleccionaron cuatro duplicados. La terapia con láser de baja intensidad se consideró un recurso terapéutico viable y prometedor para los pacientes con artritis reumatoide. Debido al escaso número de publicaciones sobre el tema, es notable la necesidad de más investigación dirigida a la aplicabilidad del láser en enfermedades reumáticas.

DESCRIPTORES: Bioestimulación láser; Artritis reumatoide; Láser de baja potencia; Terapia de luz de baja intensidad.

RESUMO

Objetivo: Analisar as evidências do tratamento com laser de baixa potência aplicada em pacientes com artrite reumatoide. **Métodos:** Este estudo trata-se de uma revisão integrativa da literatura utilizando artigos científicos indexados nas bases de dados Pubmed e Biblioteca Virtual de Saúde (BVS) através de descritores relacionados a artrite reumatoide e laser de baixa potência, de acordo com os descritores em saúde. O rastreamento foi realizado em julho de 2020. **Resultados:** Os artigos obtidos foram publicados entre os anos 2010 à 2020, foram encontrados 266 artigos, após exclusão dos artigos que não se classificavam aos critérios de inclusão e os duplicados foram selecionados quatro. Constatou-se que a terapia com laser de baixa potência é um recurso terapêutico viável e promissor para os pacientes com artrite reumatoide. Em função do baixo número de publicações sobre o assunto, é notável a necessidade de mais pesquisas direcionadas à aplicabilidade do laser nas doenças reumáticas.

DESCRIPTORES: Bioestimulação a Laser; Artrite Reumatoide; Laser de baixa potência; Terapia com Luz de Baixa Intensidade.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive, systemic and widely prevalent autoimmune disease. This clinical condition is associated with high pain levels, functional impairment, and psycho-emotional disorders that affect quality of life and can lead to disability and possible withdrawal from work activities.^{1,2} In view of the western demographic growth of individuals over 60 years of age, in approximately 30% of cases, the morbidity, mortality and disability associated with RA will increase.¹

Basically, RA affects joints in a generalized, symmetrical way, but it is characterized by a persistent inflammatory process in the synovial membranes, mainly affecting the diarthrodial joints, that is, synovial joints. These are mobile joints, formed by hyaline cartilage, at the meeting of two bones with synovial fluid (water with proteoglycans, glycosaminoglycans similar to plasma) maintained by a synovial membrane formed by fibrocartilage.³

One of the pathogenic mechanisms involved in progressive and uncontrolled immune inflammation of the synovial membrane on hinges is the imbalance between the synthesis of pro-inflammatory and anti-inflammatory cytokines, with the former predominating over the latter.⁴

This process is associated with the

migration of activated phagocytes and leukocytes to synovial and periarticular tissue.⁵ During phagocytosis, activated neutrophils and macrophages generate reactive oxygen species, destruction of lipids, proteins, hyaluronic acid (important glycosaminoglycan in the constitution of the joint) and cartilage.⁶ The destruction of lipids produces peroxidation, which was shown to be elevated in the plasma and synovial fluid of these patients; in addition to compromising the antioxidant defense systems, in favor of lipid peroxidation, causing tissue damage.⁷

Reactive nitrogen species also play a role in phagocyte-mediated oxidative reactions at sites of inflammation.⁸ They include nitric oxide, peroxy-nitrite, nitrite and nitrate. A previous study showed increased serum levels of nitric oxide in patients with RA.⁹

Of unknown etiology, RA is characterized by joint inflammation and the formation of an inflammatory and invasive tissue known as rheumatoid pannus, which eventually leads to joint destruction.¹⁰ Cytokines and other proinflammatory mediators, such as tumor necrosis factor (TNF- α), IL - 1 β and IL - 6, play important roles in inflammation and in the progressive degeneration of articular cartilage and bone.^{11,12} Persistent damage will inevitably result in disability, as most joint damage is irreversible.^{13,14}

The cytokine found in the rheumatoid synovium in the largest quantity is IL - 6. In response to acute and chronic inflammatory conditions in this rheumatologic pathology, IL-6 is responsible for stimulating hepatocytes to synthesize and secrete acute phase proteins, such as C-reactive protein (CRP) and fibrinogen. In previous studies, CRP was elevated compared to the control group, as well as the erythrocyte sedimentation rate (ESR) in the presence of fibrinogen, both in the acute phase and in patients with RA.^{15,16}

The treatment of RA aims to prevent joint deformities and their func-

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tionality, delay disease progression, and minimize symptoms.¹⁷ Non-steroidal anti-inflammatory drugs (NSAIDs) are the most prescribed for arthralgias, edema, and morning stiffness, but the triggering of gastrointestinal ulcers and kidney morbidities are some of their well-established adverse effects.¹⁶

Methotrexate is the first-line antirheumatic drug aimed at inhibiting disease activity or remission.¹⁸ In contrast, toxicity prevents many patients from reaping its benefits. In recent research, it has been reported that subtle toxicity occurs in approximately 60% of patients, and approximately 7% to 30% of patients discontinued methotrexate therapy within the first year of treatment.^{19,20} Toxicities caused by drugs greatly affect the therapeutic outcomes of these patients, and can be a challenge for the elderly.³

Quality of life (QL) is an integral feature of the patient's physical, psychological, emotional and social functioning, based on their subjective perception.¹ The objectives expected by modern therapies and rehabilitation of this public are analgesia, prevention and return of function of compromised joints and maintaining the capacity for self-care.⁸

QoL in elderly patients can be optimized with complementary and alternative medicine (CAM). The use of CAM has increased in conventional healthcare settings, for fear of adverse drug effects and the desire for symptom relief. However, many CAM modalities lack scientific evidence to support their efficacy and safety.²⁰

Laser acupuncture treatment has become widely accepted and is now offered as a powerful and effective therapy. Photobiomodulation applied to acupoints generates a physiological effect at the cellular level, triggering analgesia, modulation of the inflammatory process and oxidative stress, activation of angiogenesis, and improvement in tissue repair.^{21,22,23,24,25} Although the current literature shows positive effects in favor of laser therapy in the treatment of various types of joint inflammation, few authors have investigated the use of laser in the treatment of RA.^{24,25,26,27}

Another study reports that patients with RA have high plasma levels of leptin, which suggests an active inflammatory process, as leptin can act as a pro-inflammatory cytokine. In this same study, it is demonstrated that low-intensity intravenous laser

therapy can normalize plasma leptin levels and bring quality of life to these patients.³

The aim of the present study was to survey articles published in the last 10 years and demonstrate the clinical results of low-power lasers applied to patients with rheumatoid arthritis.

METHOD

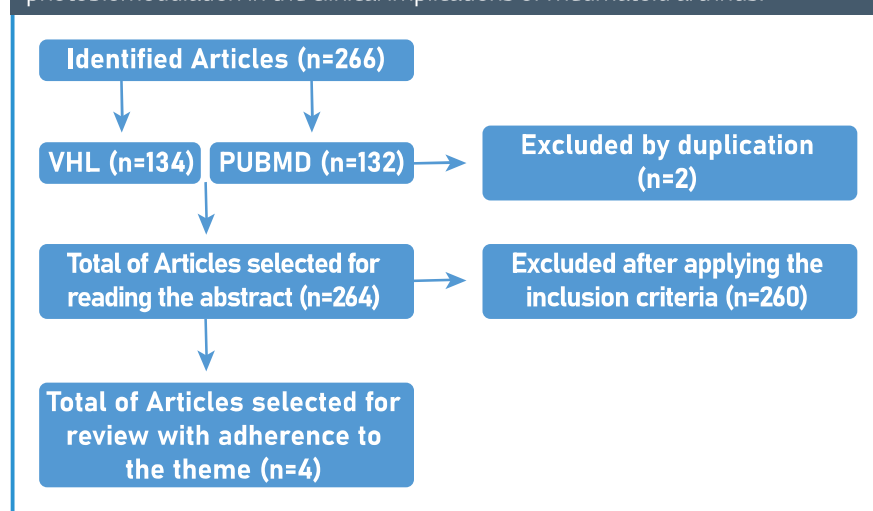
The present study is an integrative review. The steps of this research were: sampling, classification of studies, definition of selected information from publications of the results of this work. Data collection was carried out in July 2020, in the Virtual Health Library and Pubmed databases. The descriptors used, in an orderly manner, were: Photobiomodulation; photobiomodulation therapy; "low-level light therapy" OR "low-level laser therapy" OR "laser therapy" OR LLLT) AND rheumatoid arthritis, based on the Desc query and interconnected by the Boolean operators 'AND' and 'OR'.

The inclusion criteria adopted were as follows: articles published in the last ten years, controlled, randomized, double-blind, carried out on human beings, in Portuguese, English, Spanish and Russian, whose titles and/or abstracts were related to the theme of this research, with open access, available in full.

Exclusion criteria were all studies that do not meet the inclusion criteria, duplicate publications, and research that does not meet the objective of this review.

The tracking was carried out on July 4th, 2020 and 266 articles were found, 134 articles from the VHL and 132 from Pubmed, however, after filtering these databases, six articles remained in the VHL and five in Pubmed, with two in duplicate and five that did not correspond to the guiding theme of the study on screen in the title and/or abstract, totaling four articles for the construction of this review.

Figure 1. Explanatory flowchart of the selection of articles on photobiomodulation in the clinical implications of rheumatoid arthritis.



Source: the author.

RESULTS

The contents extracted from the selected articles were organized in the spreadsheet below:

DISCUSSION

RA is the most frequent and most serious disease that dominates the rheu-

matologic practice. Adly et al claim that the prevalence increases with age, and that RA-associated morbidity, mortality and disability is likely to increase among the elderly in the future, as in the West the number of individuals over 60 years of age is increasing and around 30% of RA cases occur in this age group.¹

The treatment of RA is aimed at inhibiting disease activity and promo-

ting its remission through the use of disease-modifying antirheumatic drugs such as methotrexate.¹ The anti-inflammatory drugs most frequently used in RA are non-steroids (NSAIDs), which with their chronic use lead to side effects such as gastrointestinal ulcers and renal morbidity.^{1,20}

We investigated the use of PBM as an adjunctive treatment in RA and ob-

Table 1: Characteristics of the studies included in the study. Rio de Janeiro, 2020.

DATA BASE	COUNTRY OF ORIGIN	TITLE	KIND OF STUDY	AUTHORS	JOURNALS AND YEAR OF PUBLICATION
VHL e PUBMED	England	Laser acupuncture versus reflexology therapy in elderly with rheumatoid arthritis.	Clinical Trial	Adly, Afnan Sedky; Adly, Aya Sedky; Adly, Mahmoud Sedky; Serry, Zahra M H	Laser in medical Science / 2017
VHL	Brazil	Assessment of the effectiveness of low-level laser therapy on the hands of patients with rheumatoid arthritis: a randomized double-blind controlled trial.	Clinical Trial	Meireles, Sandra Mara; Jones, Anamaria; Jennings, Fábio; Suda, Alina Lica; Parizotto, Nivaldo Antônio; Natour, Jamil.	Clinical Rheumatology/2010
VHL	Russia	The influence of intravenous laser irradiation of the blood on the dynamics of leptin levels and the quality of life of the patients presenting with rheumatoid arthritis.	Clinical Trial	Starodubtseva, I A; Vasilieva, L V; Nikitin, A V	Vopr Kurortol Fizioter Lech Fiz Kult / 2015
VHL and PUBMED	Egypt	Therapeutic antioxidant and anti-inflammatory effects of laser acupuncture on patients with rheumatoid arthritis.	Clinical Trial	Attia, Atef M M; Ibrahim, Fatma A A; Abd El-Latif, Noha A; Aziz, Samir W; Elwan, Azhar M; Abdel Aziz, Abdel Aziz A; Elgendy, Aliaa; Elgengehy, Fatema T.	Lasers in Surgery and Medicine / 2016

Source: the author.

Table 2: Main experiences and results of the articles found. Rio de Janeiro 2020.

ARTICLE TITLE	EXPERIENCES	MAIN RESULTS
Laser acupuncture versus reflexology therapy in elderly with rheumatoid arthritis.	To determine and compare the effectiveness of laser acupuncture versus reflexology in elderly people with rheumatoid arthritis. In laser acupuncture therapy, the following application parameters were used: 904 nm, beam area of 1 cm (2), power 100 mW, power density 100 mW / cm ² , energy dosage 4 J, energy density 4 J / cm ² , irradiation time 40 seconds and frequency 100,000 Hz. In the reflexology technique, the therapist's hands were used to stimulate specific points on the feet.	The applicability of laser in acupoints in elderly people with rheumatoid arthritis proved to be effective and presented superior results regarding the increase of mitochondrial ATP, angiogenesis, and range of motion in the ankle and wrist joints, reduction of oxidative stress (IL-6 and MDA), from the RAQoL and HAQe questionnaires; in relation to reflexology therapy.
Assessment of the effectiveness of low-level laser therapy on the hands of patients with rheumatoid arthritis: a randomized double-blind controlled trial.	Evaluate the effectiveness of low-level laser therapy in reducing pain and improving hand function in patients with rheumatoid arthritis	The study demonstrated that there were no relevant results in analgesia and hand function of patients with rheumatoid arthritis with low-level laser therapy with the parameters applied in this research.

The influence of intravenous laser irradiation of the blood on the dynamics of leptin levels and the quality of life of the patients presenting with rheumatoid arthritis.

To study the effect of intravenous laser therapy, using VLOK as an instrument for applying the technique on the dynamics of plasma leptin content, as well as on the quality of life of patients with RA.

The course of intravenous laser therapy was performed using the Matrix-VLOK device (Ma-Trix, Russia) and a reduction in plasma leptin levels and an increase in the quality of life of patients in the laser group was noted, demonstrating a superior result to the control group.

Therapeutic antioxidant and anti-inflammatory effects of laser acupuncture on patients with rheumatoid arthritis.

To investigate the effects of laser acupuncture on oxidative and antioxidant markers, as well as inflammatory markers and disease activity in patients with RA.

It was found that the therapeutic effects of laser acupuncture can occur through the relief of oxidative stress and modulation of the inflammatory process, in addition to improving the antioxidant and energy metabolic status in patients with rheumatoid arthritis.

served in the articles analyzed here that the most important parameter in defining the ideal light distribution regime is the energy density.¹ PBM stimulates ATP production, mitochondrial membrane potential and cell proliferation. The cytochrome C oxidase enzyme, also known as unit 4 of the respiratory chain located in the inner mitochondrial membrane, is an important chromophore.^{28,29} This protein has absorption bands that extend from red light to near infrared. After light absorption, the electron transport chain is stimulated, inducing an increase in the rate of cell respiration and cell metabolism, resulting in increased production of ATP and DNA and RNA synthesis, providing improved nutrition and oxygenation activity as a whole.¹

The primary cellular effect of the laser is to increase enzyme activity, and it should last long enough to have a real effect on cellular metabolism. As explained above, the literature indicates that the use of lasers is capable of stimulating intrinsic biological processes related to the cell cycle, such as proliferation, differentiation and growth, which is beneficial in the conservative action of this therapy in patients with rheumatoid arthritis.^{23,25}

The four studies consulted showed different laser dosimetry, locations, forms and time of application, as well as

BM stimulates ATP production, mitochondrial membrane potential and cell proliferation. The cytochrome C oxidase enzyme, also known as unit 4 of the respiratory chain located in the inner mitochondrial membrane, is an important chromophore

the wavelength, and with different therapeutic purposes. In the case of RA, it is known that application with contact allows greater penetration of the laser, and the most important application is in the articular line, since RA mainly affects synovial membranes. According to the World Association for Photobiomodulation Therapy for the wavelength 780-860 nm the applied energy should vary between 1-16 Joules and the time of 20-300 seconds, whereas for the 904 nm wavelength the applied energy should vary between 1-6 Joules and the time of 30-600 seconds, these recommended doses are for white/white skin types based on clinical trial results.³⁰

Also regarding the timing of the application, when photons are absorbed by the cytochrome c oxidase enzyme, they lead to dissociation of the inhibitory molecule ON from the O₂ binding sites in the enzyme, thus increasing the activity of the enzyme in cell respiration. If the primary cellular effect of the laser is really to increase the activity of an enzyme, it makes sense to assume that this increase in activity must last long enough to have a real effect on cellular metabolism. This explains some studies with negative results about PBM.²⁵

The number of patients analyzed in the articles ranged from 30-132, the largest number being women, due to its higher incidence in this gender, the age

ranged between 18-70 among the four studies, and only two studies reported the calibration of the devices.

Two of the articles analyzed made reference to race, but none of them reached the end of their research with black patients in the control group. It would be an interesting comparison since the initial power of the laser beam is partially lost due to absorption by melanin.³

The length of stay of the disease varied between the studies and some did not point out this fact, which can clearly interfere with the results regarding PBM. Not all articles analyzed here cited or excluded smokers from their research, which implies the lability of the PBM results, considering that smoking is considered one of the best-established risk factors for RA, as this habit triggers morphofunctional changes in the body, in addition to developing comorbidities and other diseases, which can further aggravate the arthritic condition. IL6 is primarily responsible for the progressive destruction of articular cartilage and bone, as it is the largest cytokine found in the rheumatoid synovium.¹

In the pathogenesis involved in RA, it was found that there is a progressive and uncontrolled inflammatory process of the synovial membrane in the joints, where there is an imbalance between the synthesis of pro-inflammatory and anti-inflammatory cytokines, with the former predominating over the latter. PBM can be an interesting resource, as

it presents some evidence in the reduction of TNF-alpha and modulation of the inflammatory process, factors involved in the cause of joint deformities. Another study found that patients with RA have increased plasma levels of leptin, which increases the inflammatory process.³⁰ However, they found that the combined treatment by irradiation with low-intensity intravenous laser, leptin levels are normalized, suppressing the inflammatory process and contributing to a significant improvement in QoL.²⁸

The four articles analyzed in this review evaluated, using questionnaires and other quantitative tools, different variables such as inflammatory markers, oxidants, antioxidants, pain, morning stiffness, manual dexterity, functional capacity, muscle strength, range of motion, edema and the quality of life of patients with RA, making use of heterogeneous devices, dosimetric parameters and forms of applicability of PBM. Only one article did not find results that were statistically significant, but the need for further studies with standardized dosimetry was concluded in the latter so that the real effect of photobiomodulation is clarified and well indicated.³

Of the indicators evaluated in the studies, the ones that had the greatest evidence of positive results were the reduction in inflammatory and antioxidant markers. This decrease favors the normalization of cell functioning, the normalization of ATP production, the improvement of function through the

analgesic effect, better quality of life and autonomy. It should be noted that current evidence shows that early diagnosis and immediate conventional therapeutic approach can delay or prevent disease progression, allowing the patient to return to activities in the short term and in a more productive way.

CONCLUSION

PBM is a viable and promising therapeutic resource for patients with RA, as in addition to its rapid, painless, athermic application, some evidence has shown that PBM is effective in inhibiting most of the main factors involved in the pathogenesis of this disease.

As there is no evidence pointing to adverse effects on PBM, this therapy represents a great advantage over the conventional treatment of RA symptoms with the use of NSAIDs, as it improves the antioxidant and energy metabolic status, thus reducing fatigue, modulating nociception, minimizing pain becoming a non-pharmacological alternative for the management of chronic pain, and consequently returns this individual to work and recreational activities.

It is noteworthy that more studies, with consistency and dosimetric standardization, are needed in order to clarify the real positive effects of PBM, as well as its assertive indication, so that more individuals can benefit from this easily accessible therapy. ■

REFERENCES

1. Adly, AS, Adly, SA, Adly, MS, Serry, ZMH. Laser acupuncture versus reflexology therapy in elderly with rheumatoid arthritis. *Lasers Med Sci.* 2007 Jul;32(5):1097-1103. doi: 10.1007/s10103-017-2213-y. Epub 2017 Apr 27. PMID: 28451815.
2. Starodubtseva, I A; Vasilieva, L V; Nikitin, A V. The influence of intravenous laser irradiation of the blood on the dynamics of leptin levels and the quality of life of the patients presenting with rheumatoid arthritis. *Vopr Kurortol Fizioter Lech Fiz Kult;* 92(3): 11-13, 2015. DOI: 10.17116 / kurort2015311-13.
3. Meireles SM, Jones A, Jennings F, Suda AL, Parizotto NA, Natour J. Assessment of the effectiveness of low-level laser therapy on the hands of patients with rheumatoid arthritis: a randomized double-blind controlled trial. *Clin Rheumatol.* 2010 May;29(5):501-9. doi: 10.1007/s10067-009-1347-0. Epub 2010 Jan 16. PMID: 20082104.
4. Oliveira P, Santos AA, Rodrigues T, Tim CR, Pinto KZ, Magri AM, Fernandes KR, Mattiello SM, Parizotto NA, Anibal FF, Renó AC. Effects of phototherapy on cartilage structure and inflammatory markers in an experimental model of osteoarthritis. *J Biomed Opt.* 2013 Dec;18(12):128004. doi: 10.1117/1.

REFERENCES

- JBO.18.12.128004. PMID: 24343447.
5. Sarban S, Kocyigit A, Yazar M, Isikan UE. Plasma total antioxidant capacity, lipid peroxidation, and erythrocyte antioxidant enzyme activities in patients with rheumatoid arthritis and osteoarthritis. *Clin Biochem* 2005;38:981–986.
 6. Walwadkar SD, Suryakar AN, Katkam RV, Kumbar KM, Ankush RD. Oxidative stress and calcium-phosphorus levels in rheumatoid arthritis. *Indian J Clin Biochem* 2006;21(2):134–137.
 7. Ozkan Y, Yardym-Akaydyn S, Sepici A, Keskin E, Sepici V, Simsek B. Oxidative status in rheumatoid arthritis. *Clin Rheumatol* 2007;26(1):64–68.
 8. Pacher P, Beckman JS, Liaudet L. Nitric oxide and peroxynitrite in health and disease. *Physiol Rev* 2007;87(1):315–424.
 9. Eiserich JP, Hristova M, Cross CE, Jones AD, Freeman BA, Halliwell B, van der Vliet A. Formation of nitric oxide-derived inflammatory oxidants by myeloperoxidase in neutrophils. *Nature* 1998;391(6665):393–397.
 10. Ekambaram S, Perumal SS, Subramanian V. Evaluation of antiarthritic activity of strychnos potatorum Linn seeds in Freund's adjuvant induced arthritic rat model. *BMC Complement Altern Med* 2010;13(10):1–9.
 11. Vervoordeldonk MJ, Tak PP. Cytokines in rheumatoid arthritis. *Curr Rheumatol Reports* 2002;4(3):208–217. 12. Kamanli A, Naziroglu M, Aydile K, Hacievliyagil C. Plasma lipid peroxidation and antioxidant levels in patients with rheumatoid arthritis. *Cell Biochem Funct* 2004;22:53–57.
 12. Yildirim K, Karatay S, Melioglu M, Gureser G, Ugur M, Senelk. Association between acute phase reactant levels and disease activity score (DAS28) in patients with rheumatoid arthritis. *Ann Clin Labor Sci* 2004;34(4):423–426.
 13. Ngjan GS. Rheumatoid arthritis. *Aust Fam Physician* 2010;39(9):626–628.
 14. Berard A, Solomon DH, Avorn J. Patterns of drug use in rheumatoid arthritis. *J Rheumatol* 2000;27(7):1648–1655.
 15. Carteron NL. Cytokines in rheumatoid arthritis: Trials and tribulations. *Mol Med Today* 2000;6:315–323.
 16. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *Am J Med* 1998;105:31–38.
 17. Jazayeri JA, Carrol GJ, Vernallis AB. Interleukin-6 subfamily cytokines and rheumatoid arthritis: Role of antagonists. *Int Immunopharmacol* 2010;10:1–8.
 18. Emery P, Seto Y. Role of biologics in early arthritis. *Exp Rheumatol* 2010;21(Suppl 30):191–194.
 19. Sakamoto C, Soen S. Efficacy and safety of the selective cyclooxygenase-2 inhibitor celecoxib in the treatment of rheumatoid arthritis and osteoarthritis in Japan. *Digestion* 2011;83(1-2):108–123
 20. Ernst E, Fugh-Berman A (2002) Complementary and alternative medicine: what is it all about? *Occup Environ Med* 59(2):140–144.
 21. Shea B, Swinden MV, Tanjong Ghogomu E, Ortiz Z, Katchamart W, Rader T, et al. (2013) Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *Cochrane Database Syst Rev* 56.
 22. Flores Luna GL, de Andrade ALM, Brassolatti P, Bossini PS, Anibal FF, Parizotto NA, Leal ÂMO. Biphasic Dose/Response of Photobiomodulation Therapy on Culture of Human Fibroblasts. *Photobiomodul Photomed Laser Surg*. 2020 Jul;38(7):413–418. doi: 10.1089/photob.2019.4729. Epub 2020 Mar 24. PMID: 32208063.
 23. Ferraresi C, Kaippert B, Avci P, Huang YY, de Sousa MV, Bagnato VS, Parizotto NA, Hamblin MR. Low-level laser (light) therapy increases mitochondrial membrane potential and ATP synthesis in C2C12 myotubes with a peak response at 3–6 h. *Photochem Photobiol*. 2015 Mar-Apr;91(2):411–6. doi: 10.1111/php.12397. Epub 2014 Dec 30. PMID: 25443662; PMCID: PMC4355185.
 24. Ferraresi C, de Sousa MV, Huang YY, Bagnato VS, Parizotto NA, Hamblin MR. Time response of increases in ATP and muscle resistance to fatigue after low-level laser (light) therapy (LLLT) in mice. *Lasers Med Sci*. 2015 May;30(4):1259–67. doi: 10.1007/s10103-015-1723-8. Epub 2015 Feb 21. PMID: 25700769.
 25. Hamblin MR. Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. *AIMS Biophys*. 2017;4(3):337–361. doi: 10.3934/biophys.2017.3.337. Epub 2017 May 19. PMID: 28748217; PMCID: PMC5523874.
 26. Hu W-L, Chang C-H, Hung Y-C, Tseng Y-J, Hung I-L, Hsu S-F (2014) Laser acupuncture therapy in patients with treatment-resistant temporomandibular disorders. *PLoS One* 9(10):e110528.
 27. Brosseau L, Welch V, Wells GA, de Bie R, Gam A, Harman K, Morin M, Shea B, Tugwell P (2005) Low level laser therapy (Classes I, II and III) for treating rheumatoid arthritis. *The Cochrane Library*.
 28. Ives ACA, de Carvalho PTC, Parente M, Xavier M, Frigo L, Aim-bire F, ECPL J, Albertini R (2013) Low-level laser therapy indifferent stages of rheumatoid arthritis: a histological study. *Lasers Med Sci* 28(2):529–536.
 29. Attia AM, Ibrahim FA, Abd El-Latif NA, Aziz SW, Elwan AM, Aziz A, Aziz A, Elgendy A, Elgengehy FT (2016) Therapeutic antioxidant and anti-inflammatory effects of laser acupuncture on patients with rheumatoid arthritis. *Lasers in surgery and medicine*
 30. WALT. Word Association for Laser therapy. Dosage Recommendations, WALT [internet] 2010. Disponível em: <<https://waltza.co.za/documentation-links/recommendations/dosage-recommendations/>>.
 31. Burduli NN, Burduli NM. [The influence of intravenous laser irradiation of the blood on the dynamics of leptin levels and the quality of life of the patients presenting with rheumatoid arthritis]. *Vopr Kurortol Fizioter Lech Fiz Kult*. 2015 May-Jun;92(3):11–13. Russian. doi: 10.17116/kurort2015311-13. PMID: 26285327.