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Major aspects of the use of bisphosphonates and the formation of osteonecrosis in the involvement of dental implants: a systematic review

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Abstract

Introduction: Bisphosphonates are widely used to treat osteoporosis and malignant tumors due to their effectiveness in increasing bone density and inhibiting bone resorption. Dental patients receiving bisphosphonate treatment are at higher risk of bisphosphonate-related osteonecrosis of the jaws (BRONJ), necessitating dentists' awareness of these risks. **Objective:** It was to highlight the main aspects of the use of bisphosphonates and the formation of osteonecrosis in the involvement of dental implants, as well as possible treatments. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from April to July 2024 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:** A total of 120 articles were found, 40 articles were evaluated in full and 15 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 14 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2. Most studies did not show homogeneity in their results, with X^2=89.5%>50%. Therefore, the present study suggests that patients undergoing treatment with BFs should be informed about the potential risk of BRONJ. Furthermore, it would be advisable for providers responsible for BF therapy to refer patients for dental check-ups before starting treatment, allowing for patient monitoring by a multidisciplinary team. Although the morbidity rate of this pathology is not high, prevention should be mandatory, thus avoiding mutilating and painful processes. However, if surgery is necessary, the use of these new adjuvant therapies, such as lowlevel laser therapy and magnetotherapy, can be proposed in the treatment of BRONJ. It is essential to increase our caseload and also involve other institutions in the use of these new effective and safe therapies in BRONJ.

Keywords: Bisphosphonates. Osteonecrosis. Bisphosphonate-related osteonecrosis of the jaws. Treatments. Dental implant.

Introduction

Bisphosphonates are widely used to treat osteoporosis and malignant tumors due to their effectiveness in increasing bone density and inhibiting bone resorption. However, their association with bisphosphonate-related osteonecrosis of the jaws (BRONJ) following invasive dental procedures poses a significant challenge. Dental patients receiving bisphosphonate treatment are at higher risk of BRONJ, necessitating dentists' awareness of these risks. Topical bisphosphonate applications enhance dental implant success, by promoting osseointegration and preventing

osteoclast apoptosis, and is effective in periodontal treatment. Systemic administration (intravenous or intraoral) significantly increases the risk of BRONJ following dental procedures, particularly in inflamed conditions. Prevention and management of BRONJ involve maintaining oral health, considering alternative treatments, and careful pre-operative and post-operative follow-ups [1].

With the increasing increased use of Bisphosphonates, against osteoporosis and especially in cases of women in menopause with osteopenia, proportionally, a greater incidence of the main adverse effect in the maxillomandibular region of these drugs arose: osteonecrosis of the jaws. The "gold standard" therapy of The proposed choice 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 multiple wounds with serious consequences, such as sepsis [2,3].

Bisphosphonates are a class of drugs widely used in various medical specialties. Their main property is to inhibit the precipitation of calcium phosphate, reducing calcification and bone resorption, and reducing osteoclastic action by inducing apoptosis of these cells. Its 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, they have also been widely prescribed for the treatment of osteoporosis and even as a prophylactic for osteopenia [4,5].

Among the bisphosphonate class, there are several drugs with similar effects on bone tissue, varying in potency and route of administration. Examples include Sodium Risendronate, Sodium Etidronate, Zoledronic Acid, and, the most commonly prescribed oral medication, Sodium Alendronate. These medications 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 ulcer, atypical femur fractures, atrial/ventricular fibrillation and osteonecrosis of the jaws, the latter being the object of our study. Patients who use this class of medication orally have the lowest prevalence of 0.01% to 0.04% of osteonecrosis, while those who use it intravenously are affected between 8% and 12% [3,4].

However, it should be noted that complications, when they occur, are very severe and mutilating, greatly harming the quality of life of these patients. One of the recent treatments for bone disorders is the use of antiresorptive drugs, including hormone replacement therapy, selective estrogen receptor modulators, bisphosphonates, and denosumab, which reduce the occurrence of pain, pathological fractures, and spinal cord compression. The main property of BFs is to inhibit the precipitation of calcium phosphate, reducing calcification and bone resorption, and reducing osteoclastic action, through the induction of apoptosis of these cells, which reabsorb bone tissue. These have a high affinity with bone tissue, half-life long in the bones, inhibiting bone resorption, and can be administered orally or intravenously [2-4].

The mechanisms of action of BPs on bone metabolism are complex and multifactorial, changing the osteoclastic cytoskeleton, stimulating apoptosis, and reducing, above all, the proton pump with changes in pH and acid-base balance 18. The clinical efficacy of BPs increases due to their ability to bind strongly to bone minerals. The initial release of BPs occurs by renal excretion or adsorption to bone minerals, lasting for a period of weeks to years. During bone resorption, the acidic pH in the resorption lacuna increases the dissociation of the drug in the bone [5].

BPs are synthetic analogs of organic pyrophosphates, where the unstable oxygen atom of the central structure (P-O-P) has been replaced by carbon (P-C-P), making it more resistant and unable to be broken down by enzymes [4,5]. BPs interfere with chemotaxis and the attachment of osteoclasts to bone, together with the suppression of osteoclast function. Furthermore, they block the recruitment, activation, and differentiation of osteoclast precursors. They inhibit the proliferation of macrophages, reducing 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 [1,4].

Bisphosphonates have anti-angiogenic effects. As such, impaired vascularization may play a major role in the development of osteonecrosis in the jaws. They also act on immunity, resulting in impaired function of myeloid cells, and dendritic cells and increasing the number 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 jaws [4].

The first report of osteonecrosis of the jaws due to the use of bisphosphonates was made by Marx et al in 2003 [1]. In 2007, a position paper by the American Association of Oral and Maxillofacial Surgeons (AAOMS) proposed for the first time its nomenclature "Bisphosphonates Related Osteonecrosis of the Jaws"

(BRONJ). ON is the term used to describe the death of bone cells when the osteocyte becomes necrotic. Necrosis also destroys vascular endothelial cells within the bone tissue, impairing blood flow within it 20. Patients who develop necrosis are in the age range of 35 to 95 years, with a higher prevalence between 65 and 68 years. Risk factors for the development of the disease include the dose and frequency administered, the potency of the drug, the route of administration, the duration of treatment, and the half-life of the drug in bone tissue. To confirm the diagnostic hypothesis, imaging tests should be requested, such as panoramic radiography and computed tomography of the face. These tests demonstrate the presence of bone sequestration with osteolytic areas associated with surrounding osteoblastic areas and an appearance of disorganization of the bone tissue, destruction of bone cortex, periosteal reactions, and pathological fractures [3-5].

Therefore, the present study highlighted the main aspects of the use of bisphosphonates and the formation of osteonecrosis in the involvement of dental implants, as well as possible treatments.

Methods

Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 06/16/2024. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 06/16/2024.

Data Sources and Research Strategy

The literary search process was carried out from April to July 2024 and was developed based on Scopus, PubMed, Web of Science, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various to the present. The descriptors (DeCS / MeSH Terms) were used: *"Bisphosphonates. Osteonecrosis. Bisphosphonate-related osteonecrosis of the jaws. Treatments. Dental implant"* and using the Boolean "and" between the MeSH terms and "or" between historical discoveries.

Study Quality and Risk of Bias

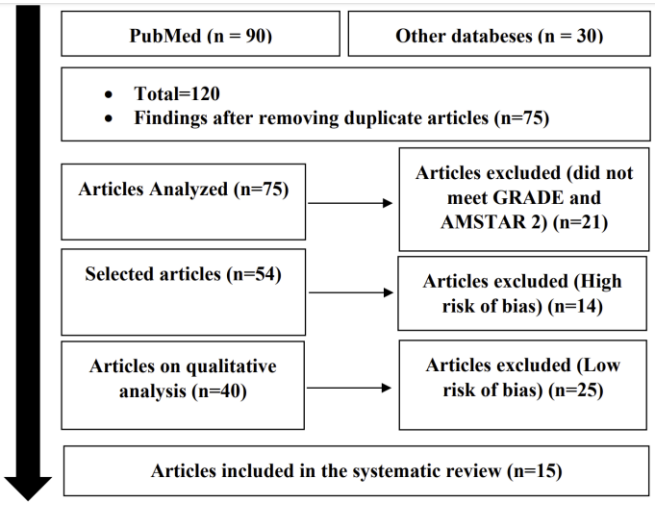
Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The 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 the Cohen test (d).

Results and Discussion

Summary of Findings

A total of 120 articles were found that were subjected to eligibility analysis, with 15 final studies being selected to compose the results of this systematic review. The studies listed 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. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with X^2=89.5%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 14 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2.

Figure 1. The article selection process by the level of methodological and publication quality.

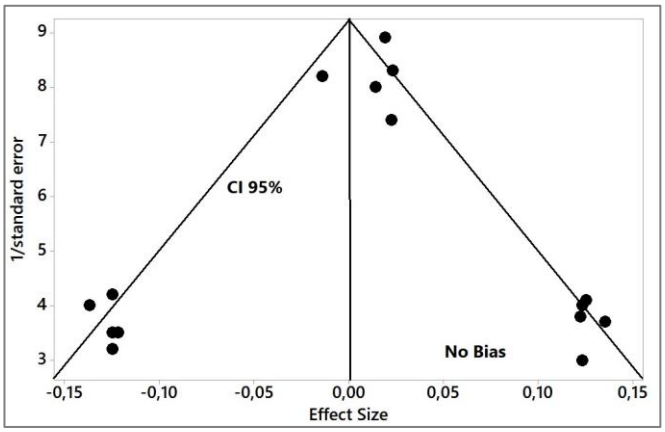


Source: Own authorship.

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 the Cohen 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 between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are

presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=15 studies).



Source: Own authorship.

Major Findings

In the dental implant setting, patients taking antiresorptive medications used to treat disorders associated with bone resorption may require dental implants to replace missing teeth. Antiresorptive medications, particularly bisphosphonates (BPs), can significantly contribute to implant failure. Antiresorptive medications, particularly BPs, can reduce implant survival and impair osseointegration of dental implants [6].

It has been a matter of debate as to whether dental implant therapies are suitable for patients subjected to long-term use of bisphosphonates (BPs). A study presented a case of a 76-year-old woman who developed BPs-related osteonecrosis of the jaw (BRONJ) in the left hemimandible after dental implant exposure. The implants and the necrotic crestal bone were removed, and postoperatively, a delay in tissue healing with bone exposure was noticed. The histological analysis of the block biopsies revealed a lamellar bone tissue exhibiting necrotic areas and bacterial colonies associated with the bone's outer surface. The bone implant showed interface viable lamellar bone with enlarged vascular spaces in the areas between the implant threads. The possible mechanisms for the loss of implants in BRONJ patients are discussed, and the potential protocols for dental implant rehabilitation for patients under BP therapies are presented [7].

According to the Ministry of Health, 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. 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 [8,9].

According to the AAOMS Guideline, clinical treatment of osteonecrosis consists of improving signs and symptoms with anti-inflammatory drugs, antibiotic therapy, analgesics, and irrigation with chlorhexidine, 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. In dentistry, low-intensity laser treatment is already well-established and has been used since the 1980s, with good results in terms of modulating inflammation, tissue repair, and analgesia. In the search for less invasive treatments for osteonecrosis, Vescovi et al. 2013 [8] developed a new preventive methodology using low-level laser therapy (LLLT) after tooth extractions in 217 patients treated with BFs, and only 5 patients observed bone exposure. Magnetotherapy (MAG) 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 [9,10].

The inflammatory phase aims to remove the cause of the injury, contain its extension, and prepare the site for cellular repair. The first event is hemostasis, through vasoconstriction, increasing local blood viscosity, allowing the formation of the clot, through the release of epinephrine by platelets and recruiting calcium to convert prothrombin into thrombin, to transform fibrinogen into fibrin fibers, forming a tangle of platelets, to form the clot [11].

The authors Weber et al. [12] found studies demonstrating favorable results with surgical therapy, combined with laser treatment50. As we observed in the postoperative period of the LBI and MAG Group, with

better mucosal healing and no recurrences or bone exposures. According to Li et al. 2020 [13], in a systematic review, observed that there was a significant change in the pain score after LLLT and in the assessment of analgesia by VAS, we observed that in the first 7 days of PO, the Laser group showed a significant reduction in pain compared to the placebo and Magneto groups, a fact that stabilized after 14 days.

Lorenzo-Pouso et al. (2019) [14] 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. In this study, to observe bone activity after the surgical procedure, the hormone PTH, alkaline phosphatase, serum calcium and phosphate, and vitamin D were measured, suggesting a greater increase in the Magnetotherapy Group.

According to Vieira (2007) [15], 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 group III Magnetotherapy concerning the Laser group, after 30 and 60 days. Suggesting a relevant role in the physiology of bone neoformation. The infrared laser, 808nm, within the dose described in the literature as an anti-inflammatory and repair therapeutic window, acts on sodium and potassium pumps and calcium channels, thus increasing protein and ATP synthesis, leading the tissue to cellular, tissue, and organic homeostasis. The results showed that the Group treated with Magnetotherapy was extremely similar to the Laser Group, thus signaling a new possibility of preventive treatment for BRONJ. Its main actions are the deflection of particles with an electrical charge in motion and, the production of currents induced by the piezoelectric effect in bone tissue and collagen, at the cellular level it normalizes the membrane potential, increases the solubility of substances, stimulates cellular metabolism, promoting an acceleration of all repair phenomena with bio-regenerative, anti-inflammatory and anti-edematous action, without demonstrating side effects. Thus, in living tissue, we mainly find alternating fields, as well as a combination of electric fields and magnetic fields, with cellular movements, ionic flows, fluids in the circulatory systems, 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 movement. Lactate dehydrogenase (LDH) is 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 LDH levels in the circulation, and can be detected in a blood test. Higher concentrations of this enzyme in the extracellular medium are related to the rupture of the plasma membrane and consequent cell death. This was not observed in our study in the LBI and MAC groups, with LDH maintained at normal levels.

Conclusion

Therefore, the present study suggests that patients undergoing treatment with BFs should be informed about the potential risk of BRONJ. Furthermore, it would be advisable for providers responsible for BF therapy to refer patients for dental check-ups before starting treatment, allowing for patient monitoring by a multidisciplinary team. Although the morbidity rate of this pathology is not high, prevention should be mandatory, thus avoiding mutilating and painful processes. However, if surgery is necessary, the use of these new adjuvant therapies, such as low-level laser therapy and MAG, can be proposed in the treatment of BRONJ. It is essential to increase our caseload and also involve other institutions in the use of these new effective and safe therapies in BRONJ.

CRediT

Author contributions: **Conceptualization -** Ariane Fontoura Custódio, Ana Carolina Dias, Fabio Alarcon Idalgo, Alvaro José Cicareli; **Data curation -** Ariane Fontoura Custódio, Ana Carolina Dias; **Formal Analysis -**Ariane Fontoura Custódio, Ana Carolina Dias, Fabio Alarcon Idalgo, Alvaro José Cicareli; **Investigation -**Ariane Fontoura Custódio, Ana Carolina Dias; **Methodology -**Ariane Fontoura Custódio, Ana Carolina Dias, Fabio Alarcon Idalgo, Alvaro José Cicareli; **Project administration-** Ariane Fontoura Custódio; **Supervision -** Fabio Alarcon Idalgo, Alvaro José Cicareli; **Writing - original draft -** Ariane Fontoura Custódio, Ana Carolina Dias, Fabio Alarcon Idalgo, Alvaro José Cicareli; **Writing-review & editing -** Ariane Fontoura Custódio, Ana Carolina Dias, Fabio Alarcon Idalgo, Alvaro José Cicareli.

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