CPQ Orthopaedics (2021) 5:5
Mini-Review

Articular Cartilage Degradation and Photobiomodulation Therapy

Ray Marks

Department of Health and Behavior Studies, Columbia University, Teachers College, New York, NY 10027, USA

***Correspondence to:** Dr. Ray Marks, Department of Health and Behavior Studies, Columbia University, Teachers College, New York, NY 10027, USA.

Received: 01 August 2021

Published: 16 August 2021

Keywords: *Cartilage; Laser Therapy; Osteoarthritis; Photobiomodulation; Repair; Treatment*

Abstract

Osteoarthritis cartilage pathology continues to be highly challenging to ameliorate effectively, and is often believed to be irreversible and impervious to restoration. Reviewed here are some current topical articles that discuss the possible influence of photobiomodulation therapy, previously termed low level laser therapy, in this regard. Specifically reviewed are relevant articles located in the **PUBMED** data base, with a focus on those published between 2017 and 2021 using the keywords: *cartilage, cartilage repair, phototherapy, photobiomodulation or laser therapy*. Results show that many forms of photobiomodulation/laser therapy appear to have the potential to influence cartilage structure and function favorably. More clinical studies are needed however, to expand upon the present largely preclinical data base in this regard, as well as on other spheres of joint pathology that appear associated with osteoarthritis and are favorably impacted by diverse laser applications.

Background

A wealth of literature for more than a century affirms the challenges in intervening favorably to reverse the presence of defective, degraded, deranged, or damaged articular cartilage, commonly the key tissue involved in fostering the pathology of painful disabling osteoarthritis. At the same time, although cited as an incurable irreversible progressive chronic disease, whose management goals of pain relief and mobility enhancement are largely palliative [1], evidence from the field of photobiomodulation, which involves the use of light waves for therapeutic purposes, shows that the disease may not be progressive under all circumstances as implied almost 10 years ago by Hamblin who examined laser applications for this purpose [2]. Indeed, also known as cold laser therapy, low-frequency continuous laser of typically 600 to 1000 nm wavelength is a non-thermal form of energy that has been applied successfully for some time for purposes of pain reduction and healing stimulation may yet be further exploited to enable osteoarthritis sufferers to experience functional as well as structural benefits in light of its established analgesic and anti-inflammatory properties as demonstrated in both experimental and clinical trials [3]. As indicated by Bozhokin *et al.* [4] as well as Sobel *et al.* [5], the targeted application of photobiomodulation therapy may have profound implications as far as reducing the severity of osteoarthritis where the problem of associated cartilage destruction of one or more joints appears hard to remediate or resolve. Due to its observed ability to control the fields of temperature, thermo mechanical stress, mass transfer, and cartilage matrix structures [5], the application of lasers is arguably likely to have a positive effect on cartilage tissue proliferation and bone remodeling. Also effective as regards other joint manifestations of osteoarthritis, such as muscle dysfunction, depression and insomnia, its possible utility appears important to continue to examine, when considering the limitations of education, exercise, and pharmacologic strategies that are the mainstream currently advocated non surgical intervention approaches for ameliorating disabling osteoarthritis. Moreover, given that intra-articular corticosteroid injections, plus medications listed for alleviating osteoarthritic pain and inflammation may inhibit, rather promote cartilage reparative mechanisms, while accelerating osteoarthritis [6,7], and excess opioid use may heighten mortality risk [8], an efficient means of reducing pain and disability that fosters cartilage viability and one that does not impact articular cartilage or other body systems adversely and can be applied in the home without excess financial costs would be of high possible value.

In this regard, and in light of the importance of chondrocyte cell injury and the ensuing destruction of cartilage collagens and proteoglycan unraveling in the osteoarthritis disease cycle, evidence in support of the possible favorable impact of carefully applied light stimuli on cartilage cellular responses, including, but not limited to the favorable stimulation of specific chondrocyte cell organelles and membranes, inflammatory mediators and redox balance, plus collagen, protein, ribonucleic acid and intercellular matrix synthesis [9-11] was sought. In addition, the impact of laser therapy on pain, an important mediator of cartilage destruction was explored. While this topic is not new, this brief updates what is known in this regard, and the possible implications of these findings.

Drawn from the contemporary research findings published predominantly over the last ten years, evidence for the consistent potential application of laser therapy in various forms as regards cartilage healing or repair indications was sought. A possible indirect role for fostering joint health in osteoarthritis via laser impacts on pain, bone, inflammation, muscle, sleep and depression was also explored. It was hypothesized that as with related data published between 1997-2017 [12,13], that articles published in the last five years [2017-2021] would continue to show immense promise for various applications that entail laser light in the context of various models of articular cartilage pathology, as well as depression and sleep in those with osteoarthritis that can disrupt cartilage integrity in their own right [14]. Although clearly requiring future work to translate the current findings into more well defined clinically meaningful and practical validated applications, since therapies that can target the multiple biological changes found in osteoarthritic cartilage, as well as those occurring in the surrounding bones, muscles, synovia, and ligaments can be regarded as being highly desirable to target, some rationale for pursuing this quest was specifically sought.

Methods

To achieve the key goals of this review, salient findings published in the peer reviewed literature published predominantly between 2000 and 2021, and located at the **PUBMED, GOOGLE SCHOLAR** and **SCIENCE DIRECT** data bases were sought. These included relevant materials published in the English language as full length articles that discussed either some aspect of the current topic of interest either independently or combined.

The search was limited however, by excluding studies detailing the link between laser therapy and many other health issues such as cancer, conference abstracts, preprints, and studies on dental or prosthetic implants. All forms of study or reports were deemed acceptable if they appeared to address one or more items of specific present interest. After examining the data, it was decided that in light of its diverse study approaches that were largely conducted in the lab, only a narrative overview of what has emerged to date was likely to prove valuable, although readers may want to examine a prior systematic review by Hamblin [2]. However, even then, the current review does not discuss the varied experimental approaches studied in detail, nor the metabolic pathways and cellular pathways and genes that potentially link the effects of laser light and cartilage structure and physiology in artificially damaged joints, as well as joints clinically affected by osteoarthritis. This review also does not question the validity of the various experimental models that are the focus of the prevailing body of research. Indeed almost all can be criticized in terms of faithfully representing chronic osteoarthritis, being largely derived from the acute induction of osteoarthritis-like pathology in rodents. In addition, the role of lasers in the healing of other joint tissues affected by osteoarthritis nor its possible utility in post surgical arthroplasty healing processes are covered substantively in any way. The varying modes of applying laser light to cartilage cells may also have a bearing on what is observed post stimulation [15], however, the article presented here does not discriminate the types of laser applied in available studies, nor the use of laser surgery. Nevertheless it was believed that the available preclinical studies would provide strong evidence of any trends as regards the potential for laser light to impact deranged cartilage tissue in an overall favorable manner, a situation not readily attainable in the context of current pharmacologic or surgical interventions applied in isolation in clinical practice. Herein, only trends that might support a need for future study and application are highlighted though. For an in depth review of what is known about this topic, the reader is referred to: Dima *et al.* [3], Ganjeh *et al.* [16] and Xiang *et al.* [17].

In this presently updated review, the desired data obtained from relevant publications housed in largely in **PUBMED** by applying the key terms: *articular cartilage/articular cartilage repair/bone healing/pain/depression and photobiomodulation therapy, phototherapy, laser therapy/low level laser therapy* were scanned, read and carefully examined, if deemed relevant. Thereafter, pertinent data extracted from these publications were duly recorded. While a large volume of research is currently being published, the key focus in this review is whether laser therapy in any form appears to impact articular cartilage pathology positively, as this is the tissue predominantly implicated in osteoarthritis.

It was hypothesized that support would be quite strong for the application of various forms of laser or photobiomodulation therapeutic application strategies that could be harnessed and examined in the future to determine their utility in offsetting cartilage damage associated with clinical osteoarthritis safely and more effectively than is presently possible with other approaches.

In this regard, all forms of study were deemed acceptable, regardless of the extent of pathology in question as well as the joint site studied. To ascertain trends in the heterogeneous body of research, the key findings were tabulated and discussed in narrative form, whereby preclinical and clinical data are reviewed separately.

Results

Preclinical Data

Since the early 1990s many researchers have studied the possible value of various forms of laser application that might be effective in averting some aspect of osteoarthritis pathology, including its potential for reversing articular cartilage damage or destruction [eg., 18]. Table 1 provides a snapshot of several key recently published research studies in this regard, as conducted in the lab. A further smaller parallel body of emerging applications is depicted in Table 2 in order to highlight the considerable scope of and future potential of studies to evaluate laser based interventions for fostering cartilage repair and regenerative strategies. As shown, even if not all inclusive and publication bias does exist in the current realm, it appears safe to say that the utility of laser applications as applied in multiple forms to variously damaged cartilage sites in diverse osteoarthritis models appears to show considerable promise. While preclinical study results may vary, Martins *et al.* [10] for example who strove to investigate the value of photobiostimulation therapy on articular cartilage of a rat knee osteoarthritis model using 27 male separated into three groups: a control, an osteoarthritic, and laser light stimulated treatment group (dimensions- 630 nm, 300 mW, 9 J/cm^2, 0.3 W/cm^2, 30 sec) and who applied the intervention, 24 hours after induction, at a rate of three sessions per week, for 8 weeks showed favorable results. That is, the phototherapy group was found to have higher average cartilage thickness compared with the osteoarthritis group and this compared favorably with the tissue thickness of the control group. Also, the number of chondrocytes was similar to that of the control group.

In earlier work, Bayat *et al.* [19] similarly found low-level helium-neon laser therapy applications to have a favorable impact on selected histological parameters of immobilized articular cartilage among 25 rabbits divided into three groups: an experimental group that received low-level helium-neon laser therapy with 13J/cm(2) three times a week post immobilization of their right knees; and a control group that did not receive laser therapy after immobilization of their knees; plus a normal group that received neither immobilization nor laser therapy. Using histological and electron microscopic examinations performed at 4 and 7 weeks after immobilization, this group showed the depth of the chondrocyte filopodia in the 4-week immobilized experiment group, as well as the depth of articular cartilage in the 7-week immobilized experiment group were significantly higher than those of relevant control groups. Moreover, the surfaces of articular cartilages of the experimental group were relatively smooth, while those of the control group were not. It was therefore concluded that low-level helium-neon laser therapy had the potential to significantly increase the depth of the chondrocyte filopodia within a 4-week period, plus the depth of articular cartilage within 7-weeks to a greater degree than was observed in the control cartilage tissue.

Research by Milares *et al.* [20] reveals that a highly favorable outcome is demonstrated in an osteoarthritis model when combining the unique effects of an exercise program along with low-level laser therapy. Starting 4 weeks after surgery to induce osteoarthritis, the laser applications which were continued 3 days/week for 8 weeks yielded a better pattern of tissue organization, with less fibrillation and irregularities along the articular surface and improved chondrocytes organization. Also, a lower cellular density and structural damage score and higher thickness values were observed in all treated groups. Additionally, the combined therapy group showed a reduced expression in inflammatory mediators as compared with the control group, which was also a finding of Carlos *et al.* [21] in acute zymosan-induced arthritis model induced among wistar rats. Similar results were also found in a study by Assis *et al.* [22].

More recently Balbinot *et al.* [23] who evaluated cartilage degradation and spinal cord sensitization using the monoiodoacetate model of osteoarthritis showed photobiomodualtion applications had positive effects on weight support and mechanical allodynia or pain. As well, greater optical densitometry of the laser-treated cartilage was evident in the superficial layers of the tissue, likely reflecting the increase of proteoglycan and chondrocyte contents. In addition, laser effects were associated with a decreased contribution of spinal glial cells to pain-like behavior. It was concluded that laser therapy applied during the chronic phases of induced osteoarthritis pathology can promote cartilage recovery, while reducing the progression of pain sensitization associated with chronic osteoarthritis. Additional contemporary research reveals a possible further beneficial impact on articular cartilage in a rat osteoarthritis model when photobiomodulation therapy is combined with viscosupplementation [24]. This finding also accords with recent findings of Trevaesan *et al.* [25] who observed a lower post-laser picture of degenerative processes and a higher collagen 2 and transforming growth factor β immune expression in rat knee cartilage representing osteoarthritis and others cited in Table 1 below.

Table 1: *Sample of Salient Findings Concerning Laser Therapy and Articular Cartilage in Various Osteoarthritis Models (2000-2021)*

Researchers	Methodology	Key Findings
Alves *et al.* [26]	60 male wistar rats randomly assigned into 4 groups	Nd:YAG laser groups showed tissue repair and inflammatory modulation in an injury model of osteoarthritis
Assis *et al.* [22]	50 male wistar rats divided onto 5 groups	Exercise training and low intensity laser effectively prevent cartilage degeneration and associated inflammatory responses in an experimental model of knee osteoarthritis
Balbinot *et al.* [23]	Rat osteoarthritis model	Irradiated cartilage was impacted favorably
Bayat *et al.* [19]	3 groups of rats who underwent immobilization to produce osteoarthritis	Cartilage improvements appeared to prevail in response to laser therapy not in control non therapy control rats
Bublitz *et al.* [27]	Rats subjected to ligamentous injury knee	Laser therapy prevented pathological joint changes

Lemos *et al.* [28]	100 male wistar rats that were subjected to osteo-arthritis changes of the temporomandibular joint	Low level laser treatments were effective in protecting joint structures, and accelerating tissue repair, especially at lower doses
Li *et al.* [29]	32 rats-with induced knee osteoarthritis	Laser moxibustion appears to ameliorates cartilage degeneration
Liao *et al.* [30]	Protein kinase rat model of osteoarthritis	Electroacupuncture appeared to prevent degeneration of articular cartilage
Mangueira *et al.* [31]	36 wistar rats divided into 4 groups control	After 14 days, low level laser therapy appeared to accelerate the initial breakdown of cartilage destroyed by collagenase and stimulated the fibroblast to synthesize the repair of collagen III
Martins *et al.* [10]	27 rats divided into 3 groups –all with induced knee osteoarthritis	Photobiomodulation therapy preserved articular cartilage
Moon *et al.* [32]	Rat model of osteoarthritis using 6 comparative groups	Magnetic infrared laser improves knee function, and has chondroprotective anti-inflammatory effects that inhibit cartilage degradation
Oliviera *et al.* [33]	80 male wistar rats divided into four groups, an uninjured group, and injured group, and two laser treated groups	At two weeks post surgery, 15 and 30 week laser applications modulated the progression of the degenerative process, showing a better cartilage structure and lower number of condrocytes compared to the other groups, although not all attrutes assessed were improved. Laser irradiated animals, at 50 J/cm(2) showed a lower amount of collagen type 1
Pan *et al.* [34]	Male Sprague-Dawley rats with induced arthritis	Laser acupuncture applications appeared to attenuate cartilage degradation
Sanchez *et al.* [35]	40 rat injury model of osteoarthritis	Photobiomodulation was effective in modulating inflammation and preventing articular tissue degradation in the osteoarthritic rats
Wang *et al.* [36]	Rabbit model of osteoarthritis	Low-level laser therapy protected against cartilage degradation and inflammation
Wang *et al.* [37]	Rat disuse model of osteoarthritis	Laser therapy appeared to prevent cartilage degradation
Yamada *et al.* [38]	Rats with induced knee osteoarthritis	Photobiomodulation therapy decreased oxidative damage, inflammation, and pain

Yip *et al.* [39]	40 Sprague-Dawley rats who underwent knee surgery to induce knee osteoarthritis	Low level laser therapy can restore cartilage thickness in a similar model
Zhao *et al.* [40]	C57 black mice with osteoarthritis	Arthritic cartilage improved significantly after combined treatments with 650nm and 10.6um lasers

Table 2: *Summary of Possible Additional Promising PhotobiomodulationLaser Applications That Might Impact Damaged or Degenerated Articular Cartilage Favorably*

Researcher Group	Prospective/Suggested Utility of Laser Application on Articular Cartilage
Fekrazad *et al.* [41]	Better healing in osteochondral defects is likely to be seen when combining stem cell approaches along with low level laser therapy
Goldberg-Bockhorn *et al.* [42]	Tissue engineered cartilage scaffolds subjected to laser may foster chondrocyte cell migration and more favorable matrix production
Kamrova *et al.* [43]	Low level laser therapy can be shown to improve cartilage formation and reduce inflammation, while promoting tissue granulation in a cartilage injury model
Niemenin *et al.* [44]	Laser ultrasound possibly employed to deliver various anabolic agents into damaged articular cartilage, might enhance its regenerative capacity
Rui *et al.* [45]	Phototherapy hydrogels applied to arthritic joints appears to mitigate joint destruction and promote cartilage regeneration
Sobel *et al.* [46]	Laser-induced pores that may play an important role in the process of cartilage regeneration especially if the pores are located predominately near chondrocytes
Soshnikova *et al.* [47]	Magnetic nanoparticles with the ability to absorb laser radiation and impregnated with starch show irradiated cartilage to exhibit a higher cell content alterations than intact tissue
Stancker *et al.* [48]	Photobiomodulation therapy may improve the bioavailability and chondroprotective benefits of mesenchymal stem cells injected into osteoarthritis joints
Su *et al.* [49]	Laser technology could be applied as an alternate means to create microfracture holes that can be used to foster cartilage repair
Schneider *et al.* [50]	Photobiomodulation can activate the chondrogenic differentiation of adipose stromal stem cells that may be mobilized to foster chondrogenesis

Clinical Data

While very few pertinent clinical studies that include measures of cartilage viability prevail, a number have shown laser irradiation applications to be effective in reducing disability in so far as pain goes [51] and cartilage thickness is concerned [52]. Stausholm *et al.* [53] further confirm that laser applications are efficacious in this respect, as do Medani *et al*. [54].

Zati *et al.* [55] who strove to evaluate the effect of a new pulsed Nd:YAG high intensity laser therapy on the regeneration of cartilage tissue in patients with traumatic lesions found a significant post laser decrease in cartilage depth in their high intensity laser therapy group at time 1. Histological and immune histochemical evaluations showed some regenerative processes in cartilaginous tissue as defined by higher volumes of cartilage proteoglycans, integration with adjacent articular cartilage and a more physiological cellular arrangement in the laser treated group. By contrast, a disorganized cartilaginous tissue appearance was observed in the control group at both baseline and the time 1 post test.

Importantly, Alfredo *et al*. [56] found positive laser effects in cases with mild to moderate knee osteoarthritis that were maintained for at least six months, while DeMatos *et al*. [57] who evaluated the effects of individual and combination therapies (low-level laser therapy and physical exercises) on pain, stiffness, function, and spatiotemporal gait variables in subjects with bilateral knee osteoarthritis showed significant improvement in pain and function. At 8 weeks all groups receiving the intervention showed a significant increase in gait speed. Only the group treated with laser + exercise showed a significant increase in cadence and single limb support duration. It was concluded that the laser and exercise combination therapy provided the best gait results. Other research that might be drawn on to foster osteoarthritis cartilage repair processes indirectly through their link to its diverse pathogenic correlates include the following:

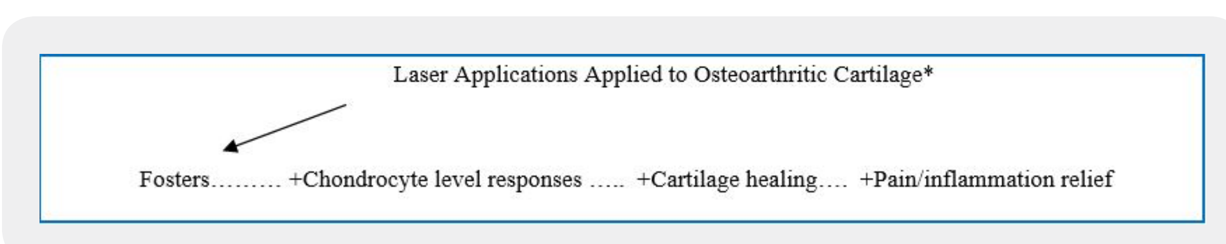
- Anxiety and depression [58]
- Bone damage [59]
- Cartilage matrix loss [60]
- Chondrocyte gene dysfunction [61]
- Joint dysfunction [62]
- Joint effusion [63]
- Joint inflammation [64,65]
- Neuropathic/joint pain [66,67]
- Insomnia [65,68]
- Ligamentous damage [69]
- Muscle strength, regeneration, and repair [70-72]
- Loss range of joint motion [70,72]
- Tendon lesions [70]

In sum, as outlined above, a high percentage of available publications listed on **PUBMED**, **SCIENCE DIRECT**, and **GOOGLE SCHOLAR** over the time periods of 2000-2021 pertaining to the current area of interest, tend to support a favorable role for laser applications in the realm of articular cartilage repair.

Explanatory mechanisms that might underpin current findings include, but are not limited to, beneficial post laser effects on damaged cartilage and joints due to enhanced anti inflammatory processes [50,73], enhanced articular chondrocyte proliferation [74] and enhanced production of articular chondrocyte stress proteins [75]. Other data imply photobiomodulation or laser therapy has the ability to enhance cellular mechanisms such as those involving mitochondrial enzymes, cytochrome-c-oxidase, and ATP formation, as well as cartilage metabolic activities and pain [76]. According to Sobel *et al.* [5] laser irradiation may specifically foster cartilage repair as a result of its ability to stimulate the differentiation of immature and resident stem cells, as well as the improved production of cartilage matrix components. In addition, mature chondrocytes might be stimulated and rejuvenated to divide and restore lost tissue. Dima *et al.* [3] stress that the properties of coherent light used in laser therapy can yield both pain relief and fibroblastic regeneration, while lowering oxidative stress, and the formation of edema and hemorrhage. As well, applications of photobiomodulation in both experimental and clinical trials show this form of intervention to enhance collagen production and wound healing, while significantly enhancing the stiffness of repair tissue in post injury osteochondral defects [77], as well as stimulating muscle and bone healing [13,59,70]. It may also have a bearing on intracellular reactive oxygen species, key secondary messengers, implicated in the functional regulation of cells [78] and synovial membrane protein synthesis [79].

Felizatti *et al*. [80] who evaluated the effects of a gallium arsenide laser application (λ = 830nm) on the articular cartilage organization of rat knee joint tissues using an experimental model of arthritis did find favorable results in this respect. That is, following daily laser applications, the AsGa-830 nm laser therapy tended to preserve the glycosaminoglycan content of the cartilage tissues, and reduced those cellular changes and associated inflammatory processes that were seen in the cartilage tissues of the untreated group. Possible processes favoring these observed cartilage tissue improvements in the laser treated experimental group were: the presence of enhanced chondrocyte gene expression [4] and differentiation [50], improvements in bone status [81] and/or according to Dos Santos *et al.* [82] post photobiomodulation therapy decreases in lipid peroxidation and increases in antioxidant activity, often associated with cartilage destruction.

Other mechanisms potentially evoked by laser therapy applied to damaged cartilage that may help to stimulate matrix deposition and cartilage thickening are related to its pain relieving effect, as well as its effect on aiding joint microcirculation in the irradiated areas [83-85]. The hypothetical application of these data to the clinical realm is depicted in Figure 1.



Extracted from citations 40, 81-91
*Note: Factors influencing the outcome of photobiomoduation/laser irradiation to damaged or osteoarthritic cartilage include the mode of application, the illumination parameters, and the nature of underlying tissue

Figure 1: *Hypothesized overall impact of photobiomodulation therapy on damaged cartilage tissue*

Discussion

Osteoarthritis, one of the most prevalent chronic diseases, and one commonly deemed to be progressive with no known cure is strongly associated with marked functional declines and losses in the quality of life, along with immense health care and societal costs in all aging populations [1]. Although universally deemed to be a progressive disease, efforts to reverse the pathology of osteoarthritis have ensued for many years. In particular, a vast body of literature for over 30 years has attempted to overcome the challenges hitherto believed in reference to the limited ability to repair damaged or injured articular cartilage, the tissue most affected by the disease, by applying various forms of laser light to foster cartilage repair, with some degree of success.

Moreover, given that osteoarthritis is now understood to be a complex disease implicating numerous local and systemic factors [92,93], a growing body of evidence supports the view that it is possible to impact extrinsically upon one or more of these pathways and processes in a favorable manner, rather than awaiting their possible destruction or dysfunction. Indeed, several modalities that appear to effectively modulate one or more of these multiple pathogenic pathways have been described to date, and may prove highly valuable in this regard, including laser or phototherapy [94,95], even if somewhat discounted as efficacious in the context of clinical practice [96]. As well, the explanatory mechanisms of action attributed to the known extracellular effects of photobiomodulation therapy, as well as their associated mechanical and biochemical influences on chondrocytes and their cellular responses, are those that would theoretically be anticipated to impact multiple aspects of the osteoarthritis pathology disease cycle in a positive way.

As such, even if we did not critically report on the flaws in the present data base, and did not attempt to examine all available studies, and negative studies may not be published, the fact that favorable results are replicated in most available sufficiently powered and well-controlled preclinical studies, where subjective biases have been eliminated, is significant. Additionally, it seems various degrees of cartilage repair are observed, not only in one species or form of osteoarthritis, but in multiple models of the disease, and with diverse modes of application. A limited number of clinical studies also support this finding, as do studies in the purely cellular realm. Other related data show laser therapy applications to effectively reduce various forms of pain, the symptom of most concern to osteoarthritis patients, as well as having the proven ability to foster the status of surrounding joint tissues, while reducing inflammation. In addition, as mentioned, these responses tend to parallel both the known attributes of phototherapy dynamics and mechanisms of action, regardless of the nature of the mode of laser light or osteoarthritic characteristics employed and examined, and are hence tentatively generalizable. Indeed, based on what has been demonstrated in multiple randomized trials to date, it appears that the perception that osteoarthritis is inevitably progressive must be challenged, even if it means extending clinical studies employing laser therapy to include more tissue based observations in this respect over longer time periods using advanced technologies that attempt to go beyond the present focus of pain assessments and subjective instrumentation in short-term studies. As discussed by Tomazoni *et al*. [11] photobiomodulation appears to be the most effective therapy in stopping osteoarthritis disease progression, and improving inflammatory conditions observed in this disease, and hence strongly warrants attention in our view through the implementation of insightfully designed clinical as well as lab studies of various forms of osteoarthritis pathology, and the ensuing extracellular as well as cellular responses of cartilage chondrocytes to diverse modes of laser application.

This idea is consistent with the enormous need to identify novel strategies to reduce the immense adverse impact of osteoarthritis as recounted by Nelson [97], and based on current research, great advances in the ability to alleviate suffering would be expected to follow.

In the interim, and based on the body of available clinical research, the utility of low level laser applications and other forms of phototherapy may yet provide a supplementary and safe form of intervention for ameliorating osteoarthritis pain in those patients suffering from intractable pain as well those with more acute osteoarthritis symptoms. Alone or in combination, it appears that those who seek to reverse, prevent, or mitigate some aspects of osteoarthritis disability will be well-served and should be strongly encouraged to consider the potential value of one or more modes of laser therapy and its possible extensive reservoir of promising applications.

Educating future clinicians and researchers in this regard, as well as helping the current osteoarthritis patient to understand the potential of laser for improving their status, is also likely to prove helpful as well in its own right until more data emerge. As well the recognition by funders of the potential benefits of funding comprehensive efforts to carefully validate current findings is encouraged. In this regard, it is hoped that a careful review of the current and past literature alluded to in this report can serve as testimony that can be applied towards advancing the well-being of many current and future osteoarthritis sufferers who might otherwise have to endure preventable degrees of pain and rapidly progressive morbidity and excess disability.

Unfortunately, unless more attention and visibility is given to this potentially viable adjunctive treatment option, it will probably tend to remain unlisted among the evidence-based osteoarthritis management guidelines recommended by experts [eg., 98]. Moreover, the potentially 'impoverished' view of the reparative potential of damaged adult articular cartilage, and its inevitable osteoarthritis progression will also likely ensue unless researchers and clinicians are motivated to harness the data and do more to address this gap sooner, rather than later.

In this regard, the basic studies and others presented here, many of which are robust in design, show great promise that should not be ignored, but employed as a framework for exploring and advancing this possible fruitful, far-reaching, and impactful line of inquiry to avert or prevent osteoarthritis disease progression.

Conclusions

A wide range of well-controlled studies on the current topic over the years indicates that within the limits of this review and the research strategies themselves, it appears early treatment of an injured joint as well as carefully construed well-delineated prolonged laser therapy in cases with chronic osteoarthritis is likely to alleviate much suffering with few side effects or financial costs.

Subject to further investigation, a more optimistic view may be forthcoming concerning the inevitability of progression in all osteoarthritis cases.

Examining whether efforts to integrate photobiomodulation or laser therapy, which has proven benefits for pain relief, inflammation, bone structural benefits, muscle function, depression, and insomnia, and can be applied by the patient in the home is efficacious, especially insofar as cartilage repair is an important outcome criterion, is strongly encouraged.

Bibliography

1. Pereira. D., Ramos, E. & Branco, J. (2015). Osteoarthritis. *Acta Med Port., 28*(1), 99-106.

2. Hamblin, M. R. (2013). Can osteoarthritis be treated with light? *Arthritis Res Ther., 15*(5), 120.

3. Dima, R., Tieppo, Francio, V., Towery, C. & Davani, S. (2018). Review of literature on low-level laser therapy benefits for nonpharmacological pain control in chronic pain and osteoarthritis. *Altern Ther Health Med., 24*(5), 8-10.

4. Bozhokin, M. S., Vcherashnii, D. B., Yastrebov, S. G., Beilinson, L. L., Zherebtsova, J. V., & Khotin, M. G. (2021). Low-intensity photobiomodulation at 632.8 nm increases tgfβ3, col2a1, and sox9 gene expression in rat bone marrow mesenchymal stem cells *in vitro. Lasers in Medical Science*.

5. Sobol, E., Shekhter, A., Guller, A., Baum, O. & Baskov, A. (2011). Laser-induced regeneration of cartilage. *J Biomed Opt., 16*(8), 080902.

6. Hauser, R. A. (2009). The deterioration of articular cartilage in osteoarthritis by corticosteroid injections. *J Prolotherap., 1*(2), 107-123.

7. Dingle, J. T. (1991). Cartilage maintenance in osteoarthritis: Interaction of cytokines, NSAID and prostaglandins in articular cartilage damage and repair. *J Rheumatol.,* Suppl. 28, 30-37.

8. Zeng, C., Dubreuil, M., LaRochelle, M. R., Lu, N., Wei, J., *et al.* (2019). Association of Tramadol with all-cause mortality among patients with osteoarthritis. *JAMA., 321*(10), 969-982.

9. Gray, M. G., Lackey, B. R., Patrick, E. F., Gray, S. L. & Hurley, S. G. (2016). Multiple integrated complementary healing approaches: Energetics & light for bone. *Med Hypotheses., 86,* 18-29.

10. Martins, L. P., Santos, F. F., Costa, T. E., Lacerda, A. C., Santos, J. M., *et al.* (2021). Photobiomodulation therapy (light-emitting diode 630nm) favored the oxidative stress and the preservation of articular cartilage in an induced knee osteoarthritis model. *Photobiomodulation, Photomedicine, and Laser Surg., 39*(4), 272-279.

11. Tomazoni, S. S., Leal-Junior, E. C., Frigo, L., Pallotta, R. C., Teixeira, S., *et al.* (2016). Isolated and combined effects of photobiomodulation therapy, topical nonsteroidal anti-inflammatory drugs, and physical activity in the treatment of osteoarthritis induced by papain. *J Biomed Opt., 21*(10), 108001.

12. Marks, R. & de Palma, F. (1999). Clinical efficacy of low power laser therapy in osteoarthritis. *Physiother Res Int., 4*(2), 141-157.

13. Marks, R. (2017). Laser therapy and osteoarthritis. *Novel Tech Arthritis Bone Res.,* 292.

14. Ranjan, K. C., Li, X., Voigt, R. M., Ellman, M. B., Summa, K. C., *et al.* (2015). Environmental disruption of circadian rhythm predisposes mice to osteoarthritis-like changes in knee joint. *J Cell Physiol., 230*(9), 2174-2183.

15. Zein, R., Selting, W. & Hamblin, M. R. (2018). Review of light parameters and photobiomodulation efficacy: Dive into complexity. *J Biomed Opt., 23*(12), 1-17.

16. Ganjeh, S., Rezaeian, Z. S. & Mostamand, J. (2020). Low level laser therapy in knee osteoarthritis: A narrative review. *Adv Ther., 37*(8), 3433-3449.

17. Xiang, A., Deng, H., Cheng, K., Liu, H., Lin, L., *et al.* (2020). Laser photobiomodulation for cartilage defect in animal models of knee osteoarthritis: A systematic review and meta-analysis. *Lasers Med Sci., 35*(4), 789-796.

18. Guzzardella, G. A., Torricelli, P., Fini, M., Morrone, G. & Giardino, R. (1999). [Cartilage cell stimulation with low-power laser: experimental assessment]. *Acta Biomed Ateneo Parmense., 70*(3-4), 43-47.

19. Bayat, M., Ansari, E., Gholami, N. & Bayat, A. (2007). Effect of low-level helium-neon laser therapy on histological and ultrastructural features of immobilized rabbit articular cartilage. *J Photochem Photobiol B., 87*(2), 81-87.

20. Milares, L. P., Assis, L., Siqueira, A., Claudino, V., Domingos, H., *et al.* (2016). Effectiveness of an aquatic exercise program and low-level laser therapy on articular cartilage in an experimental model of osteoarthritis in rats. *Connect Tissue Res., 57*(5), 398-407.

21. Carlos, F. P., de Paula Alves da Silva, M., de Lemos Vasconcelos Silva Melo, E., Costa, M. S. & Zamuner, S. R. (2014). Protective effect of low-level laser therapy (LLLT) on acute zymosan-induced arthritis. *Lasers Med Sci., 29*(2), 757-763.

22. Assis, L., Milares, L. P., Almeida, T., Tim, C., Magri, A., *et al.* (2016). Aerobic exercise training and low-level laser therapy modulate inflammatory response and degenerative process in an experimental model of knee osteoarthritis in rats. *Osteoarthritis Cartilage., 24*(1), 169-177.

23. Balbinot, G., Schuch, C. P., Nascimento, P. S., Lanferdini, F. J., Casanova, M., *et al.* (2019). Photobiomodulation therapy partially restores cartilage integrity and reduces chronic pain behavior in a rat model of osteoarthritis: Involvement of spinal glial modulation. *Cartilage.,* 1947603519876338.

24. Tim, C. R., Martignago, C. C. S., Assis, L., Andrade, A. L., Neves, L. M., Castro, C., *et al.* (2021). Effects of photobiomodulation associated with chitosan viscosupplementation for osteoarthritis: An *in vitro* and *in vivo* study. *Res Biomed Engineer., 37*(1), 65-77.

25. Trevisan, E. S., Martignago, C. C. S., Assis, L., Tarocco, J. C., Salman, S., *et al.* (2020). Effectiveness of LED photobiomodulation therapy on treatment with knee osteoarthritis: A rat study. *Am J Phys Med & Rehabil., 99*(8), 725-732.

26. Alves, A. C., Albertini, R., dos Santos, S. A., Leal-Junior, E. C., Santana, E., *et al.* (2014). Effect of low-level laser therapy on metalloproteinase MMP-2 and MMP-9 production and percentage of collagen types Iand III in a papain cartilage injury model. *Lasers Med Sci., 29*(3), 911-919.

27. Bublitz, C., Medalha, C., Oliveira, P., Assis, L., Milares, L. P., *et al.* (2014). Low-level laser therapy prevents degenerative morphological changes in an experimental model of anterior cruciate ligament transection in rats. *Lasers Med Sci., 29*(5), 1669-1678.

28. Lemos, G. A., Batista, A. U. D., da Silva, P. L. P., Araújo, D. N., Sarmento, W. E. A., *et al*. (2020). Photobiostimulation activity of different low-level laser dosage on masticatory muscles and temporomandibular joint in an induced arthritis rat model. *Lasers Med Sci., 35*(5), 1129-1139.

29. Li. Y., Wu, F., Wei, J., Lao, L. & Shen, X. (2020). The effects of laser moxibustion on knee osteoarthritis pain in rats. *Photobiomodul Photomed Laser Surg., 38*(1), 43-50.

30. Liao, Y., Li, X., Li, N. & Zhou, J. (2016). Electroacupuncture protects against articular cartilage erosion by inhibiting mitogen-activated protein kinases in a rat model of osteoarthritis. *Acupunct Med., 34*(4), 290-295.

31. Mangueira, N. M., Xavier, M., de Souza, R. A., Salgado, M. A., Silveira, L Jr., *et al.* (2015). Effect of low-level laser therapy in an experimental model of osteoarthritis in rats evaluated through Raman spectroscopy. *Photomed Laser Surg., 33*(3), 145-153.

32. Moon, C. H., Kwon, O., Woo, C. H., Ahn, H. D., Kwon, Y. S., *et al.* (2014). Therapeutic effect of irradiation of magnetic infrared laser on osteoarthritis rat model. *Photochem Photobiol., 90*(5), 1150-1159.

33. Oliveira, P., Santos, A. A., Rodrigues, T., Tim, C. R., Pinto, K. Z., *et al.* (2013). Effects of phototherapy on cartilage structure and inflammatory markers in an experimental model of osteoarthritis. *J Biomed Opt., 18*(12), 128004.

34. Pan, T. C., Tsai, Y. H., Chen, W. C. & Hsieh, Y. L. (2019). The effects of laser acupuncture on the modulation of cartilage extracellular matrix macromolecules in rats with adjuvant-induced arthritis. *PLoS One., 14*(3), e0211341.

35. Sanches, M., Assis, L., Criniti, C., Fernandes, D., Tim, C., *et al.* (2018). Chondroitin sulfate and glucosamine sulfate associated to photobiomodulation prevents degenerative morphological changes in an experimental model of osteoarthritis in rats. *Lasers Med Sci., 33*(3), 549-557.

36. Wang, P., Liu, C., Yang, X., Zhou, Y., Wei, X., *et al.* (2014). Effects of low-level laser therapy on joint pain, synovitis, anabolic, and catabolic factors in a progressive osteoarthritis rabbit model. *Lasers Med Sci., 29*(6), 1875-1885.

37. Wang, Q., Guo, X., Liu, M. Q., Wang, X. Y. & Zheng, Y. P. (2012). Effect of laser acupuncture on disuse osteoarthritis: An ultrasound biomicroscopic study of patellar articular cartilage in rats. *Evid Based Complement Alternat Med., 2012,* 838420.

38. Yamada, E. F., Bobinski, F., Martins, D. F., Palandi, J., Folmer, V., *et al.* (2020). Photobiomodulation therapy in knee osteoarthritis reduces oxidative stress and inflammatory cytokines in rats. *J Biophotonics., 13*(1), e201900204.

39. Yip, K. K., Leung, C. P., Cheung, W. H. & Lai, Y. M. (2016). Effects of low level laser therapy: a study of status of cartilage, subchondral bone and gait adaptation in the rat anterior cruciate ligament transection model of osteoarthritis. *Osteoarthritis and Cartilage., 24*(Suppl 1), S487-S488.

40. Zhao, L, Shen, X. Y., Cao, Y. L., Wang, L. Z., Deng, H. P., *et al.* (2011). Effects of laser irradiation on arthritic histopathology and heat shock protein 70 expression in C57 black mice with osteoarthritis. *Zhong Xi Yi Jie He Xue Bao., 9*(7), 761-767.

41. Fekrazad, R., Eslaminejad, M. B., Shayan, A. M., Kalhori, K. A., Abbas, F. M., *et al.* (2016). Effects of photobiomodulation and mesenchymal stem cells on articular cartilage defects in a rabbit model. *Photomed Laser Surg., 34*(11), 543-549.

42. Goldberg-Bockhorn, E., Schwarz, S., Subedi, R., Elsässer, A., Riepl, R., *et al.* (2018). Laser surface modification of decellularized extracellular cartilage matrix for cartilage tissue engineering. *Lasers Med Sci., 33*(2), 375-384.

43. Kamrava, S. K., Farhadi, M., Rezvan, F., Sharifi, D., Ashrafihellan, J., *et al.* (2009). The histological and clinical effects of 630 nanometer and 860 nanometer low-level laser on rabbits' ear punch holes. *Lasers Med Sci., 24*(6), 949-954.

44. Nieminen, H. J., Barreto, G., Finnilä, M. A., García-Pérez, A., Salmi, A., *et al.* (2017). Laser-ultrasonic delivery of agents into articular cartilage. *Sci Rep., 7*(1), 3991.

45. Rui, X., Yang, Y., Chen, Q., Wu, J., Chen, J., *et al.* (2020). Imperative and effective reversion of synovial hyperplasia and cartilage destruction in rheumatoid arthritis through multiple synergistic effects of O_2 and Ca^2. *Mater Sci Eng C Mater Biol Appl., 114,* 111058.

46. Sobol, E., Baum, O., Shekhter, A., Wachsmann-Hogiu, S., Shnirelman, A., *et al.* (2017). Laser-induced micropore formation and modification of cartilage structure in osteoarthritis healing. *J Biomed Opt., 22*(9), 91515.

47. Soshnikova, Y. M., Shekhter, A. B., Baum, O. I., Shcherbakov, E. M., Omelchenko, A. I., *et al.* (2015). Laser radiation effect on chondrocytes and intercellular matrix of costal and articular cartilage impregnated with magnetite nanoparticles. *Lasers Surg Med., 47*(3), 243-251.

48. Stancker, T. G., Vieira, S. S., Serra, A. J., do Nascimento Lima, R., Dos Santos Feliciano, R., *et al.* (2018). Can photobiomodulation associated with implantation of mesenchymal adipose-derived stem cells attenuate the expression of MMPs and decrease degradation of type II collagen in an experimental model of osteoarthritis? *Lasers Med Sci., 33*(5), 1073-1084.

49. Su, E., Sun, H., Juhasz, T. & Wong, B. J. (2014). Preclinical investigations of articular cartilage ablation with femtosecond and pulsed infrared lasers as an alternative to microfracture surgery. *J Biomed Opt., 19*(9), 98001.

50. Schneider, C., Dungel, P., Priglinger, E., Danzer, M., Schädl, B., *et al.* (2021). The impact of photobiomodulation on the chondrogenic potential of adipose-derived stromal/stem cells. *J Photochem Photobiol B., 221,* 112243.

51. Gworys, K., Gasztych, J., Puzder, A., Gworys, P. & Kujawa, J. (2012). Influence of various laser therapy methods on knee joint pain and function in patients with knee osteoarthritis. *Ortop Traumatol Rehabil., 14*(3), 269-277.

52. Akaltun, M. S., Altindag, O., Turan, N., Gursoy, S. & Gur, A. (2020). Efficacy of high intensity laser therapy in knee osteoarthritis: A double-blind controlled randomized study. *Clin Rheumatol., 40*(5), 1989-1995.

53. Stausholm, M. B., Naterstad, I. F., Joensen, J., Lopes-Martins, R. Á. B., Sæbø, H., *et al.* (2019). Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: Systematic review and meta-analysis of randomised placebo-controlled trials. *BMJ Open., 9*(10), e031142.

54. Madani, A., Ahrari, F., Fallahrastegar, A. & Daghestani, N. (2020). A randomized clinical trial comparing the efficacy of low-level laser therapy (LLLT) and laser acupuncture therapy (LAT) in patients with temporomandibular disorders. Lasers Med Sci., 35(1), 181-192.

55. Zati, A., Desando, G., Cavallo, C., Buda, R., Giannini, S., *et al.* (2012). Treatment of human cartilage defects by means of Nd:YAG Laser Therapy. *J Biol Regul Homeost Agents., 26*(4), 701-711.

56. Alfredo, P. P., Bjordal, J. M., Junior, W. S., Lopes-Martins, R. Á. B., Stausholm, M. B., *et al.* (2018). Long-term results of a randomized, controlled, double-blind study of low-level laser therapy before exercises in knee osteoarthritis: laser and exercises in knee osteoarthritis. *Clin Rehabil., 32*(2), 173-178.

57. de Matos Brunelli Braghin, R., Libardi, E. C., Junqueira, C., Rodrigues, N. C., Nogueira-Barbosa, M. H., *et al.* (2019). The effect of low-level laser therapy and physical exercise on pain, stiffness, function, and spatiotemporal gait variables in subjects with bilateral knee osteoarthritis: a blind randomized clinical trial. *Disabil Rehabil., 41*(26), 3165-3172.

58. Eshaghi, E., Sadigh-Eteghad, S., Mohaddes, G. & Rasta, S. H. (2019). Transcranial photobiomodulation prevents anxiety and depression via changing serotonin and nitric oxide levels in brain of depression model mice: A study of three different doses of 810nm laser. *Lasers Surg Med., 51*(7), 634-642.

59. Buchignani, V. C., Germano, E. J., Dos Santos, L. M., Gulinelli, J. L., Ishikiriama, B. L. C., *et al.* (2019). Effect of low-level laser therapy and zoledronic acid on bone repair process. *Lasers Med Sci., 34*(6), 1081-1088.

60. Collier, M. A., Haugland, L. M., Bellamy, J., Johnson, L. L., Rohrer, M. D., *et al.* (1993). Effects of holmium: YAG laser on equine articular cartilage and subchondral bone adjacent to traumatic lesions: A histopathological assessment. *Arthroscopy., 9*(5), 536-545.

61. Holden, P. K., Li, C., Da Costa, V., Sun, C. H., Bryant, S. V., *et al.* (2009). The effects of laser irradiation of cartilage on chondrocyte gene expression and the collagen matrix. *Lasers Surg Med., 41*(7), 487-491.

62. Alghadir, A., Omar, M. T., Al-Askar, A. B. & Al-Muteri, N. K. (2013). Effect of low-level laser therapy in patients with chronic knee osteoarthritis: A single-blinded randomized clinical study. *Lasers Med Sci., 29*(2), 749-755.

63. Marini, I., Gatto, M. R. & Bonetti, G. A. (2010). Effects of superpulsed low-level laser therapy on temporomandibular joint pain. *Clin J Pain., 26*(7), 611-516.

64. Barretto, S. R., de Melo, G. C., dos Santos, J. C., de Oliveira, M. G., Pereira-Filho, R. N., *et al.* (2013). Evaluation of anti-nociceptive and anti-inflammatory activity of low-level laser therapy on temporomandibular joint inflammation in rodents. *J Photochem Photobiol B., 129,* 135-142.

65. Trawitzki, B. F., Lilge, L., de Figueiredo, F. A. T., Macedo, A. P. & Issa, J. P. M. (2017). Low-intensity laser therapy efficacy evaluation in mice subjected to acute arthritis condition. *J Photochem Photobiol B., 174,* 126-132.

66. Angelova, A. & Ilieva, E. M. (2016). Effectiveness of high intensity laser therapy for reduction of pain in e osteoarthritis. *Pain Res Manag., 2016,* 9163618.

67. de Andrade, A. L., Bossini, P. S. & Parizotto, N. A. (2016). Use of low level laser therapy to control neuropathic pain: A systematic review. *J Photochem Photobiol B., 164,* 36-42.

68. Chen, C. K., Lin, Y. C., Cheng, J. W., Pei, Y. C., Liu, G. H., *et al.* (2019). Effectiveness of laser acupuncture in alleviating chronic insomnia: A single-blinded randomized controlled trial. *Evid Based Complement Alternat Med., 2019*(8136967).

69. Ng, G. Y., Fung, D. T., Leung, M. C. & Guo, X. (2004). Comparison of single and multiple applications of GaAlAs laser on rat medial collateral ligament repair. *Lasers Surg Med., 34*(3), 285-289.

70. Baltzer, A. W. A., Stosch, D., Seidel, F. & Ostapczuk, M. S. (2017). Low level laser therapy: A narrative literature review on the efficacy in the treatment of rheumatic orthopaedic conditions. *Z Rheumatol., 76*(9), 806-812.

71. Vatansever, F., Rodrigues, N. C., Assis, L. L., Peviani, S. S., Durigan, J. L., *et al.* (2012). Low intensity laser therapy accelerates muscle regeneration in aged rats. *Photonics Lasers Med., 1*(4), 287-297.

72. Youssef, E. F., Muaidi, Q. I., & Shanb, A. A. (2016). Effect of laser therapy on chronic osteoarthritis of the knee in older subjects. *J Lasers Med Sci., 7*(2), 112-119.

73. Issa, J. P. M., Trawitzki, B. F., Ervolino, E., Macedo, A. P. & Lilge, L. (2017). Low-intensity laser therapy efficacy evaluation in FVB mice subjected to acute and chronic arthritis. *Lasers Med Sci., 32*(6), 1269-1277.

74. Pfander, D., Jörgensen, B., Rohde, E., Bindig, U., Müller, G., *et al.* (2006). The influence of laser irradiation of low-power density on an experimental cartilage damage in rabbit knee-joints: An *in vivo* investigation considering macroscopic, histological and immunohistochemical changes]. *Biomed Tech (Berl), 51*(3), 131-138.

75. Lin, Y. S., Huang, M. H., Chai, C. Y. & Yang, R. C. (2004). Effects of helium-neon laser on levels of stress protein and arthritic histopathology in experimental osteoarthritis. *Am J Phys Med Rehabil., 83*(10), 758-765.

76. Cantero-Téllez, R., Villafañe, J. H., Valdes, K., García-Orza, S., Bishop, M. D., *et al.* (2020). Effects of high-intensity laser therapy on pain sensitivity and motor performance in patients with thumb carpometacarpal joint osteoarthritis: A randomized controlled trial. *Pain Med., 21*(10), 2357-2365.

77. Kamali, F., Bayat, M., Torkaman, G., Ebrahimi, E. & Salavati, M. (2007). The therapeutic effect of low-level laser on repair of osteochondral defects in rabbit knee. *J Photochem Photobiol B., 88*(1), 11-15.

78. Kushibiki, T., Hirasawa, T., Okawa, S. & Ishihara, M. (2013). Blue laser irradiation generates intracellular reactive oxygen species in various types of cells. *Photomed Laser Surg., 31*(3), 95-104.

79. Barabás, K., Bakos, J., Zeitler, Z., Bálint, G., Nagy, E., *et al.* (2014). Effects of laser treatment on the expression of cytosolic proteins in the synovium of patients with osteoarthritis. *Lasers Surg Med., 46*(8), 644-649.

80. Felizatti, A. L., do Bomfim, F. R. C., Bovo, J. L., de Aro, A. A., do Amaral, M. E. C., *et al.* (2019). Effects of low-level laser therapy on the organization of articular cartilage in an experimental microcrystalline arthritis model. *Lasers Med Sci., 34*(7), 1401-1412.

81. Bashardoust Tajali, S., MacDermid, J. C. & Houghton, P. (2010). Effects of low power laser irradiation on bone healing in animals: A meta-analysis. *J Orthop Surg Res., 5*(1).

82. Dos Santos, S. A., Dos Santos Vieira, M. A., Simões, M. C. B., Serra, A. J., Leal-Junior, E. C., *et al.* (2017). Photobiomodulation therapy associated with treadmill training in the oxidative stress in a collagen-induced arthritis model. *Lasers Med Sci., 32*(5),1071-1079.

83. Hegedus, B., Viharos, L., Gervain, M. & Gálfi, M. (2009). The effect of low-level laser in knee osteoarthritis: A double-blind, randomized, placebo-controlled trial. *Photomed Laser Surg., 27*(4), 577-584.

84. Franco, W. F., Galdino, M. V. B., Capeletti, L. R., Sberowsky, B. H., Vieira, R. A., *et al.* (2020). Photobiomodulation and mandibular advancement modulates cartilage thickness and matrix deposition in the mandibular condyle. *Photobiomodul Photomed Laser Surg., 38*(1), 3-10.

85. S, G. N., Kamal, W., George, J. & Manssor, E. (2017). Radiological and biochemical effects (CTX-II, MMP-3, 8, and 13) of low-level laser therapy (LLLT) in chronic osteoarthritis in Al-Kharj, Saudi Arabia. *Lasers Med Sci., 32*(2), 297-303.

86. Zou, Y. C., Deng, H. Y., Mao, Z., Zhao, C., Huang, J., *et al.* (2017). Decreased synovial fluid ghrelin levels are linked with disease severity in primary knee osteoarthritis patients and are increased following laser therapy. *Clinica Chimica Acta., 470,* 64-69.

87. Reed, S. C., Jackson, R. W., Glossop, N. & Randle, J. (1994). An *in vivo* study of the effect of excimer laser irradiation on degenerate rabbit articular cartilage. *Arthroscopy., 10*(1), 78-84.

88. Peimani, A., & Sardary, F. (2014). Effect of low-level laser on healing of temporomandibular joint osteoarthritis in rats. *J Dent (Tehran)., 11*(3), 319-327.

89. de Oliveira. V. L., Silva. J. A. Jr., Serra. A. J., Pallotta. R. C., da Silva. E. A., *et al.* (2017). Photobiomodulation therapy in the modulation of inflammatory mediators and bradykinin receptors in an experimental model of acute osteoarthritis. *Lasers Med Sci,. 32*(1), 87-94.

90. Lee, J. Y., Lee, S. U., Lim, T. & Choi, S. H. (2014). Healing effects and superoxide dismutase activity of diode/Ga-As lasers in a rabbit model of osteoarthritis. *In Vivo., 28*(6), 1101-1106.

91. Ebrahimi, T., Moslemi, N., Rokn, A., Heidari, M., Nokhbatolfoghahaie, H., *et al.* (2012). The influence of low-intensity laser therapy on bone healing. *J Dent (Tehran)., 9*(4), 238-248.

92. Abramoff, B. & Caldera, F. E. (2020). Osteoarthritis: Pathology, diagnosis, and treatment options. *Med Clin North Am., 104*(2), 293-311.

93. Vina, E.R. & Kwoh, C. K. (2018). Epidemiology of osteoarthritis: literature update. *Curr Opin Rheumatol., 30*(2), 160-167.

94. Lu, Y., Li, L., Lin, Z., Wang, L., Lin, L., *et al.* (2018). A new treatment modality for rheumatoid arthritis: combined photothermal and photodynamic therapy using Cu7.2 S4 nanoparticles. *Adv Healthc Mater., 7*(14), e1800013.

95. Nürnberger, S., Schneider, C., Keibl, C., Schädl, B., Heimel, P., *et al.* (2021). Repopulation of decellularised articular cartilage by laser-based matrix engraving. *E BioMedicine., 64*(103196).

96. Rayegani, S. M., Raeissadat, S. A., Heidari, S. & Moradi-Joo, M. (2017). Safety and effectiveness of low-level laser therapy in patients with knee osteoarthritis: a systematic review and meta-analysis. *J Lasers Med Sci., 8*(Suppl 1), S12-S19.

97. Nelson, A. E. (2018). Osteoarthritis year in review 2017: Clinical. *Osteoarthritis Cartilage., 26*(3), 319-325.

98. Kolasinski, S. L, Neogi, T., Hochberg, M. C., Oatis, C., Guyatt, G., *et al.* (2020). 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res., 72*(2), 149-162.