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PHOTOBIOMODULATION AS AN ADJUVANT THERAPEUTIC APPROACH IN THE TREATMENT OF DRUG-INDUCED OSTEONECROSIS OF THE JAWS

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ABSTRACT

Drug-induced osteonecrosis of the jaws (RONJM) represents a serious adverse complication, characterized by a degenerative process associated with the use of antiangiogenic and antiresorptive drugs. This condition manifests itself through the presence of an area of exposed bone in the maxillofacial region that persists for more than eight weeks, particularly in patients undergoing prolonged bisphosphonate or denosumab therapies with no history of prior radiotherapy to the craniofacial region. The management of RONJM is highly varied and challenging, depending on clinical assessment, imaging findings, and the patient's general health status. This study aimed to perform an integrative literature review to evaluate the efficacy of photobiomodulation as a complementary therapy in the treatment and/or prevention of this condition. The research was conducted through active searches in the PubMed, ScienceDirect, Embase, Scopus and Web of Science databases, covering the period from 2014 to 2023. A total of 2,324 articles were found, of which 10 were selected for the extraction of relevant data. Photobiomodulation as a complementary therapy in the treatment of RONJ plays a significant and promising role, compared to conventional surgical methods alone, presenting superior results. The combination of antibiotic therapy, antimicrobial photodynamic therapy (PDT), surgical removal of the lesion, and consecutive applications of low-level laser has demonstrated complete tissue repair in the affected regions. Therefore, it is concluded that photobiomodulation as an adjuvant intervention in the treatment and prevention of RONJM is an effective and reliable protocol.

Keywords: Osteonecrosis. Therapeutics. Photobiomodulation.

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INTRODUCTION

Drug-induced osteonecrosis of the jaws represents a serious and challenging adverse complication , with a degenerative character, associated with the use of antiangiogenic and antiresorptive medications, especially bisphosphonates and denosumab, respectively (Seyed Javad Kia *et al.,* 2021). This condition occurs in approximately five percent of people who use these medications for the treatment of osteoporosis, metastasis This condition is characterized by an area of exposed bone in the maxillofacial region that does not heal after eight weeks in patients who have undergone prolonged bisphosphonate or denosumab therapy, with no warning history of radiation therapy to the maxillofacial region (Momesse *et al.,* 2020).

Bisphosphonates have been identified as the main triggers of osteonecrosis in the jaws, presenting a mechanism that reduces bone renewal through the reduction of osteoclastic activity and induction of apoptosis. In addition, it is suggested that the presence of a local infection with inhibited osteoclastic activity is a contributing factor to bone necrosis. To date, there is no clear consensus nor defined guidelines for the management of osteonecrosis (Mobadder *et al*., 2023).

Current treatment options for osteonecrosis include the administration of antibiotics, hyperbaric oxygen therapy, bone resection, use of low- and high-power lasers, and cell therapies. Photobiomodulation therapy (PBM) or low-intensity laser or LED light therapy, represents an innovative strategy that has been shown to have several positive effects, including pain relief, wound healing, and nerve regeneration, as well as antimicrobial and biostimulant effects when applied to oral tissue, improving tissue healing (Momesso *et al.,* 2020; Mobadder *et al.,* 2023).

It is noteworthy that, despite the wide use of photobiomodulation, the mechanism of action is not yet fully understood. Literature studies demonstrate the involvement associated with light uptake by cell-specific chromophores, such as cytochrome c oxidase, which leads to an increase in cellular energy production in the form of adenosine triphosphate (ATP) and improved cellular metabolism. In addition, PBM therapy has been shown to modulate the expression of genes involved in inflammation and tissue repair and stimulate the release of growth factors and other cellular healing mediators (Razavi *et al.,* 2022).

In this context, photobiomodulation emerges as a promising adjunct therapeutic approach, offering an innovative perspective to improve clinical outcomes. The objective of our study is to perform an integrative literature review to evaluate the efficacy of

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photobiomodulation as an adjuvant therapy in the treatment of drug-induced osteonecrosis of the jaws, especially due to the fact that the mechanisms of action of the therapy and the optimal dosage for different conditions are not yet fully understood.

METHODOLOGY

It is an integrative literature review with a theoretical-methodological framework based on the model proposed by Hermont et al. (2021) that describes the process of elaborating an integrative review in 7 phases: 1st) establishment of the research question, 2nd) establishment of inclusion and exclusion criteria, 3rd) literature search, 4th) data collection, 5th) evaluation of studies, 6) interpretation of the results, 7) presentation of the review.

The research was guided by the following question: **"**Are there consistent and reliable data in the literature that allow us to affirm the use of a protocol with photobiomodulators as a preventive or attenuating measure of osteonecrosis of the jaws induced by medications?"

For the elaboration and structuring of the research question, the strategic conceptual model with emphasis on scientific evidence, PICO strategy, was used, which has the acronyms: P = Population or Patient; I= Intervention; C= Control and compare and O= Outcomes/outcome, as shown in Chart 1. In addition, the present study will be designed in accordance with the recommendations and guidelines of the guide "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) published in 2020, in order to evaluate the effects of health interventions, regardless of the design of the included studies.

Table 1. PICO strategy used.

P- Population	Patients using antiangiogenic and antiresorptive medications
I- Intervention	Use of photobiomodulators
C- Comparador	Use of laser therapy and other types of therapies (medical and surgical) for patients with RONJ to verify the best therapeutic approach
O- Outcome	Reduction of side effects of antineoplastic therapy - Stimulation of the tissue repair process and attenuation of drug-induced osteonecrosis

Source: Authors, 2024

The research was based on active searches in the databases, CAPES journals, using the PubMed, ScienceDirect, Embase, Scopus and web of science platforms. The search strategies corresponded to Osteonecrosis, Laser Therapy Jaws and Mouth. The

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terms were searched and are duly registered in the descriptors in health science (DeCS) and in the Medical Subject Headings (MeSH); the investigations were conducted by combining the descriptors Osteonecrosis, Laser Therapy, Jaws, Mouth, using the Boolean operator AND and OR. In summary, the search strategy used consisted of: (Osteonecrosis AND Laser Therapy AND Jaws) OR (Osteonecrosis AND Laser Therapy AND Mouth).

A total of 2,324 articles were identified and incorporated into the RAYYAN® systematic review management program to facilitate organization, deletion of duplicate records, and reading selection. The inclusion criteria consisted of relevant clinical studies, including clinical trials, case series, case reports, and retrospective and pilot studies, published in English and involving patients with drug-induced osteonecrosis associated with photobiomodulatory therapy, Chart 2.

The studies were selected with a time frame of 10 years, in order to cover the most recent literature. Duplicate samples were removed as the analysis progressed, ensuring the integrity and relevance of the chosen data.

Table 2. Selection, inclusion and exclusion criteria

Selection criteria	Inclusion Criteria	Exclusion Criteria
Population	Patients treated with photobiomodulation for medication-induced osteonecrosis of the jaws	Studies that do not address the research population
Intervention	Use of photobiomodulation as an adjuvant treatment for drug-induced osteonecrosis	Studies involving medication-induced osteonecrosis that do not use photobiomodulation as an adjunctive agent
Type of study	Clinical trials, Case series, Case reports, Pilot study, Retrospective study	In vivo animal studies, in vitro studies, literature review, book chapter
Time Period	Studies published between 2014 and 2023	Studies published in years prior to 2014

Source: Authors 2024

RESULTS

Database searches identified a total of 2,324 articles: (103) captured by PUBMED, (564) SCIENCEDIRECT, (83) EMBASE, (1,474) SCOPUS and (100) WEB OF SCIENCE as shown in Figure 1. Initially, the selection of studies was carried out using as criteria only the records between the years 2014 and 2023, resulting in 1,905. Subsequently, 665 duplicate samples were excluded, summarized in a total of 1,238 articles. Subsequently, the inclusion of articles was carried out using the title and abstract of the records as inclusion criteria.

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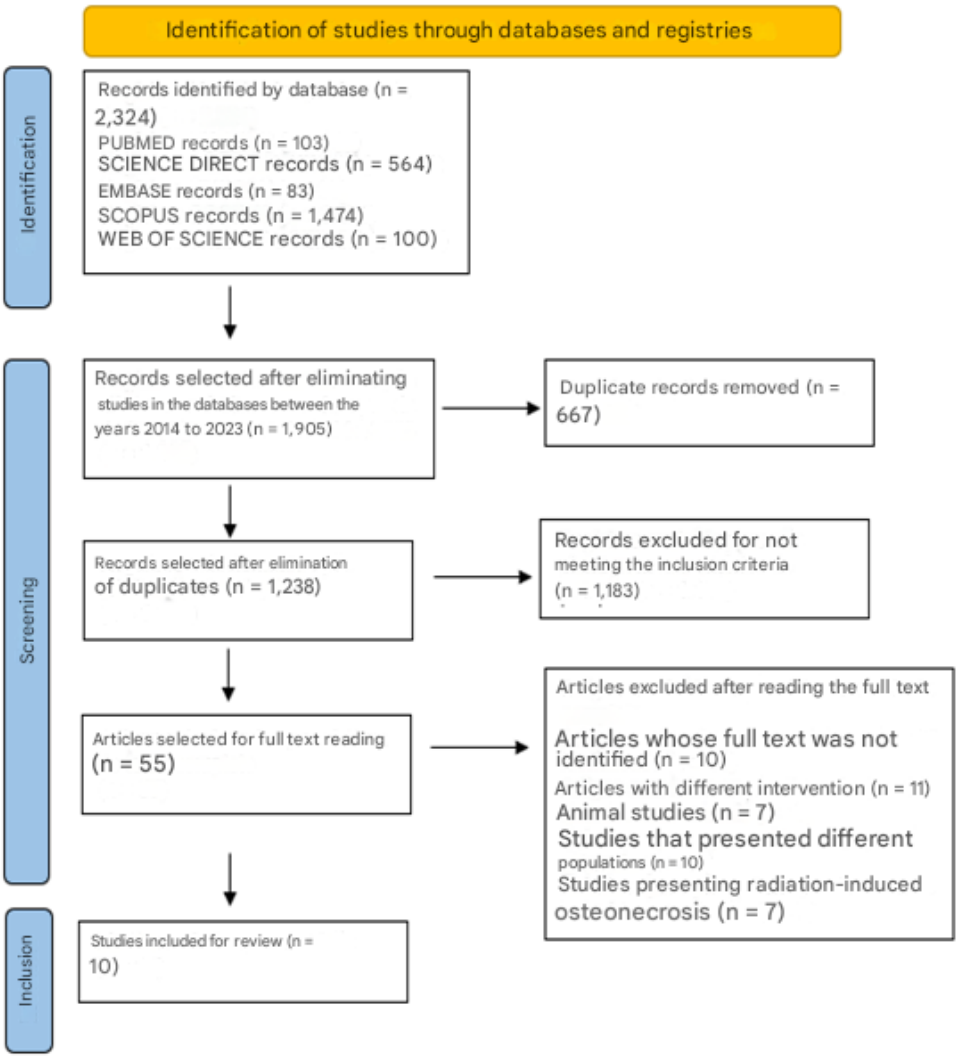
During the reading of the titles and abstracts, 1,183 articles were removed for not meeting the inclusion criteria, obtaining (55) articles for complete and full reading of the texts. The analyses identified (10) articles whose full text was not identified, (10) studies presented a treatment intervention different from the objective of the present review, (7) animal studies, (10) articles that presented a different population. In summary, 10 studies were included for review for data extraction, according to Table 1, which lists the authors, year of the articles, main objectives and conclusions of the studies included in this review.

Figure 1. Systematization of the methodology used for selected data extraction



Source: PRISMA, 2020 (Adapted and translated)

Table 1. Results of the bibliographic survey presenting the authors/year, objectives and conclusion.

Author/Year	Objective	Type of study	Conclusion
Nica *et al.*, 2021	The aim of the study was to apply and analyze the results of a therapy combining antibiotic therapy, surgical	Case series	Patients at almost all stages of osteonecrosis can benefit from the combination of photobiomodulation

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	treatment and photobiomodulation for the prevention and treatment of medication-induced mandibular osteonecrotic lesions.		and laser surgery with superior clinical outcomes compared to classical therapies.
Altay *et al.*, 2014	To evaluate and report the outcomes of medical-surgical treatment supported by low-level laser therapy (LLLT) of 11 patients with bisphosphonate-related osteonecrosis lesions of the jaws (BRONJ).	Pilot study	The combination of antibiotic therapy, surgical removal of the lesion and consecutive applications of low-level diode laser provided favorable results in all patients. Considering the findings of the study, it can be assumed that LLLT can be used as a safe and effective adjunct to the medical-surgical treatment of BRONJ lesions.
Rodriguez *et al.*, 2019	To evaluate photobiomodulation therapy as an adjunctive response in the surgical treatment of bisphosphonate-related osteonecrosis in the jaws (BRONJ).	Pilot study	This pilot study demonstrated that photobiomodulation can be an effective treatment modality against BRONJ. LLLT showed a significant improvement as an adjuvant treatment, facilitating postoperative recovery.
Minamizako *et al.*, 2016	The present case-control study aimed to evaluate the efficacy of low-level laser therapy (LLLT) and antimicrobial photodynamic therapy (PDT) in the management of drug-induced osteonecrosis of the jaws (MRONJ).	Case report	The proposed new therapeutic approach led to the reduction of the MRONJ lesion stage, acting as an adjuvant treatment within a set of clinical maneuvers, bringing beneficial effects in the control of the disease and providing improvement in the patient's quality of life. Based on the results, the use of LLLT and PDT as adjunctive treatment of MRONJ is recommended.
Tartaroti *et al.*, 2020	To observe the long-term results of two photonics-based protocols, antimicrobial photodynamic therapy (PDT) and photobiomodulation (PBM) for prevention and treatment of MRONJ lesions.	Case series	PDT and PBM therapy protocols appear to be effective as an adjunctive approach, not only to prevent the development of MRONJ due to tooth extraction, but to treat MRONJ lesions in early stages without adverse effects.
Tenore *et al.*, 2020	The purpose of this study was to retrospectively compare the effect of three different treatment protocols on cure outcome in patients with established medication-related mandibular osteonecrosis (MRONJ)	Retrospective study	The combination of antibiotic therapy, surgery, L-PRF, and photobiomodulation can effectively contribute to the management of RONJM. Despite the growing awareness of MRONJ, a standardized treatment protocol is still lacking. Further research with a larger sample size, including all stages of MRONJ, is needed to confirm our promising results.
Vescovi *et al.*, 2015	The aim of this study was to propose an autofluorescence (AF)-guided surgical approach performed with Er:YAG laser	Case report	The AF-guided surgical approach performed with Er:YAG and Nd:YAG laser and LLLT had not been

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	and low-level Nd:YAG laser therapy (LLLT).		previously reported. Given the demonstrated advantages associated with laser therapy compared to traditional surgery, and the possible efficacy of AF in enhancing surgical margins, this approach has obtained excellent results.
Poli, *et al.*, 2019	The study aimed to describe the use of antimicrobial photodynamic therapy (PDT) in the prevention of medication-related mandibular osteonecrosis (MRONJ)	Case series	The results showed complete healing in all cases, highlighting the efficacy of PDT and low-level laser therapy as preventive measures for MRONJ.
El Mobadder, *et al.*, 2023	This case report describes the successful treatment of stage II medication-related osteonecrosis of the jaw.	Case reports	Within the limitations of this case report, PBM as an additional approach, for minimal surgical intervention in stage II medication-related osteonecrosis of the jaw, can be considered an effective therapeutic approach if used within our suggested irradiation parameters and treatment protocol.
Vescovi *et al.*, 2015	To evaluate the safety and efficacy of the protocol using photobiomodulation in patients at high risk for medication-related mandibular osteonecrosis (MRONJ) and who have been previously affected.	Case series	The data confirmed that laser biostimulation is a reliable technique that can be considered in the surgical protocol for patients undergoing bisphosphonate treatment.

Source: Authors 2024

DISCUSSION

Drug-induced osteonecrosis of the jaws (MRONJ) represents a serious adverse manifestation characterized by the presence of exposed bone or probing of the bone through a fistula, either in the intraoral or extraoral region, in the maxillofacial region. Clinically, for diagnostic confirmation of the condition, the lesion must persist for more than 8 weeks, with no history of radiotherapy to the jaws or evidence of obvious metastatic disease in this area. (Poli et al., 2019)

MRONJ presents diversified management depending on the detailed clinical examination performed, results obtained from imaging tests, and the patient's general health status. The primary goal of treatment strategies is based on minimizing or, ideally, preventing pain, reducing the risk of infection, and declining the individual's overall health. (Diniz-Freitas & Limeres, 2016)

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To scientifically support the diagnostic characteristics of this complication, the American Association of Oral and Maxillofacial Surgeons (AAOMS) proposed the adoption of the revised staging system, as described in Chart 3.

Table 3. Staging stages of osteonecrosis of the jaws, according to the American Association of Oral and Maxillofacial Surgeons (AAOMS).

Internship	Characteristics	Observed changes
Stage 0	No clinical evidence of necrotic bone	Nonspecific clinical signs and symptoms; No evidence of infection; Possible radiographic changes: bone alveolar resorption or loss, changes in the trabecular pattern of dense bone, osteosclerosis, periodontal ligament thickening
Stage 1	Exposure of necrotic bones or presence of fistula	Absence of signs of disease or infection; Possible radiographic changes as mentioned in stage 0
Stage 2	Exposure of necrotic bone or fistulas	Evidence of microbial infection; Pain and erythema in the exposed bone region with or without drainage; Presents radiographic findings mentioned in stage 0
Stage 3	Alterations mentioned in stage 2, bone exposure beyond the alveolar bone region, pathological fracture, extraoral fistula, oral, antral or oral nasal communication, osteolysis extending to the lower border of the mandible or sinus floor	Presents radiographic findings mentioned in stage 0

Source: American Association of Oral and Maxillofacial Surgeons (AAOMS)

Understanding the exact pathophysiology of drug-induced osteonecrosis of the jaws remains challenging, with several theories proposed that include inhibition of bone remodeling, immune system impairment, soft tissue toxicity, inflammatory or infectious processes, and inhibition of the formation of new blood vessels (angiogenesis) (Scribante *et al.,* 2023).

Because the pathophysiology is partially mysterious, and the challenges associated with ineffective treatment and disease recurrence, research efforts have been geared toward improving established treatment protocols by integrating complementary therapeutic strategies. These approaches aim not only to improve clinical outcomes but also to enrich the quality of life of patients. Among the innovations adopted, laser photobiomodulation therapy stands out. (Govaerts *et al.,* 2020)

The use of photobiomodulation therapy or low-level laser stands out for promoting cell proliferation and differentiation, significantly reducing pain and inflammation (Dompe *et*

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al., 2020). This method can contribute to a substantial improvement in wound healing, offering a promising approach in the management of drug-induced osteonecrosis of the jaws and in assisting the recovery process of patients.

In this context, a study conducted by Vescovi *et al.,* 2015 highlighted the use of low-level laser therapy in conjunction with tooth extraction surgeries for high-risk patients, treated with bisphosphonates, and with a history of osteonecrosis of the jaws. Patients were evaluated for 3 days and once a week for 2 months after extractions after receiving low-level laser therapy. A total of 82 extractions were performed, and minimal bone exposure was observed in only 2 cases, which continued to receive treatment with Er:YAG laser vaporization and achieved complete healing afterwards.

Poli *et al.,* 2019 investigated the use of antimicrobial photodynamic therapy in conjunction with low-level laser therapy as prevention for RONJ in osteoporotic patients receiving non-intravenous antiresorptive treatments. In the study, 62 extractions were made between teeth and implants, and after their extraction, methylene blue and a diode laser (660 ± 10 nm) were used, followed by low-level laser therapy to aid healing for six weeks. The results showed complete healing in all cases, highlighting the efficacy of PDT and low-level laser therapy as preventive measures against MRONJ.

In addition, in a comparative retrospective analysis between different treatment protocols conducted by Tenore *et al.,* (2020), it was evidenced that the combination of antibiotic therapy, surgery, leukocyte and platelet-rich fibrin (L-PRF) and PBM, were effective in achieving complete cure of MRONJ. This study reinforced the importance of multidisciplinary approaches in the effective management of this condition, demonstrating that photobiomodulation therapy plays a significant role in this context.

Pilot studies, such as those conducted by Altay *et al.*, (2014) and Rodrigues *et al.*, (2019), provided evidence of photobiomodulation therapy as an aid in the surgical treatment of osteonecrosis of the jaws related to the use of bisphosphonates. Both studies concluded that photobiomodulation can be an effective method in combating MRONJ, noting that the use of low-level laser therapy (LLLT) provided a significant improvement, aiding in the post-surgical recovery of patients.

Minamisako *et al.,* (2016) described the case of an 85-year-old man with bisphosphonate-caused osteonecrosis of the jaws (MRONJ), presenting with bone exposure, suppuration, and pain. Treatment included the use of antibiotics, conservative debridement, low-level laser therapy (LLLT), and photodynamic therapy (PDT). This

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adjuvant approach improved the patient's life picture, highlighting the potential benefits of using LLLT and PDT in the treatment of JRONJM.

Mobadder *et al.,* (2023) reported a successful case in the management of medication-related osteonecrosis of the jaws in an 83-year-old female patient with symptoms of pain and difficulties in swallowing and phonation. Treatment involved three sessions of photobiomodulation therapy (PBM), followed by minimal surgical intervention and three more sessions of PBM. Although it is only a case report, the use of PBM as an adjunct to minimal surgical intervention for MRONJ and can be considered an effective therapeutic approach.

The use of low-level laser as an adjuvant therapy for the management of medication-induced osteonecrosis in the jaws has often been associated with methods that involve: antimicrobial photodynamic therapy (PDT), laser ablation protocol, antibiotic therapy, leukocytes and platelets-rich fibrin, and Er:YAG laser, mainly. Such combined methods have shown considerable and effective progress in preventing or attenuating the clinical condition presented by patients (Weber *et al.,* 2016; Vescovi *et al.,* 2015).

In consensus among most of the studies evaluated in the present review, PBM as an adjuvant in the treatment of ONJM plays a significant and prominent role when compared to conventional surgical methods, for example. Thus, when used in associated protocols, biological results outperform classical therapies (Nica *et al*., 2021; Altay *et al.,* 2014; Rodriguez *et al.,* 2019; Minamisako *et al.,* 2016; Tartaroti *et al.,* 2020; Vescovi *et al.,* 2015).

CONCLUSION

Therefore, it is concluded that the use of laser has demonstrated more effective results in curing or improving osteonecrosis of maxillary lesions associated with medications, compared to conventional and/or conservative surgical drug therapy. The gold standard for the management of bisphosphonate-related maxillary osteonecrosis in the early stages of the disease consists of a combination treatment involving antibiotics, minimally invasive surgery (such as Er:YAG laser surgery), and low-level laser therapy.

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