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Major approaches and clinical evidence of oral and maxillofacial regenerative treatments for the process of osteonecrosis associated with the use of bisphosphonates: a systematic review

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Abstract

Introduction: Bone tissue is a specialized connective tissue made up of cells and a mineralized extracellular matrix. To reduce the excessive resorption observed in these pathologies, more rigorous studies have been carried out in pre-clinical and clinical studies to improve antiresorptive medications that allow the treatment or prevention of bone metabolism pathologies. Thus, anti-resorptive agents, such as Bisphosphonates (BFs) and Denosumab (DN), as well as some angiogenesis inhibitors, can induce osteonecrosis of the jaw. **Objective:** It was to develop a systematic review to specify the main approaches and clinical evidence on the process of osteonecrosis associated with the use of bisphosphonates, as well as the main oral and maxillofacial regenerative treatments. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from February to April 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 124 articles were found, 36 articles were evaluated in full and 14 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 25 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=77.7%>50%. It was concluded 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 a surgical procedure is necessary, the use of new adjuvant therapies such as hyperbaric camera, teriparatide, pentoxifylline, and alpha-tocopherol can be proposed.

Keywords: Bone tissue. Antiresorptive medications. Bisphosphonates. Osteonecrosis. Jaw. Regenerative process.

Introduction

Bone tissue is a specialized connective tissue made up of cells and mineralized extracellular matrix. Under conditions of homeostasis, bone tissue cells, that is, osteoblasts, bone lining cells, osteocytes, and osteoclasts act in the matrix remodeling process. The balance of bone matrix remodeling and, consequently, bone tissue homeostasis are compromised, for example, in the face of postmenopausal hormonal changes and cases of bone metastases [1,2].

To reduce the excessive resorption observed in these pathologies, more rigorous studies have been carried out in pre-clinical and clinical studies to improve antiresorptive medications that allow the treatment or prevention of bone metabolism pathologies [3,4]. In this sense, anti-resorptive agents, such as Bisphosphonates (BFs) and Denosumab (DN), as well as some angiogenesis inhibitors, can induce osteonecrosis of the jaw (OJ). In women, the incidence of OJ is about 15% at age 50, 30% at age 70, and 40% at age 18 to 80. Current literature indicates that a complex combination of factors is required to induce OJ. Several hypotheses regarding the pathophysiology of OJ have been previously reported [3-6].

Thus, according to the American Association of Oral and Maxillofacial Surgeons (AAOMS), the criteria for diagnosing OJ are the following: the presence of exposed bone or fistula for at least 8 weeks, in a patient with a previous or current history of the use of antiresorptives, who did not undergo radiotherapy in the cervicofacial region.3 In addition to BPs and DN, antiangiogenic medications such as Sunitinib, Sorafenib, and Bevacizumab have been associated with the occurrence of OJ [7,8].

Bone tissue has significant healing potential, which involves significant interaction between bone and immune cells [9]. Although fracture healing represents a useful model to investigate endochondral bone healing, intramembranous bone healing models have yet to be developed and characterized [10]. The development of a temporary immature granulation tissue (7 days) is evident, characterized by marked cell proliferation, angiogenesis, and infiltration of inflammatory cells, associated with growth factors (BMP-2-4-7, TGFβ1, VEGFa), cytokines (TNFα, IL-10), chemokines and receptors (CXCL12, CCL25, CCR5, CXCR4), matrix (Col1a1-2, ITGA4, VTN, MMP1a) and expression of MSCs markers (CD105, CD106, OCT4, NANOG, CD34, CD146) [11].

In this sense, the granulation tissue is sequentially replaced by more mature connective tissue (14 days), characterized by the reduction of the inflammatory infiltrate along with the increase in bone formation, marked expression of matrix remodeling enzymes (MMP-2-9), bone formation/maturation (RUNX2, ALP, DMP1, PHEX, SOST) markers and chemokines and receptors associated with healing (CCL2, CCL17, CCR2) [11]. The extraction socket healing process is considered complete (21 days) when the tooth cavity is filled with trabecular bone with well-defined medullary canals; the expression of mature bone markers is prevalent in this period [12].

In this context, BFs such as zoledronic, alendronic, and risedronic acids are a class of drugs used clinically to prevent loss of bone density and osteoporosis [13]. Thus, new BFs was synthesized to target human farnesyl pyrophosphate synthase and human geranylgeranyl pyrophosphate synthase, key enzymes of the mevalonate pathway, and capable of antiproliferative action in several cell lines (PC3, MG63, MC3T3, RAW 264.7, J774A. 1, bone marrow cells) involved in bone homeostasis, bone formation, and death. Among sixteen compounds, [1-hydroxy-2-(pyrimidine-2-arylamino)ethane-1,1-diyl]bis(phosphoric acid) was effective in reducing PC3 and RAW 264.7 cells. Furthermore, they reduced the number of differentiated osteoclasts similarly to zoledronic acid in the osteoclastogenesis assay [13].

In general, the mechanism of action of clodronate and etidronate alendronate, pamidronate, risedronate, and ibandronate involves the replacement of the oxygen atom with a spinal carbon atom renders the molecule incapable of decomposition by hydrolysis and binds it tightly to the circulating calcium or calcium from hydroxyapatite crystals in bone. Once BFs is internalized by osteoclasts, inhibition of the enzyme farnesyl synthetase of the mevalonate pathway occurs. With the interruption or loss of this intracellular metabolic pathway, osteoclastism becomes less efficient in its resorptive activity and then undergoes programmed cell death by apoptosis [1-3].

Thus, antiresorptive agents and angiogenesis inhibitors can induce osteonecrosis of the jaw. However, the exact mechanisms of OJ are unclear, and definitive treatment strategies have not yet been developed [14]. Added to this, the aging of the population requires antiresorptive agents and angiogenesis inhibitors, which are increasing worldwide. In this sense, age and duration of administration of antiresorptive agents are risks for the development of OJ [14].

Therefore, the present study developed a systematic review to specify the main approaches and clinical evidence of the osteonecrosis process associated with the use of bisphosphonates, as well as the main oral and maxillofacial regenerative 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: 03/21/2024. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 03/21/2024.

Data Sources and Research Strategy

The literary search process was carried out from February to April 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: *"Bone tissue. Antiresorptive medications. Bisphosphonates. Osteonecrosis. Jaw. Regenerative process"* and using the Boolean "and" between the MeSH terms and "or" between historical discoveries.

Study Quality and Risk of Bias

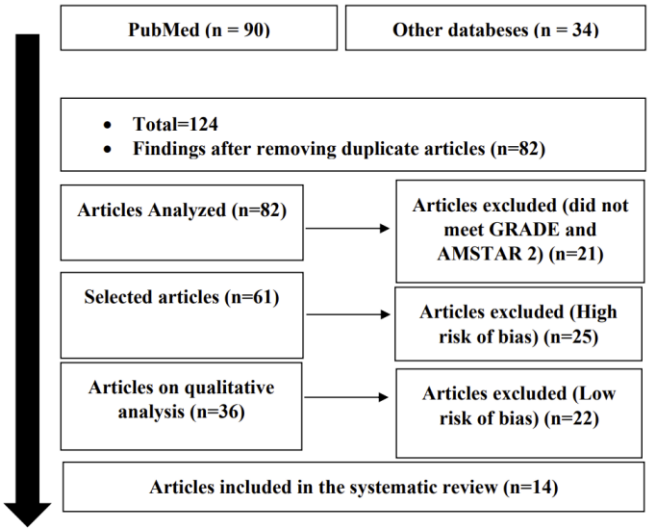
Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The 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 124 articles were found that were subjected to eligibility analysis, with 14 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=77.7%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 25 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2.

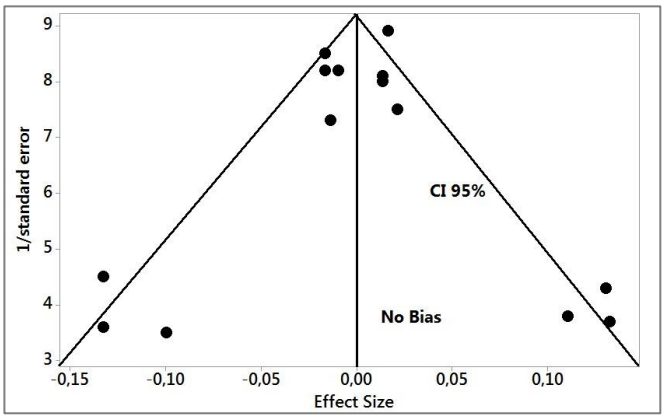
Figure 1. The article selection process by the level of methodological and publication quality.



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= 14 studies).



Source: Own authorship.

Major Approaches and Clinical Findings

Bones are constantly remodeled through osteoclasts and osteoblasts to maintain skeletal strength and integrity in individuals. However, the imbalance between these phenomena affects bone mineral density, leading to bone disorders [15]. One of the recent treatments of 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 [16].

The starting point for studies was natural pyrophosphates, widely used in industry, for their action in dissolving calcium carbonate, used in cleaning detergents and soap. Bisphosphonates (BFs) constitute a group of drugs first synthesized in 1880 but developed in the last 50 years for the treatment of bone disorders and abnormalities of calcium metabolism [17].

The first report on the medicinal use of BFs was published in 1969 by Bassett et al, in the treatment of progressive myositis with oral Etidronate in a 16-month-old baby. In 1970, Fleisch et al, in animal studies, demonstrated that BFs inhibited bone resorption and balanced calcium metabolism [18,19].

The main property of BFs is to inhibit the precipitation of calcium phosphate, reducing calcification and bone resorption, reducing osteoclastic action, through inducing apoptosis of these cells, which reabsorb bone tissue. These have a great affinity with bone tissue, a long half-life in bones, inhibiting bone reabsorption, and can be administered orally or intravenously [20]. The mechanisms of action of BFs on bone metabolism are complex and multifactorial, changing the osteoclastic cytoskeleton, stimulating apoptosis, and mainly reducing the proton pump with changes in pH and acid-base balance [16].

The clinical efficacy of BFs increases due to their ability to strongly bind to bone minerals. The initial release of BFs occurs through renal excretion or adsorption to bone mineral, lasting for a period of weeks to years. During bone resorption, the acidic pH in the reabsorption gap increases the dissociation of the drug in the bone [1,3].

BFs interfere with chemotaxis and attachment of osteoclasts to bone along with suppression of osteoclast function. Furthermore, these 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 [22].

The first report of osteonecrosis of the jaw due to the use of bisphosphonates was made by Marx et al in 2003. In 2007, a position paper by the American Association of Oral and Maxillofacial Surgeons (AAOMS) proposed the nomenclature "Bisphosphonates" for the first time. 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 [21].

Jaw osteonecrosis is the term suggested for intraoral lesions with bone exposure, which simulate dental abscesses or osteomyelitis, in patients undergoing therapy with bisphosphonates and who have not undergone radiotherapy in the head and neck region. Jaw osteonecrosis can be considered a severe adverse effect of BF therapy [4,22]. ON has also been defined using a variety of terms, including: "bisphosphonate-induced osteonecrosis of the jaw (BIONJ)", "bisphosphonate-associated osteonecrosis of the jaw (BAONJ)", "bisphosphonate-associated osteomyelitis of the jaw (BAOMJ)" and "bisphosphonate-related osteomyelitis of the jaw (BROMJ)". The terms cited were recently called "antiresorptive drug-related osteonecrosis of the jaw (ARONJ)" and are currently consolidated as "Medication-related osteonecrosis of the Jaws (MRONJ)" due to clinical reports of antiresorptive drug-related osteonecrosis of the jaw. -resorptive [17].

The main clinical aspects of osteonecrosis of the jaw are areas with bone exposure in the oral cavity, tooth mobility, ulcerations and fistulas in the mucosa, exposure of devitalized bone, with a yellowish color with tissue inflammation around the bone exposure, presence of painful symptoms and with characteristic odor [23].

Patients who develop necrosis are aged between 35 and 95 years, with a higher prevalence between 65 and 68 years. Among the risk factors for developing the disease, we can mention: 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 [16].

Treatment of Jaw Osteonecrosis

Clinical treatment consists of improving signs and symptoms, reducing inflammation in soft and hard tissue, eliminating pain, and reducing the size of the lesions. Control of inflammation, infection, and pain must be done with anti-inflammatories, antibiotic therapy, and analgesics [22]. Conservative treatment can last months, with frequent consultations causing adverse effects, such as microbial resistance and oral candidiasis, worsening local conditions [17]. Adjuvant systemic treatments, such as the hyperbaric chamber, teriparatide, pentoxifylline, and alpha-tocopherol, are also used [22].

The first treatment option is surgical debridement, removal of necrotic bone and bone sequestration with curettage, obtaining bleeding margins to make them more accessible to antibiotics, and preserving non-

necrotic bone [16,22]. Despite the difficulty encountered in determining the exact extent of the necrotic bone, complete removal of the lesion is essential to prevent its progression or recurrence. Another challenge in surgical treatment is the lack of standardization for procedures, depending on the skill and experience of the surgeon, making it difficult to compare and reproduce the methods used in the literature [16].

The incision must always be made, thinking about leaving a tension-free mucoperiosteal flap for the suture, covering the entire area of necrosis. The marginal mucosa at the edge of the lesion must be removed, as it is altered by chronic inflammation and is not ideal for covering [17]. One of the parameters adopted is the surgeon's intraoperative perception, removing the necrotic bone until the normal appearance of color, texture, and bleeding of the remaining bone tissue. Considering that the exposed necrotic bone will not be revitalized, the ONJ must be removed in its entirety [16,17].

The exposed bone shows a yellowish, darkened color, with greater porosity in its consistency. Computed tomography of the face is suggested to determine the margins of the lesion and fluorescence can also be used. After eliminating the necrosis, the edges must be abraded and smoothed, removing ridges and bone spicules. This is an important step described in the literature because as the turnover is impaired by the action of BFs, the remodeling of the area will occur very slowly, and these remnants may become new factors of aggression, disrupting the mucosa, and causing secondary infections and recurrence of the disease. injury [16,17,23,24].

Furthermore, the exposed bone is always colonized with bacteria from the mouth, increasing microbial adhesion in the bone tissue altered by the BFs, thus adjuvant treatments for disinfection are described as Laser therapy, ozone therapy, hyperbaric oxygen, local irrigation with 0.12% chlorhexidine and the closure with coverage of healthy tissues, when possible, are important. Oral hygiene must be rigorous and chlorhexidine mouthwash must be frequent [17,22].

According to Fliefel et al (2015) [22], in a systematic review of 97 articles from 2003 to 2014, in 4879 cases of BRONJ, they found that the most used local treatment was minimally invasive surgery. This consists of surgical debridement, removal of bone sequestration, curettage, regularization of bone edges, and primary closure with mucosa, followed by the use of a laser.

Vescovi, Paolo, et al (2013) [23] reported their experience in 217 patients undergoing therapy with BFs, in a total of 589 dental extractions at the University of Parma, Italy, supporting the hypothesis that the association of antibiotic treatment and use of low power laser, was effective in preventing BRONJ after tooth extractions in patients under BFs.

The treatment result is considered successful when the healing of the oral mucosa is maintained without bone exposure or infection and when there is an acceptable radiographic image, without signs of injury, for 12 months after surgery. Just maintenance, containing the evolution of the disease and improvement in local conditions, does not mean treatment success [17,22,24]. The success rates of surgical treatment are significantly higher compared to conservative treatment (85% to 20%) [20].

Conclusion

It was concluded 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 a surgical procedure is necessary, the use of new adjuvant therapies such as hyperbaric camera, teriparatide, pentoxifylline, and alpha-tocopherol can be proposed.

CRediT

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Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate@.

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It was performed.

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