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# Evaluation of the response to photobiomodulation and magnetotherapy in osteonecrosis of the jaws induced by the use of bisphosphonates: a systematic review

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## Abstract

**Introduction:** Bisphosphonates are drugs that act on bone metabolism, inhibiting calcium precipitation and bone resorption. When used for long periods to control osteoporosis, these drugs can cause adverse effects, such as osteonecrosis of the jaws (Bisphosphonate-Related Osteonecrosis of the Jaws - BRONJ), which is more frequent in 8% to 12% of patients when administered intravenously. However, it should be noted that complications, when they occur, are very severe and mutilating, greatly impairing the quality of life of these patients. Energy-based devices (EBD), described in the biophotonic literature, reveal effective anti-inflammatory, analgesic, neoangiogenic, and reparative action. **Objective:** It was conducted a systematic review to present the main clinical considerations and consequences of the use of bisphosphonates in the occurrence of osteonecrosis of the jaw, as well as to discuss the treatments of photobiomodulation and magnetotherapy. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from November 2024 to January 2025 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** 118 articles were found, 30 articles were evaluated in full and 12 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 31 studies that did not meet GRADE and AMSTAR-2. Most studies did not show homogeneity in their results, with $X^2$=88.5%>50%. It is concluded that with the increasing use of bisphosphonates against osteoporosis especially in cases of postmenopausal women with osteopenia, a proportionally higher incidence of the main adverse effect of these drugs in the maxillomandibular region, osteonecrosis of the jaw, has emerged. The "gold standard" therapy of choice proposed for this disease is surgical treatment. Complications, when present, are very severe and mutilating, greatly impairing the quality of life of these patients. Morbidities include extensive resections, secondary infections, lack of tissue for primary closure, dehiscence, and fistulas, which can evolve into multilateral wounds with serious consequences, such as sepsis. In this regard, photobiomodulation therapy and magnetotherapy demonstrated safety and efficacy in the treatment of bisphosphonate-related osteonecrosis of the jaw, through reduction of inflammatory signs, faster healing, and reduction of postoperative morbidity. Thus, it was demonstrated that only four applications of low-intensity laser and magnetotherapy were sufficient to reduce the inflammatory process in the surgical wound, stimulate the tissue repair process, and provide postoperative analgesia.

**Keywords:** Bisphosphonates. Osteonecrosis. Jaw. Low-intensity laser. Pulsed magnetic field. Osteoporosis.

## Introduction

According to epidemiological results, the failure rate of dental implants due to the occurrence of osteonecrosis of the jaw after the use of bisphosphonates (BP) reaches approximately 23%, with 83% of failures attributed to medication-related osteonecrosis of the jaw (MRONJ). The average time from the start of antiresorptive medication to the development of MRONJ can be approximately 34 months [1,2]. Bisphosphonates are drugs from a class widely used in several medical specialties. Their main property is to inhibit the precipitation of calcium phosphate, decreasing calcification and bone resorption, and reducing osteoclastic action by inducing apoptosis of these cells. Their prescription was initially restricted to diseases that interfered with bone metabolism, such as Paget's disease, malignant hypercalcemia, bone metastases, osteolytic lesions, and multiple myeloma. Currently, it has also been widely prescribed for the treatment of osteoporosis and even as a prophylaxis for osteopenia [3,4].

Among the bisphosphonate class, there are several drugs with similar effects on bone tissue, varying in potency and route of administration. Examples include Sodium Risedronate, Sodium Etidronate, Zoledronic Acid, and the most commonly prescribed oral drug, Sodium Alendronate [1,5]. These drugs can cause serious adverse effects on the body, including, among the most frequent, hypocalcemia, impaired renal function, complications in the digestive tract such as esophageal ulcers, atypical femur fractures, atrial/ventricular fibrillation and osteonecrosis of the jaws, the latter being the subject of our study. Patients who use this class of medication orally have the lowest prevalence of osteonecrosis (0.01% to 0.04%), while those who use it intravenously are affected by 8% to 12% [3-5].

It should be noted that complications, when they occur, are very severe and mutilating, greatly impairing the quality of life of these patients. One of the recent treatments for bone disorders is the use of anti-resorptive drugs, including hormone replacement therapy, selective estrogen receptor modulators, bisphosphonates, and denosumab, which reduce the occurrence of pain, pathological fractures and spinal cord compression [1-5]. The main property of BP is to inhibit the precipitation of calcium phosphate, reducing calcification and bone resorption, and reducing osteoclastic action, by inducing apoptosis of these cells, which reabsorb bone tissue. These have a high affinity for bone tissue, a long half-life in bones, inhibiting bone resorption, and can be administered orally or intravenously [1].

The mechanisms of action of BPs in bone metabolism are complex and multifactorial, changing the osteoclastic cytoskeleton, stimulating apoptosis, and, above all, reducing the proton pump with changes in pH and acid-base balance. The clinical efficacy of BP increases due to their ability to bind strongly to bone minerals. The initial release of BP occurs by renal excretion or adsorption to bone minerals, lasting for weeks to years. During bone resorption, the acidic pH in the resorption lacuna increases the dissociation of the drug in the bone [5].

Also, BP are synthetic analogs of organic pyrophosphates, where the unstable oxygen atom of the central structure (P-O-P) was replaced by Carbon (P-C-P), making it more resistant and unable to be broken down by enzymes. BP interfere with chemotaxis and osteoclast attachment to bone, together with the suppression of osteoclast function. In addition, they block the recruitment, activation, and differentiation of osteoclast precursors. They inhibit the proliferation of macrophages, decreasing their recruitment and differentiation into osteoclasts, in addition to reducing the number of osteoclasts, altering the cytoskeleton of these cells, depolymerizing the microtubules and retracting the rough membrane, thus hindering their adhesion to the bone [3,4].

Besides, BP have anti-angiogenic effects. As such, impaired vascularization may play a major role in the development of osteonecrosis of the jaw. They also affect immunity, resulting in impaired function of myeloid cells, dendritic cells, and increased numbers of T cells. These increase the antigenicity of cancer cells as targets and increase adaptive immunity. This impairment of local immunity with a greater tendency to infect may be a key element in osteonecrosis of the jaw [1,2].

In this context, as forms of treatment, photobiomodulation [6-10] and magnetotherapy [11-15] may be helpful in the repair process, as adjuvants to the surgical treatment of Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ). In dentistry, low-intensity laser treatment is already consolidated, having been performed since the 1980s, with good results when it comes to modulating inflammation, tissue repair and analgesia. In the search for less invasive treatments for osteonecrosis, Vescovi et al. 2003 [16] developed a new preventive methodology using low-intensity laser after dental extractions in 217 patients treated with BP and only 5 patients observed bone exposure. Magnetotherapy has been approved by

the FDA and studies have demonstrated the benefits of the electromagnetic field for the treatment of edema, osteoarthritis, wounds, hemodynamic modulation, pain relief, inflammation, tissue regeneration, and bone formation. It is an important tool in Physiotherapy around the world, as it is a non-invasive, safe, and easy-to-use method.

Therefore, the present study aimed to carry out a systematic review to present the main clinical considerations and the consequences of the use of bisphosphonates in the occurrence of osteonecrosis of the jaw, as well as to discuss the treatments of photobiomodulation therapy and magnetotherapy.

## Methods

### Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 12/20/2024. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 12/20/2024.

### Search Strategy and Sources

The literature search process was carried out from November 2024 to January 2025 and developed based on Web of Science, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors were used in health sciences (DeCS/MeSH): "Bisphosphonates. Osteonecrosis. Jaw. Low-intensity laser. Pulsed magnetic field. Osteoporosis", and the Boolean "and" was used between the MeSH terms and "or" between the historical findings.

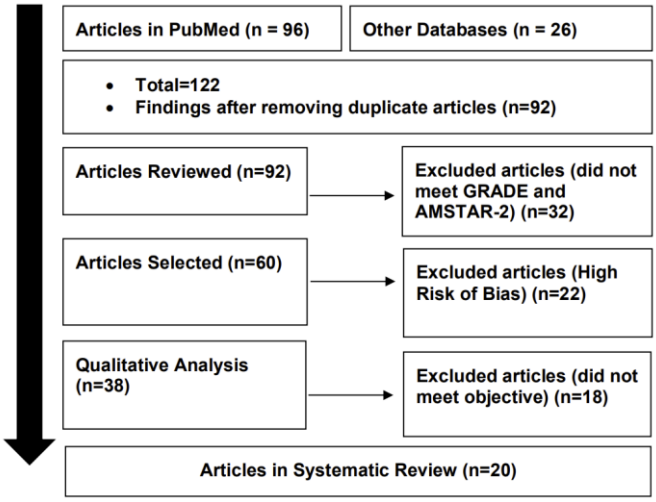
### Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

### Summary of Findings

A total of 122 articles were found and submitted to eligibility analysis, with 20 final studies selected to compose the results of this systematic review. The listed studies were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with $X^2$=88.5%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 22 studies with a high risk of bias and 32 studies that did not meet GRADE and AMSTAR-2.

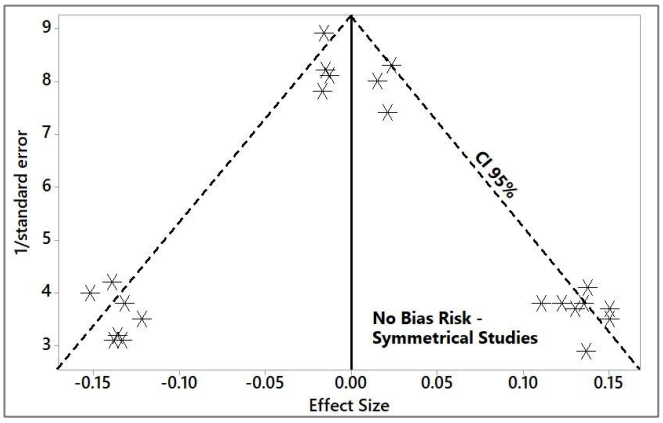
Figure 1. Flowchart showing the article selection process.




Source: Own Authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that are presented at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=20 studies).




Source: Own Authorship.

## Main Outcomes

Osteoporosis is an osteometabolic disease characterized by decreased bone mass and destruction of the microarchitecture of bone tissue with increased bone fragility. Its clinical complications include fractures, chronic pain, depression, deformities, loss of independence, and increased mortality. It is estimated that approximately 50% of women and 20% of men aged 50 years or older will suffer an osteoporotic fracture throughout their lives. Among the medications that reduce osteoporotic fractures, oral bisphosphonates are the first-choice medications in the treatment of osteoporosis [1-3].

These drugs can have several adverse effects, including osteonecrosis of the jaw, which affects 0.01% to 0.04% of patients who use the drug orally. However, although rare, complications, when they occur, are severe and mutilating, impairing the quality of life of these individuals [17,18]. According to the WHO Guideline, clinical treatment of osteonecrosis consists of improving signs and symptoms with anti-inflammatory drugs, antibiotic therapy, analgesics, and chlorhexidine irrigations, which can last for months, worsening local conditions. Surgical treatment, for the removal of necrotic bone and curettage of the bone sequestration, has higher success rates than conservative treatment, but with a high rate of recurrence, causing infections, lack of tissue for primary closure, and the need for new resections with mutilation of the face [19].

In this scenario, the authors Weber et al. 2016 [20] found studies demonstrating favorable results with surgical therapy combined with laser treatment. According to Li et.al. 2020 [21], in a systematic review, observed that there was a significant change in the pain score after low-intensity laser treatment (LLLT) and in the assessment of analgesia by VAS, we observed that in the first 7 days of PO, the Laser group presented a significant reduction in pain compared to the placebo and magnet groups, a fact that stabilized after 14 days.

It was also observed that Lorenzo-Pouso et al. 2019 [22] in a systematic review suggest that there are currently no markers available to assess the risk of BRONJ. However, the work indicates that a paradigm shift in bone remodeling, angiogenesis, and endocrine biomarkers could be useful in new research.

According to Vieira 2007 [23], during bone formation, the production of the collagen matrix precedes mineralization. The collagen matrix production phase coincides with the highest production of alkaline phosphatase, in addition to being more effective for bone formation at the beginning than in later stages, because in the first stage of bone healing, cellular components are more important and, therefore, more susceptible to the action of the laser. LLLT in bone tissue causes an increase in the amount of mRNA used to synthesize type I collagen, which stimulates the formation and repair of bone tissue. This fact was more observed in the magnetotherapy group in the laser group, after 30 and 60 days. Suggesting a relevant role in the physiology of bone neoformation.

It was also found that the results of patients treated with magnetotherapy were very similar to those of patients treated with LLLT, thus signaling a new possibility of preventive treatment for BRONJ. Its main actions are the deflection of electrically charged particles in motion, the production of currents induced by the piezoelectric effect in bone tissue and collagen, and, at the cellular level, it normalizes the membrane potential, increases the solubility of substances, stimulating cellular metabolism, and promoting an acceleration of all reparative phenomena with regenerative, anti-inflammatory, and anti-edematous action, without demonstrating side effects. Thus, in living tissue, one finds mainly alternating fields, as well as a combination of electric and magnetic fields, with cellular movements, ionic flows, fluids in the circulatory systems, the mitochondrial electron transport chain, action potentials in the membranes, and so on. In other words, all systems of an organism, from the molecular level to the organ level, are more or less in motion [11-15].

With the use of laser therapy and magnetotherapy, studies show a reduction in the enzyme lactate dehydrogenase (LDH), an intracellular enzyme that is present in practically all tissues of the body and participates in the process of transforming glucose into energy in the cells of animals, plants and even bacteria. LDH is released into the bloodstream when cells are damaged or destroyed, increasing the levels of LDH in the circulation, and can be detected in a blood test. A higher concentration of this enzyme in the extracellular medium is related to the rupture of the plasma membrane and consequent cell death [6-15].

In addition, normal levels of the enzyme creatine phosphokinase (CPK) have been observed through the use of laser therapy and magnetotherapy. This enzyme

is found in the heart, brain, skeletal muscles, and several other tissues. CPK catalyzes the conversion of creatine and consumes adenosine triphosphate (ATP) to create phosphocreatine (PCr) and adenosine diphosphate (ADP). This reaction of the CPK enzyme is reversible and, therefore, ATP can be generated from PCr and ADP. In skeletal and cardiac muscle cells, most of the energy is used for muscle contraction. An increased CPK generally indicates that there has been muscle injury. Therefore, patients undergoing treatment with BPs should be informed about the potential risk of BRONJ [7,8,11,12].

It would be advisable for providers responsible for BP therapy to refer patients for dental check-ups before starting treatment, allowing the patient to be monitored by a multidisciplinary team. Although the morbidity rate of this pathology is not high, prevention should be mandatory, thus avoiding mutilating and painful processes. Nevertheless, if surgery is necessary, the use of these new adjuvant therapies, such as photobiomodulation and magnetotherapy, can be proposed in the treatment of BRONJ [6-15].

## Conclusion

It is concluded that with the increasing use of bisphosphonates against osteoporosis especially in cases of postmenopausal women with osteopenia, a proportionally higher incidence of the main adverse effect of these drugs in the maxillomandibular region, osteonecrosis of the jaw, has emerged. The "gold standard" therapy of choice proposed for this disease is surgical treatment. Complications, when present, are very severe and mutilating, greatly impairing the quality of life of these patients. Morbidities include extensive resections, secondary infections, lack of tissue for primary closure, dehiscence, and fistulas, which can evolve into multilateral wounds with serious consequences, such as sepsis. In this regard, photobiomodulation therapy and magnetotherapy have demonstrated safety and efficacy in the treatment of bisphosphonate-related osteonecrosis of the jaw, through reduction of inflammatory signs, faster healing, and reduction of postoperative morbidity. Therefore, it was demonstrated that only four applications of low-intensity laser and magnetotherapy were sufficient to reduce the inflammatory process in the surgical wound, stimulate the tissue repair process, and provide analgesia in the postoperative period.

## CRediT

Author contributions: **Conceptualization -** Noroel Rosa da Silva Junior, Letícia Vitória de Oliveira Passoni; **Formal Analysis-** Noroel Rosa da Silva Junior, Letícia Vitória de Oliveira Passoni, Igor Mariotto Beneti; **Investigation-** Noroel Rosa da Silva Junior, Letícia Vitória de Oliveira Passoni; **Methodology-** Noroel Rosa da Silva Junior, Letícia Vitória de Oliveira Passoni; **Project administration-** Noroel Rosa da Silva Junior, Letícia Vitória de Oliveira Passoni; **Supervision-**Igor Mariotto Beneti; **Writing - original draft-** Noroel Rosa da Silva Junior, Letícia Vitória de Oliveira Passoni, Igor Mariotto Beneti; **Writing-review & editing-** Noroel Rosa da Silva Junior, Letícia Vitória de Oliveira Passoni, Igor Mariotto Beneti.

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## Informed Consent

Not applicable.

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## Data Sharing Statement

No additional data are available.

## Conflict of Interest

The authors declare no conflict of interest.

## Similarity Check

It was applied by Ithenticate@.

## Peer Review Process

It was performed.



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