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BISPHOSPHONATES AND OSTEONECROSIS OF THE JAW: THE IMPACT OF ANTINEOPLASTIC THERAPIES ON THE BONE STRUCTURES OF THE ORAL CAVITY

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ABSTRACT
Objective: The objective of this narrative literature review article is to address the use of bisphosphonates in antineoplastic therapies and how these bisphosphonates may be related to the triggering of osteonecrosis of the jaw. Methodology: During the construction and development of this narrative literature review article, the work of Rother (2007) was used, a study that addresses the differences between a narrative and systematic literature review, highlighting how the approach and structuring of each respective type of article should be carried out, assisting the development of the article. Searches were carried out in online databases that could contribute with relevant data and information related to the topic addressed in the article. Searches were carried out in the following databases: Web of Science, BVS/BIREME, PUBMED Central, PROSPERO, Scielo, The Cochrane Library in conjunction with Google Academy. Results: Bisphosphonates are drugs that suppress bone resorption by osteoclasts, interrupting bone remodeling, resulting in higher density bone tissue, and also acting as an inhibitor of inflammatory mediators, which is why these drugs are commonly used in the treatment of bone metabolism diseases or bone tissue neoplasia. Conclusion: Osteonecrosis of the jaw is a worrying condition triggered by chronic use of bisphosphonates, but further studies are needed to provide higher levels of evidence on its pathophysiology and how the treatment of this condition should be conducted, a role that should be played by the doctor in conjunction with the dentist.

Keywords: Bisphosphonate. Bisphosphonate-Associated Osteonecrosis. Osteonecrosis. Maxilla. Mandible.

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INTRODUCTION

Some pathologies such as Paget's disease, osteoporosis, neoplasms that have bone metastases or not, among other diseases that affect bone metabolism, will interfere with the balance in the bone remodeling process, triggering an imbalance, resulting in exaggerated reabsorption, which will result in a decrease in the quality and quantity of matrix, density and bone thickness, initiating a pathological process (Fernandes et al., 2005; Sousa & Jardim Junior, 2008; Mendes, 2017). Due to the large number of diseases that cause bone loss through reabsorption, pharmaceutical companies were concerned with creating medications that would induce the production of bone matrix by osteoblasts and that at the same time would reduce osteoblast activity, decreasing bone reabsorption. In this way, antiresorptive medications began to be created (Sousa & Jardim Junior, 2008; Mendes, 2017). Synthetic analogue bisphosphonates of the substance pyrophosphate are a medication that causes homeostasis during the remodeling process in physiological situations. These types of drugs cause apoptosis in osteoclasts, which consequently causes a decrease in osteoclastic activity, promoting osteoblastic activity that will stand out, producing bone matrix. However, these drugs have adverse effects that can cause harm to the human body, especially in the area where dentists work, in the jaws (Santos & Ferreira Neto, 2021; Carlessi & Maragno, 2017; Parrião et al., 2021).

Although Bisphosphonates have a range of benefits in the treatment of different pathologies, since 2005, more and more studies have been observing and studying a possible correlation between the medication and an extremely debilitating and severe pathological condition, in which its clinical manifestations exclusively affect the maxilla and mandible, a condition called "osteonecrosis of the jaws". In the vast majority of cases, osteonecrosis of the mandible and/or maxilla occurs as a result of being induced by infections, radiotherapy and certain drugs. However, as this pathology does not yet have a defined etiology, several case reports and studies have observed the relationship of this pathology in patients who underwent bisphosphonate-based treatments and who underwent some dental procedure, such as surgeries or tooth extractions in the bone tissue regions of the region (Gegler et al., 2006; Ruggiero et al., 2006; Marx et al., 2005; Bagan et al., 2005).

Thus, given the high correlation between osteonecrosis of the jaw and the use of bisphosphonates, it is clear that it is important for dentists to be aware of the medications their patients are using and have used in recent months, what pathologies they have and

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whether they are undergoing any treatment, since this, when combined with certain dental procedures, can end up causing serious pathologies. Thus, the objective of this narrative review of the literature is to address the use of bisphosphonates in antineoplastic therapies and how these bisphosphonates may be related to the onset of osteonecrosis of the jaw.

METHODOLOGY

During the construction and development of this narrative literature review article, it was necessary to use scientific evidence already proven and published in the literature, which would serve as a guide for how to structure an article of this type. Thus, the work of Rother (2007) was used, a study that addresses the differences between a narrative and systematic literature review, highlighting how the approach and structuring of each respective type of article should be carried out, assisting the development of the article. In addition, because this is a literature review article, searches were carried out in online databases that could contribute with relevant data and information related to the topic addressed in the article. Searches were carried out in the following databases: Web of Science, BVS/BIREME, PUBMED Central, PROSPERO, Scielo, The Cochrane Library in conjunction with Google Academy. Targeting only studies and articles related to the topic addressed in the article, the following keywords were used in the data searches: Bisphosphonate; Bisphosphonate-Associated Osteonecrosis; Osteonecrosis; Maxilla; Mandible.

RESULTS

BISPHOSPHONATES: FUNCTIONALITY AND APPLICABILITY

Bisphosphonates are synthetic analogs of inorganic pyrophosphate that bind avidly to hydroxyapatite in bone matrix, particularly in regions of high remodeling activity such as trabecular bone. Their mechanism involves the inhibition of farnesyl pyrophosphate synthase within the mevalonate pathway, which is essential for osteoclast function. This inhibition results in osteoclast apoptosis, leading to a marked reduction in bone resorption and remodeling (Russell et al., 2008).

Clinically, bisphosphonates have revolutionized the management of skeletal-related events in patients with metastatic bone disease from breast, prostate, and lung cancers, as well as multiple myeloma. They are also first-line agents for the treatment and prevention of osteoporosis, Paget's disease of bone, and glucocorticoid-induced bone loss (Fleisch,

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2000). By stabilizing bone microarchitecture, bisphosphonates help reduce pathological fractures, bone pain, and hypercalcemia of malignancy, thereby improving both survival and quality of life in patients with advanced neoplasms.

SIDE EFFECTS OF BISPHOSPHONATES (SHORT VS LONG TERM)

While bisphosphonates are generally well tolerated, their side effects can be divided into short-term and long-term manifestations.

Short-term: adverse effects typically include flu-like symptoms (particularly with IV administration), nausea, vomiting, abdominal pain, diarrhea, esophagitis (in oral formulations), and acute-phase reactions mediated by cytokines such as IL-6 and TNF-α. Hypocalcemia is also common, particularly in patients with predisposing factors such as vitamin D deficiency.

Long-term: adverse effects become more relevant with extended use (generally beyond three years), especially in oncologic settings. These include atypical femoral fractures, atrial fibrillation, osteomalacia, and most notably, bisphosphonate-related osteonecrosis of the jaw (BRONJ), a serious but rare complication marked by bone exposure, pain, and infection (Khosla et al., 2007; Woo et al., 2006; Ruggiero et al., 2014). The cumulative dose, route of administration, and individual patient susceptibility significantly influence the risk profile.

RISK FACTORS FOR DEVELOPING OSTEONECROSIS

BRONJ is a multifactorial condition, with several key predisposing elements:

Type and potency of bisphosphonate: Intravenous formulations such as zoledronate and pamidronate are significantly more potent and have a higher affinity for bone than oral bisphosphonates, leading to greater accumulation and longer bone retention, hence increasing the risk of osteonecrosis (Ruggiero et al., 2014).

Duration of therapy: Treatment durations beyond two years, particularly in high doses as used in cancer therapies, correlate with a higher incidence of BRONJ.

Invasive dental procedures: Tooth extractions, periodontal surgeries, and implant placements are the most common triggering events. Bone trauma creates a favorable environment for necrosis in patients with impaired bone turnover (Marx et al., 2005).

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Concomitant therapies: Use of corticosteroids, antiangiogenic agents, chemotherapy, and radiotherapy further impairs healing capacity and immune defense, exacerbating the risk (Vandone et al., 2007).

Oral hygiene and periodontal status: Poor oral hygiene, advanced periodontal disease, and local infections significantly contribute to BRONJ onset (Otto et al., 2012).

Comorbidities: Systemic conditions like diabetes mellitus, anemia, renal insufficiency, smoking, and immunosuppression lower the bone's regenerative capacity and increase vulnerability to necrosis.

DIFFERENCE BETWEEN TYPES OF BISPHOSPHONATES (ORAL AND INTRAVENOUS)

The route of administration significantly influences the pharmacokinetics, efficacy, and risk of complications.

Oral bisphosphonate: such as alendronate and risedronate, are primarily prescribed for osteoporosis and require strict administration protocols (e.g., fasting, upright posture) to prevent esophageal irritation. These drugs have low oral bioavailability (~1%) and are associated with a lower incidence of BRONJ, generally ranging from 0.01% to 0.1%.

Intravenous bisphosphonates: particularly zoledronic acid and pamidronate, are used for malignant bone conditions and exhibit far greater bioavailability and potency. The cumulative risk of BRONJ in cancer patients treated with IV bisphosphonates can range from 1% to 11% depending on the duration and intensity of treatment (Khosla et al., 2007; Woo et al., 2006).

OSTEONECROSIS OF THE JAW

Osteonecrosis of the jaw (ONJ), specifically bisphosphonate-related osteonecrosis of the jaw (BRONJ), is a severe adverse effect primarily associated with high-potency bisphosphonates, particularly in oncologic patients receiving intravenous formulations. According to the diagnostic criteria established by the American Association of Oral and Maxillofacial Surgeons (AAOMS, 2014), BRONJ is defined as exposed bone in the maxillofacial region that does not heal within eight weeks in patients treated with antiresorptive or antiangiogenic agents, without any history of radiation therapy to the craniofacial area.

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The clinical presentation is often insidious in early stages and may include asymptomatic bone exposure. As the condition progresses, symptoms intensify and may involve persistent and severe orofacial pain, localized or diffuse soft tissue swelling, erythema, mucosal ulceration, and signs of secondary infection such as purulent discharge or halitosis. The development of cutaneous or oral fistulas, pathological fractures, and maxillary sinus involvement can occur in advanced cases. Some patients report numbness or paresthesia, typically related to mandibular nerve involvement.

The mandible is more frequently affected than the maxilla, with estimates suggesting mandibular involvement in approximately two-thirds of BRONJ cases. This higher prevalence is attributed to the mandible's dense cortical bone and lower vascularization, which reduce its capacity to repair microtraumas and withstand infectious processes.

Radiographic evaluation plays a crucial role in the diagnosis and staging of BRONJ. Imaging may reveal osteolytic areas, cortical bone disruption, increased bone density (sclerosis), periosteal bone formation, and the presence of sequestra. Advanced imaging techniques, such as cone-beam computed tomography (CBCT) and magnetic resonance imaging (MRI), are often required for surgical planning and assessment of the extent of bone necrosis and adjacent soft tissue involvement. The disease course is typically chronic and refractory to treatment due to impaired bone remodeling and compromised vascularity. Management remains challenging and involves a combination of conservative and surgical strategies, including antimicrobial therapy, pain control, antiseptic mouth rinses, and debridement. In some cases, segmental resection of necrotic bone may be necessary. The prognosis depends on the lesion's stage, patient comorbidities, and adherence to preventive protocols prior to initiating bisphosphonate therapy.

DIRECT DENTAL IMPACT: EXTRACTIONS, ILL-FITTING DENTURES, ETC

Among the most recognized risk factors for the onset of BRONJ are invasive dental procedures, particularly tooth extractions, which account for a large percentage of reported cases. The surgical trauma associated with these procedures can expose alveolar bone and disrupt local vascular supply, especially in patients with compromised bone healing due to bisphosphonate-induced inhibition of osteoclastic activity. The exposed bone, in turn, becomes vulnerable to microbial colonization and infection, initiating the necrotic process. Ill-fitting dentures represent another significant trigger, especially in edentulous individuals undergoing bisphosphonate therapy. The chronic irritation and repeated mucosal trauma

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caused by unstable prostheses can result in ulceration and thinning of the overlying mucosa, facilitating the exposure of underlying bone. This scenario is particularly dangerous when the underlying alveolar ridge has already experienced bisphosphonate-induced remodeling suppression.

Periodontal disease, especially in its advanced stages, is another potent risk factor. Chronic inflammation and microbial biofilms in periodontal pockets can extend into the alveolar bone, creating a localized environment of persistent infection. The bisphosphonate-compromised bone is unable to respond adequately to this microbial challenge, further contributing to necrosis. Endodontic infections and periapical lesions may similarly serve as sources of infection that compromise bone viability. Preventive dental care is therefore of paramount importance. Pre-treatment dental assessments allow for the identification and resolution of potential foci of infection or trauma. Clinical protocols recommend that all necessary extractions and invasive dental procedures be performed prior to initiating bisphosphonate therapy whenever possible. Non-surgical periodontal treatments, such as scaling and root planing, and restorative interventions that minimize trauma are preferred during treatment. According to Bagan et al. (2007), preventive strategies significantly reduce the incidence and severity of BRONJ, especially when multidisciplinary collaboration is established between dental and oncology teams.

BISPHOSPHONATES ASSOCIATED WITH OSTEONECROSIS OF THE JAW

The pathophysiology of BRONJ is intricate and involves multiple biological mechanisms that collectively comprise bone viability and reparative ability. Suppressed angiogenesis is one of the key mechanisms. Bisphosphonates have been shown to exhibit antiangiogenic properties by downregulating angiogenic factors such as vascular endothelial growth factor (VEGF), thereby impairing the formation of new blood vessels. This inhibition leads to reduced vascular supply to bone tissue, especially in areas like the jaws that already have relatively limited collateral circulation, ultimately hindering tissue repair and regeneration. Reduced bone turnover results from direct suppression of osteoclast-mediated bone resorption. Bisphosphonates interfere with the mevalonate pathway, inhibiting farnesyl diphosphate synthase and leading to osteoclast apoptosis. While this mechanism is beneficial in reducing bone loss, it also diminishes the bone's ability to remodel and repair microdamage, especially under mechanical stress from mastication or dental trauma.

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Infection and chronic inflammation also play pivotal roles. The oral cavity harbors a complex and diverse microbiota, and the exposure of necrotic bone allows for bacterial colonization. The presence of Actinomyces species in histological specimens from BRONJ lesions is well documented and considered a hallmark of the disease (Sedghizadeh et al., 2008). These bacteria often form biofilms on necrotic bone surfaces, which are resistant to host immune responses and antibiotic therapy, contributing to the chronicity and persistence of the condition. Histopathologically, BRONJ lesions exhibit classic signs of avascular necrosis. There is widespread presence of necrotic lamellar bone with empty osteocyte lacunae, absence of osteoblastic activity, and often a peripheral infiltrate composed of neutrophils, lymphocytes, and plasma cells. Colonies of filamentous bacteria (predominantly Actinomyces) are frequently observed. Sequestration of devitalized bone and chronic sinus tract formation may also be present. In advanced stages, the necrosis can extend into adjacent soft tissues and sinuses, complicating treatment and increasing morbidity.

The unique anatomy and physiology of the jaws — constant mechanical stress, high bone turnover rate, and exposure to the external environment through the oral cavity — render them particularly vulnerable to the cascade of pathological events leading to BRONJ. Understanding the interplay of these mechanisms is essential for developing effective preventive and therapeutic strategies.

DISCUSSION

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) remains a significant clinical complication, especially in oncology patients receiving high-potency intravenous bisphosphonates. The findings of this review are consistent with current literature, which confirms that risk factors such as drug type, administration route, and treatment duration play central roles in BRONJ development (Khosla et al., 2007; Marx et al., 2005). By inhibiting osteoclast-mediated bone remodeling, bisphosphonates reduce the jawbone's ability to respond to microtrauma and infection. This is particularly problematic in the maxillofacial region due to its high remodeling rate and frequent exposure to dental interventions. Additionally, the drugs' antiangiogenic effects impair vascular repair, compounding necrotic processes (Allen & Burr, 2009; Otto et al., 2012).

Preventive dental care is crucial, as underscored by Ruggiero et al. (2014), especially before starting intravenous therapy. Patients should undergo thorough dental

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assessments to eliminate potential sources of infection or trauma. This is vital in oncology settings, where intravenous bisphosphonate use is often long-term and high-dose. Moreover, the multifactorial nature of BRONJ is evident in studies showing that microbial infection (e.g., Actinomyces) is a frequent secondary contributor to lesion chronicity (Sedghizadeh et al., 2008). This reinforces the importance of combining antibiotic therapy with conservative surgical strategies. Oral bisphosphonates present a much lower risk of BRONJ. Nevertheless, even in low-risk patients, education on oral hygiene and avoidance of unnecessary invasive dental procedures is recommended (Woo et al., 2006). Finally, early diagnosis and interdisciplinary management are essential to reduce BRONJ progression and improve patient outcomes (AAOMS, 2014).

CONCLUSION

Although bisphosphonates are an extremely efficient medication in the treatment of a range of pathologies that affect the bone structure, osteonecrosis of the jaw is a worrying condition triggered by the chronic use of bisphosphonates, but more studies are needed to provide greater levels of evidence about its pathophysiology and how the treatment of this condition should be conducted, a role that should be played by the doctor together with the dentist.

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