

Medication-related osteonecrosis of the jaw and the role of the doctor of dental surgery: a literature review

Osteonecrose dos maxilares associada a medicamentos e o papel do cirurgião-dentista: uma revisão de literatura

Osteonecrosis de los maxilares asociada a fármacos y el papel del cirujano dentista: una revisión de la literatura

Received: 03/30/2023 | Revised: 04/11/2023 | Accepted: 04/12/2023 | Published: 04/17/2023

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Abstract

Introduction: Medication-related Osteonecrosis of the Jaw (MRONJ) is a condition that may affect patients undergoing oral surgery procedures that use antiresorptive drugs. It is essential that the Doctor of Dental Surgery (DDS) is familiar with the pathology and how to diagnose, prevent and approach it. **Objectives:** To perform a literature review on MRONJ and to guide the DDS on how to manage the affected patients. **Methodology:** a systematized search was conducted on the PubMed virtual database using the terms: "diphosphonates", "dentist's practice pattern", "dentists", "dentist's role" and "Bisphosphonate-Associated Osteonecrosis of the Jaw". 29 articles in English, published in the last 5 years, were included. **Results and discussion:** MRONJ is characterized by exposed and necrotic bone that persists for more than 8 weeks and happens in patients taking antiresorptive agents. It is multifactorial and its severity depends on the dosage, route of administration, and treatment duration. Its management must be multidisciplinary to improve the patient's quality of life. The DDS must focus on prevention. Every patient should have their oral health evaluated before starting antiresorptive therapy and be informed of its risks and benefits. Most DDSs do not feel confident to adequately manage these cases, even though information on MRONJ is more widespread among younger DDSs and recent graduates. **Conclusion:** MRONJ is a harmful condition for the patient and it is the DDS's responsibility to know how to treat and prevent it, by having adequate knowledge of this pathology and making decisions based on the latest scientific evidence. **Keywords:** Bisphosphonate-associated osteonecrosis of the jaw; Diphosphonates; Dentist's role.

Resumo

Introdução: A Osteonecrose dos Maxilares Associada a Medicamentos (MRONJ) é uma condição que pode acometer pacientes submetidos a cirurgias orais que usam medicamentos antirreabsortivos. É imprescindível que o cirurgião-dentista (CD) conheça a patologia e saiba como a diagnosticar, prevenir e manejar. **Objetivos:** realizar uma revisão de literatura sobre a MRONJ e orientar o CD para as melhores condutas e manejo desses pacientes. **Metodologia:** foi

realizada uma busca sistematizada na plataforma de dados PubMed com os termos: “diphosphonates”, “dentist's practice pattern”, “dentists”, “Dentist's Role”, “Bisphosphonate-Associated Osteonecrosis of the Jaw” e seleção de 29 artigos em inglês, publicados nos últimos 5 anos. Resultados e discussão: a MRONJ é uma exposição de osso necrótico por mais de 8 semanas em pacientes que fazem uso de medicamentos antirreabsortivos. É multifatorial e sua gravidade depende da dose, via de administração e do tempo de uso do medicamento. Sua abordagem deve ser multidisciplinar para melhorar a qualidade de vida do paciente. O CD deve atuar na prevenção. Todo paciente deve passar por uma avaliação de saúde oral antes do início da terapia e deve ser informado dos riscos e benefícios. A maioria dos CDs não possui segurança para manejar adequadamente esses pacientes, apesar da percepção sobre a MRONJ ser mais bem difundida entre CDs mais novos e com menos tempo de formados. Conclusão: A MRONJ é uma condição prejudicial para o paciente e é dever do CD saber atuar no tratamento e prevenção, através de conhecimento adequado da patologia, e tomar decisões baseadas em referências científicas atualizadas.

Palavras-chave: Osteonecrose da arcada osseodentária associada a difosfonatos; Difosfonatos; Papel do dentista.

Resumen

Introducción: La Osteonecrosis de los maxilares asociada a medicamentos (MRONJ) es una condición que puede afectar a pacientes sometidos a cirugía bucal que utilizan fármacos antirresortivos. Es fundamental que el cirujano dentista (CD) conozca la patología y sepa como diagnosticarla, prevenirla y manejarla. Objetivos: realizar una revisión bibliográfica sobre la MRONJ y orientar al odontólogo la mejor conducta de estos pacientes. Metodología: se realizó una búsqueda sistemática en la plataforma de datos PubMed con los términos: “diphosphonates”, “dentist's practice pattern”, “dentists”, “Dentist's Role”, “Bisphosphonate-Associated Osteonecrosis of the Jaw” y selección de 29 artículos en inglés, publicados en los últimos 5 años. Resultados y discusión: La MRONJ es una exposición de hueso necrótico durante más de 8 semanas en pacientes que toman fármacos antirresortivos. Es multifactorial y su gravedad depende de la dosis, vía de administración y tiempo de uso. Su abordaje debe ser multidisciplinar para mejorar la calidad de vida del paciente. El odontólogo debe trabajar en la prevención. Cada paciente debe someterse a una evaluación de su salud bucodental antes de iniciar la terapia y debe ser informado de los riesgos y beneficios. La mayoría de los odontólogos no tienen la confianza necesaria para manejar adecuadamente a estos pacientes, aunque la percepción de MRONJ está más extendida entre los odontólogos que tienen menos tiempo como titulados. Conclusión: La MRONJ es una patología perjudicial para el paciente y es deber del odontólogo saber actuar en el tratamiento y prevención, y tomar decisiones basadas en referencias científicas actualizadas.

Palabras clave: Osteonecrosis de los maxilares asociada a difosfonatos; Difosfonatos; Papel del dentista.

1. Introduction

Bisphosphonates (BPs) are antiresorptive drugs widely used to treat some types of cancer, such as breast, prostate, and lung, when there is bone metastasis. BPs are also widely prescribed by rheumatologists for fracture prevention in patients with osteopenia and osteoporosis, and in the treatment of Paget's disease and osteogenesis imperfecta (Ruggiero et al., 2022; Daron et al., 2018).

Although BPs are able to treat cancer, reduce fractures and improve patients' quality of life, these drugs have side effects, among which is Medication-related Osteonecrosis of the Jaw (MRONJ) (Ruggiero et al., 2022; Daron et al., 2018).

MRONJ is a specific type of osteonecrosis that, although its pathophysiology is not very well understood, can affect some patients that have taken antiresorptive agents for some period of time and underwent oral surgery procedures. It is a rare condition that has a multifactorial nature. Its development and severity are closely related to the dosage and route of administration. According to the American Association of Oral and Maxillofacial Surgeons, the risk of developing MRONJ is higher in patients being treated for malignant diseases (< 5%) than in patients being treated for osteoporosis (< 0.05%) (Ruggiero et al., 2022).

Furthermore, treatment for MRONJ is complex and encompasses conservative, non-surgical treatments and surgical therapies, depending on the stage of the disease. Exposed and necrotic bone increases the risk of local infection, causing pain and discomfort to patients. In advanced stages, the need for surgical interventions to remove bony sequestrum and necrotic tissue increases the cases' morbidity and results in a worse prognosis (Ruggiero et al., 2022).

Thus, it is essential that the Doctor of Dental Surgery (DDS) is able to prevent and correctly diagnose this disease. It is also important that they know how to analyse the risks involved in performing invasive procedures in patients at risk of MRONJ.

Therefore, this study aims to perform an integrative literature review on antiresorptive drugs, such as BPs, and osteonecrosis of the jaw, and to guide the DDS on the more appropriate procedures and what the affected patient's dental care should address.

2. Methodology

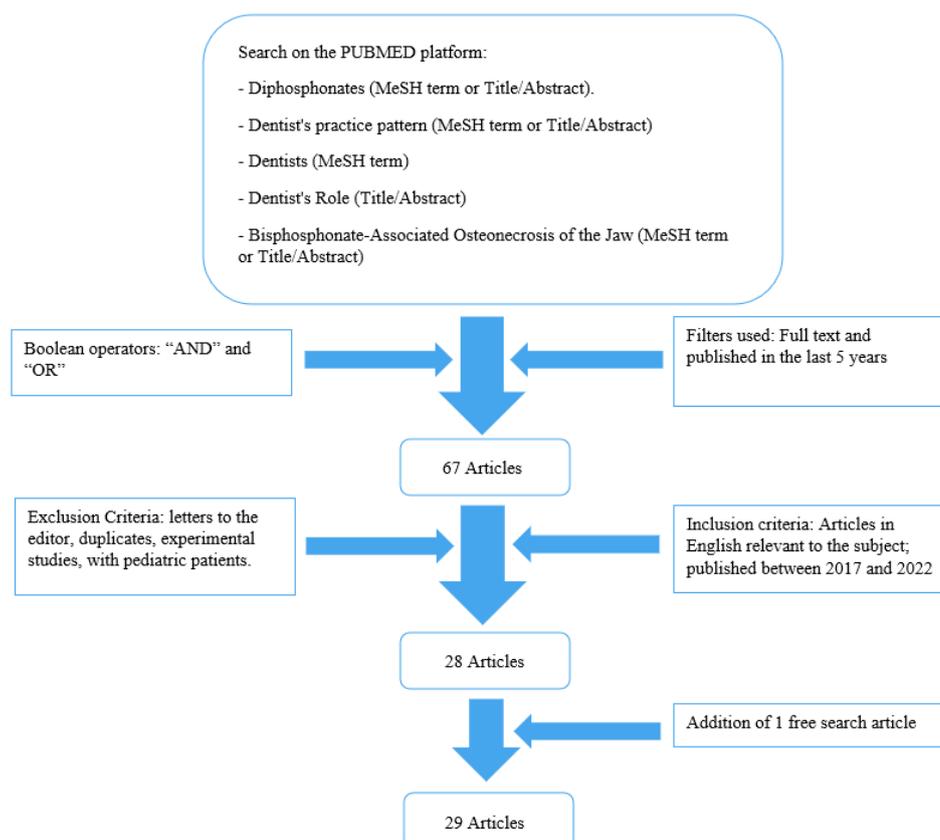
The present study is an integrative literature review and, therefore, focuses on analyzing and synthesizing results from different studies on MRONJ and the role of the DDS to promote a better understanding of the theme (Souza et al., 2010; Whittemore & Knafl, 2005).

A systematized search on the PubMed virtual database was conducted in June 2022. The Health Science Descriptors (DeCs) were selected and, through them, the equivalent controlled vocabulary terms - Medical Subject Headings (MeSH) - were identified and used in the platform's advanced search. These terms were also used in the Title/Abstract mode and associated with the Boolean operator "AND". The search obtained 67 results.

Inclusion criteria were: full articles in English related to Medication-related Osteonecrosis of the Jaw / BPs and the role of the Doctor of Dental Surgery in the management of the condition. They must have been published between 2017 and 2022 and both free and paid versions were included. Articles that did not fit these criteria, were published in letters to the editor format, had duplicates, were experimental studies, or analyzed pediatric patients were excluded. One free search article was included because it met the inclusion criteria and its subject was pertinent to the theme of this study.

After establishing the aforementioned criteria, the final search resulted in 29 articles. Figure 1 presents the steps taken to obtain the article's bibliography.

Figure 1 - Flowchart of the methodology used in article selection.



Source: Elaborated by the authors.

3. Results

According to the American Association of Oral and Maxillofacial Surgery (AAOMS), MRONJ is defined as exposed or necrotic bone that can be probed through an intraoral or extraoral fistula, for more than eight weeks in patients currently using antiresorptive drugs, immunomodulatory or antiangiogenic agents or who have taken these medications and no history of radiotherapy to the head and neck region or metastatic disease of the jaws (Ruggiero et al., 2022).

Until 2014 MRONJ had another name: bisphosphonate-related osteonecrosis of the jaw. However, in the AAOMS' 2014 position paper, the term "BPs" was substituted for "drugs", since other drug classes are also associated with this pathology (Patil et al., 2020).

The class of drugs most commonly related to MRONJ are BPs, antiresorptive agents similar to pyrophosphate, that bind strongly to the bone's hydroxyapatite crystals. They inhibit bone resorption by osteoclasts and induce their apoptosis (Chalem et al., 2020). As a clinical effect, there is an increase in bone density and a lower risk of fractures, because they decrease bone fragility (Aparecida et al., 2018). For this reason, they are widely used in the treatment and prevention of osteoporosis and osteopenia, myelomas, Paget's syndrome, and osteogenesis imperfecta (Patil et al., 2020). Additionally, this class of drugs is widely used in breast, prostate, and lung cancer cases, to prevent bone metastasis, as they are able to block tumor growth and angiogenesis (Patil et al., 2020; Kizub et al., 2021). BPs remain for many years in the body due to their incorporation into the bone matrix and have an average half-life of 10 years (Escobedo et al., 2018; Ozkan et al., 2021). Even after the medication is no longer being used, its side effects can still be observed (Han, 2021). Some examples of BPs are alendronate, zoledronic acid, ibandronate, clodronate, and pamidronate (Ruggiero et al., 2022; Kizub et al., 2021).

Another antiresorptive agent used in the treatment and prevention of osteoporosis, osteopenia, and bone metastases is denosumab, a human monoclonal antibody that can bind to the receptor activator of nuclear-kappa B ligand (RANK-L). It keeps osteoblasts from binding to osteoclast precursor cells, inhibiting their maturation and, consequently, bone resorption. Unlike BPs, denosumab is not incorporated into the bone matrix and its effects are seen for only six months after the drug was last used (Chalem et al., 2020; Escobedo et al., 2018).

Other drugs reported in the literature that may be associated with MRONJ are: adalimumab (tumor necrosis factor - TNF inhibitor), bevacizumab, and rituximab (tyrosine kinase inhibitors). Favia et al. (2017) reported a case in which infliximab, a monoclonal antibody that binds to TNF, used in the treatment of Crohn's disease, triggered MRONJ. However, the mechanism of action of this substance in the development of the pathology is not yet well elucidated.

To fully comprehend MRONJ, it is important that the DDS knows the available drugs used to treat it and their therapeutic indication. Therefore, Table 1 shows the osteonecrosis-related drugs marketed in Brazil, their posology, and therapeutic indication.

Table 1 - Osteonecrosis-Related Drugs Marketed in Brazil.

Medication	Commercial Presentation	Posology	Therapeutical Indication
Sodium alendronate	Fosamax (reference - MERCK manufacturer) Sodium Alendronate (generic drug) Terost (similar - Aspen Pharma manufacturer)	70 mg/week Tablets	Treatment of postmenopausal osteoporosis for fracture prevention.
Sodium Ibandronate	Bonviva (reference - Roche manufacturer) Sodium Ibandronate (generic drug) Osteoban (similar - Aché manufacturer)	150 mg/month Tablets	Treatment of postmenopausal osteoporosis for fracture prevention.
Risedronate Sodium	Actonel (reference - Sanofi Aventis manufacturer) Risedronate sodium (generic drug) Riasedross (similar - EMS manufacturer)	35 mg/week Tablets	Prevention and treatment of osteoporosis in postmenopausal women and for men. The delayed-release tablet is used in the treatment of osteoporosis and maintenance of bone mineral density in patients on long-term corticosteroid therapy.
Disodium Pamidronate	Fauldpami (reference - Libbs Pharmaceuticals manufacturer)	60 mg/3 months Injectable solution	Treatment of conditions related to increased osteoclastic activity: bone metastases, multiple myeloma, tumor-induced hypercalcemia and Paget's disease.
Zoledronic Acid	Blaztere (reference - Dr. Reddy's manufacturer) Aclasta (reference - Novartis manufacturer) Zometa (reference - Novartis manufacturer) Zoledronic Acid (generic drug)	4 mg/6 months Aclasta: 5mg/year Injectable solution	Treatment of bone metastases and reduction of calcemia in patients with cancer-induced hypercalcemia.
Denosumab	Prolia (reference - Amgen manufacturer) Xgeva (reference - Amgen manufacturer)	Prolia: 60mg/6 months Xgeva: 120mg/4 weeks	Prolia: Osteoporosis in postmenopausal women; bone loss in patients undergoing prostate or breast cancer treatment that causes hormone depletion; osteoporosis in men; glucocorticoid-induced osteoporosis. Xgeva: prevention of complications in adults with multiple myeloma; prevention of serious complications in adults with cancer with bone metastasis; treatment of cancer-induced hypercalcemia; treatment of giant cell tumor of bone.

Sources: adapted from BRASIL. Agência Nacional de Vigilância Sanitária (2013). Efficacy and Safety of long-term use of Bisphosphonates for prevention of osteoporotic fractures in menopausal women. *Brazilian Bulletin of Health Technology Assessment*, 8 (21). CONSULTA REMÉDIOS. *Consulta Remédios* (2000). Retrieved <https://consultaremedios.com.br/bulas>

Pathophysiology of MRONJ

Despite being first described almost 20 years ago, the pathophysiology of MRONJ is still not well understood. It is a multifactorial disease and, therefore, some hypotheses have been raised to explain its pathogenesis (Ruggiero et al., 2022; Han, 2021).

The first hypothesis is that the use of antiresorptive medication suppresses bone resorption and prevents new bone formation. However, medication alone does not trigger osteonecrosis; factors such as infection and inflammation must act together to cause necrosis. However, this relationship is not yet well elucidated, as it is not known whether osteonecrosis must occur first for the lesion to subsequently become infected, or whether the presence of an initial infected site in the oral cavity induces bone necrosis (Kim et al., 2021).

Furthermore, another effect caused by drugs, such as BPs, is the inhibition of angiogenesis. Thus, one explanation for the pathogenesis of osteonecrosis is that these substances cause a reduction in the amount of blood vessels in the jawbone and, consequently, there is a decrease in blood supply and a lesion is formed. However, more clinical research is needed to prove this hypothesis (Kim et al., 2021).

In addition to concentrating on bone tissues, BPs also exhibit some toxicity to soft tissues, such as the oral mucosa. In the review conducted by Kim et al. (2021), it was found that these drugs are able to suppress the proliferation and keratinocyte contribution of mucosal epithelial cells, triggering tissue fragility. If the patient is subjected to local trauma, such as surgery, this

fragility can result in bone exposure and eventual osteonecrosis. However, as the concentration of BPs in soft tissues is low, it is possible that this mechanism rarely occurs.

Another important factor in the pathophysiology of MRONJ is the patient's immune system. Individuals taking immunosuppressive drugs, such as steroids, or undergoing chemotherapy during antiresorptive therapy with BPs have an increased risk of developing MRONJ after an invasive procedure in the oral cavity (Kim et al., 2021).

Risk Factors Associated with MRONJ

Although antiresorptive and antiangiogenic drugs play a key role in the pathogenesis of osteonecrosis of the jaw, their use alone is not enough to trigger the disease. Because it is multifactorial, there are risk factors associated with MRONJ. Knowing how to identify them is fundamental for an appropriate dental treatment plan (Ruggiero et al., 2022; Kim et al., 2021).

Bisphosphonates and other drugs associated with MRONJ are widely used in patients in the treatment of bone diseases, such as osteoporosis and osteopenia, and in the treatment and prevention of metastasis in some types of cancer. Therefore, important factors that are linked to a higher risk of developing MRONJ are: the dosage, route of administration, and treatment duration (Chalem et al., 2020; Kim et al., 2021). According to the review by Gelazius et al. (2018), patients who take higher medication doses during cancer treatment, intravenously administered, are seven times more likely to develop MRONJ than those that take it orally. The duration of the therapy is another relevant aspect, due to the fact that BPs accumulate in tissues even after treatment stops. Chronic administration, for over 2 years, results in a prevalence of MRONJ that ranges from 0.05% to 0.21% (Kim et al., 2021). Generally, patients treating malignant diseases for longer than 4 years are considered to be at high risk for MRONJ (Ruggiero et al., 2022; Aparecida et al., 2018).

Comorbidities and the use of associated medications are also features that elevate the risk of MRONJ. Systemic diseases such as diabetes mellitus, rheumatoid arthritis, hyperthyroidism, and smoking can influence the development and course of the pathology (Kim et al., 2021). Oral infections, periodontal disease, and dental calculus may increase the incidence and severity of osteonecrosis (Chalem et al., 2020; Kizub et al., 2021). Furthermore, postmenopausal women and the elderly are at additional risk due to their need for the prevention and treatment of osteoporosis using antiresorptive medication (Ruggiero et al., 2022; Han, 2021; Kim et al., 2021). In addition, the joint use of BPs with glucocorticoids, other antiangiogenic medications, chemotherapy, or radiation therapy is also an aggravating factor in the development of MRONJ (Kim et al., 2021).

Some procedures performed in the oral cavity also influence the occurrence of MRONJ. Among these interventions are those directly related to the alveolar bone, which expose or traumatize it. Oral surgery procedures are described as the main factor that triggers osteonecrosis of the jaw, and dental extractions are responsible for its appearance in 52 to 61% of the cases. In patients on oral antiresorptive drugs, there is an average risk of 0.5%, while in intravenous therapy for cancer, it can range from 1.6 to 14.8% (Ruggiero et al., 2022; Kim et al., 2021; Şahin et al., 2019). The presence of local infection in teeth, as caries and periodontal or periapical diseases, contributes to the severity of the cases (Ruggiero et al., 2022; Kizub et al., 2021). In addition to surgeries, poor oral hygiene, with the presence of biofilm and calculus, and ill-fitting dental prostheses, that may traumatize the oral mucosa, are other risk factors for MRONJ (Ruggiero et al., 2022; Chalem et al., 2020).

Regarding the location, MRONJ tends to be more frequent in the mandible than in the maxilla. This is due to the fact that the lower jaw is formed by thicker bone, with less blood supply, than the upper jaw (Kim et al., 2021; El-Rabbany et al., 2017). In a study by Kizub et al. (2021), of the 57 analyzed MRONJ cases, 42 (73.7%) happened in the mandible. This prevalence was also found in the studies by Simpione et al. (2020) and Shin and Kim (2018), with percentages of 52.4% and 65.4%, respectively.

Diagnosis, Treatment and Prevention

For the correct management and prevention of medication-related osteonecrosis of the jaw, it is necessary to know, first, how to correctly diagnose it. According to the AAOMS, the diagnosis should be made by analyzing the information collected during the patient's anamnesis and dental clinical examination, both intraoral and extraoral (Ruggiero et al., 2022). The DDS should be aware that MRONJ may be mistaken for other pathologies, such as alveolar osteitis, sinusitis, gingivitis and periodontitis, caries, periapical diseases, odontalgia, sarcoma, and chronic sclerosing osteomyelitis (Ruggiero et al., 2022; Santos et al., 2019). This leads to an inappropriate treatment. Differential diagnosis is essential to avoid improper treatment and the consequent progression and worsening of the condition (Viviano et al., 2017).

The DDS can also use imaging exams to diagnose MRONJ. The use of CT scans allows a better analysis of the lesions and their characteristics, assists in the understanding of the disease, and in the process of choosing the most appropriate treatment (Ruggiero et al., 2022; Simpione et al., 2020). In the study by Simpione et al. (2020), the most present consequences of MRONJ lesions were bony sequestrum (52.4%), bone exposure (42.9%), and osteosclerosis (28.6%). The authors also observed some changes in the bone in the regions where there were no lesions, such as widened periodontal ligament space (33.3%), alterations in the maxillary sinus (23.8%), and cortical bone thickness of the mandibular canal (19%), suggesting that the use of antiresorptive drugs may cause some changes resulting from alterations in osteoclastic activity.

After collecting information from exams and anamnesis, the DDS should be able to identify if the patient is at risk of MRONJ and, if he already presents the pathology, in which stage it currently is. For this purpose, the AAOMS classifies MRONJ stages, presented in Table 2, according to the current alterations. Only after classifying his patient can the DDS choose the best treatment (Ruggiero et al., 2022).

Table 2 - Osteonecrosis-related drugs marketed in Brazil.

Stage	Definition
Patient at risk	No necrotic bone apparent. Asymptomatic patient that is or has been on intravenous or oral antiresorptive therapy.
Stage 0	Patients without clinical evidence of necrotic bone but presenting non-specific symptoms or clinical and radiographic findings. Symptoms: Odontalgia with no apparent dental cause; dull jaw pain that may radiate to the temporomandibular region; sinusitis; altered neurosensory function. Clinical Findings: Tooth loss unrelated to chronic periodontal disease; intraoral or extraoral swelling. Radiographic Findings: Alveolar bone resorption unrelated to periodontal disease; changes in trabecular bone and absence of bone formation at tooth extraction sites; osteosclerosis involving alveolar bone; periodontal ligament widening.
Stage 1	Exposed or necrotic bone that can be probed through a fistula in asymptomatic patients, with no evidence of infection/inflammation. There may also be radiographic findings mentioned in Stage 0.
Stage 2	Exposed or necrotic bone that can be probed through a fistula, with evidence of infection/inflammation. These patients are symptomatic and may have radiographic findings mentioned in Stage 0.
Stage 3	Exposed or necrotic bone that can be probed through a fistula, with evidence of infection, and one or more of the following signs: <ul style="list-style-type: none"> • Exposed necrotic bone extending beyond the alveolar bone (i.e., lower border and mandibular ramus, maxillary sinus, and zygoma when the maxilla is affected). • Pathological fracture. • Extraoral fistula. • Oro-antral/oral-nasal communication. • Osteolysis reaching the inferior border of the mandible or the maxillary sinus floor.

Source: Adapted from Ruggiero, S. L., Dodson, T. B., Aghaloo, T., Carlson, E. R., Ward, B. B., & Kademani, D. (2022). American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws-2022 Update. *Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons*, 80(5), 920–943. <https://doi.org/10.1016/j.joms.2022.02.008>.

MRONJ's treatment will depend mainly on the severity of the case and may range from conservative, non-surgical approaches to complex surgical procedures. Overall, treatment should be performed with a multidisciplinary team and always prioritize improving the patient's quality of life by controlling pain, secondary infections, and preventing the development of lesions in other sites (Ruggiero et al., 2022; Kizub et al., 2021). During the early stages, conservative measures aimed at improving the intraoral environment are indicated, such as oral hygiene instructions, antibacterial rinse, and in some cases, the use of antibiotics (Kizub et al., 2021; Kim et al., 2021). In severe stages, with infection and wide lesions, a more invasive approach, with surgery may be indicated. In these cases, the focus will be on pain management and infection control, using analgesics and antibiotics. Resection surgeries or debridements are performed to remove bony sequestrum and necrotic tissue, for example (Kizub et al., 2021; Kim et al., 2021; El-Rabbany et al., 2017).

Surgical therapy can be associated with other treatments so that the patient's prognosis is more favorable. Cavalcante and Tomasetti (2020) suggested the use of pentoxifylline, which promotes vasodilation and improves blood circulation, and tocopherol, which reduces inflammation and fibrosis in tissues. This is called the PENTO protocol and is used in the treatment of complex cases. It is already applied by some professionals in the treatment of osteoradionecrosis and, according to the authors' study, proved to be relevant in the treatment of MRONJ, being well tolerated and cost-effective, with few side effects. Another treatment that can be associated with surgeries is laser therapy, which aims to control edema and inflammation (Torres et al., 2020).

Another aspect to be considered during the management of patients at risk of MRONJ is pausing the antiresorptive therapy (drug holiday) before surgical procedures are performed or during the treatment of patients that already present the pathology. However, there is no consensus in the literature regarding its benefits (Ruggiero et al., 2022; Han, 2021; Kim et al., 2021).

The main role of the DDS in the management of MRONJ is to act directly in its prevention. According to the literature reviewed, every patient that will start antiresorptive therapy should have their oral health evaluated before treatment begins. During the dental consultation, the patient should be informed of the medication's risks and benefits. If there are any oral health issues that require specific procedures, such as dental extractions, they should be done before the start of antiresorptive therapy, if the patient's systemic conditions allow it. This entire approach should be multidisciplinary, including the physician, the dentist, and the patient, valuing communication as a key point of the treatment (Ruggiero et al., 2022; Aparecida et al., 2018; Kim et al., 2021).

In the case of patients who have already started antiresorptive therapy, the DDS should evaluate the risk factors present and highlight the importance of maintaining good oral health. In the need to perform surgical procedures, good planning and all protocols that facilitate the postoperative period should be adopted (Ruggiero et al., 2022; Chalem et al., 2020; Kim et al., 2021).

DDS knowledge on MRONJ

Regarding the knowledge of MRONJ among DDS, it was found that younger dentists and recent graduates mastered the subject better (Daron et al., 2018; Patil et al., 2020; Escobedo et al., 2018; Ozkan et al., 2021; Arnaud et al., 2022; Bruckmoser et al., 2021). Moreover, DDS register the medications used by their patients, however, most do not ask the reason why they are being used (Daron et al., 2018; Han, 2021). When it comes to the indications and adverse effects of BP, few professionals knew how to correctly answer the therapeutic indications of antiresorptive and antiangiogenic medications, their trade names, and side effects associated with the oral cavity (Patil et al., 2020; Arnaud et al., 2022; Miranda-Silva et al., 2020).

Regarding confidence in their knowledge about BPs and MRONJ, most DDS did not feel comfortable with performing surgical procedures on patients using these medications because they thought that their knowledge of the management of these cases might be insufficient (Daron et al., 2018; Patil et al., 2020; Dahlgren & Larsson, 2020).

4. Discussion

Jaw osteonecrosis is defined by the AAOMS as exposed or necrotic bone, which can be probed through an intraoral or extraoral fistula, for more than eight weeks in patients who take or have taken antiresorptive, immunomodulatory, or antiangiogenic agents, without a history of radiotherapy to the head and neck region (Ruggiero et al., 2022). Although the clinical manifestation of the disease is well known, its pathophysiology is still not well explained. It is a multifactorial disease linked to drug-induced suppression of bone resorption (Kim et al., 2021). It has specific risk factors that are extremely important for its occurrence, evolution, and severity. High drug dosage, intravenous administration and prolonged therapy time increase considerably the risk of MRONJ (Chalem et al., 2020; Kim et al., 2021). These characteristics are corroborated by the AAOMS guidelines for the diagnosis and management of patients with MRONJ (Ruggiero et al., 2022; Gelazius et al., 2018). Other conditions that may corroborate the development of MRONJ are comorbidities, including diabetes mellitus, rheumatoid arthritis, smoking, associated medications, such as glucocorticoids, chemotherapies, antiangiogenics, and postmenopausal women that undergo treatment for osteoporosis (Ruggiero et al., 2022; Han, 2021; Kim et al., 2021).

In a case reported by Tajima et al. (2022), an 88-year-old female patient, hypertensive, took bisphosphonate for more than 4 years to treat osteoporosis and had poor oral hygiene, presented MRONJ associated with orbital cellulitis. The worsening of the case may be related to the combination of the present risk factors.

Oral surgery procedures are described as the factor most associated with the development of osteonecrosis of the jaw. Dental extractions account for more than 50% of the appearance of these lesions in patients undergoing antiresorptive therapy, with a higher the risk in those treating cancer intravenously (1.6 to 14.8%) (Ruggiero et al., 2022; Kim et al., 2021; Şahin et al., 2019). In the literature review conducted by Gelazius et al. (2018), about dental implant placements on this group of patients, it was found that patients on intravenous therapy should not undergo this procedure, as the chance of MRONJ occurring is seven times higher compared to the oral administration of BPs. In the review by Aparecida et al. (2018), surgeries were found to be safe in patients who presented no risk factors and those who had used BPs for less than four years. However, in patients who received BPs intravenously or antiangiogenic drugs for cancer treatment, procedures involving direct bone injury were not recommended.

Regarding the diagnosis of MRONJ, it was found that it should be made through an extensive analysis of the information collected in the anamnesis and during the dental clinical examination (intraoral and extraoral) (Ruggiero et al., 2022). Differential diagnosis may be necessary in some cases since this pathology can be mistaken for other conditions affecting the jaws, such as alveolar osteitis and chronic sclerosing osteomyelitis (Santos et al., 2019). An incorrect diagnosis results in inadequate treatment and a worse prognosis. In a case report by Viviano et al. (2017), a 69-year-old female patient was using intravenous zoledronate to treat breast cancer and, due to an incorrect approach, developed osteonecrosis in the maxilla and mandible. Because of the associated comorbidities, the patient's condition worsened, resulting in mandibular fracture, edema, suppuration, pain, and systemic involvement that culminated in septic shock and death. Early diagnosis and appropriate treatment are important to avoid cases like this, especially in patients with unfavorable health conditions. Therefore, imaging exams, such as Cone-Beam Computed Tomography (CBCT), can be good allies during the diagnostic process. By using a CBCT, the DDS can observe bone changes common in MRONJ lesions. According to Simpione et al. (2020) and Kim et al. (2020), the most frequent alterations are bony sequestrum, bone exposure, and osteosclerosis. In the study by Ogura et al. (2021), in addition to CBCT images,

histopathology was also used to identify the main microscopic features of MRONJ, including necrotic bone, granulation tissue surrounded by bone and inflammatory cells; osteoclasts are rarely found around the necrotic bone, but were seen on its surface, in contact with the granulation tissue.

When it comes to interventions, it has been found that they can range from conservative, non-surgical treatments to more complex surgical procedures, depending on the patient's condition (Ruggiero et al., 2022). Priority should be given to multidisciplinary management, to prevent lesion expansion, decrease morbidity, and improve the patient's quality of life (Kizub et al., 2021; El-Rabbany et al., 2022). For early stages, conservative measures of intraoral environment improvement and the use of antibiotics, for infection control, should be the first choice. In severe stages, surgical therapy may be indicated to remove bony sequestrum and necrotic tissue (Kizub et al., 2021; Kim et al., 2021; El-Rabbany et al., 2017). Cavalcante and Tomasetti (2020) suggested the use of pentoxifylline and tocopherol in association with surgery for treating complex cases. These drugs were successfully used by Santos et al. (2019) to stimulate vascularization and prevent fibrosis after a total maxillectomy in a case with an extensive necrotic area that reached the skull base. Laser therapy is also beneficial and can be used associated with surgery, as performed by Torres et al. (2020), who reported considerable improvement in the signs of inflammation, and better healing of the mucosa adjacent to the bone. In addition, laser therapy decreased fistula formation and prevented the progression of MRONJ from stage 2 to 3.

As for drug holidays before surgical procedures, there was no consensus in the literature regarding their adoption. Some authors, such as Han (2021), recommend a 2-3-month pause for patients on therapy with BPs for more than 3 years and for patients at low risk of MRONJ. Nevertheless, the AAOMS 2022 guideline determined that the adoption of this protocol is still inconclusive, and its effectiveness has not yet been proven (Ruggiero et al., 2022). In the review conducted by Kim et al. (2021), the results were also heterogeneous, and the authors recommended a 2-month pause before performing surgical procedures on patients that have been taking BP for a long time or have concomitant risk factors until the approached site has healed. In the case of denosumab, Han (2021) found no evidence that recommends drug holidays, while Kim et al. (2021) suggested that it is beneficial in patients being treated for osteoporosis due to the reversibility of its effects.

The DDS plays a key role in preventing MRONJ. It is important to inform the patient of the need to evaluate their oral health before beginning an antiresorptive treatment, answer questions, and discuss the risks and benefits of the therapy. The multidisciplinary nature of the treatment must be prioritized, and the DDS should communicate with the patient's physician whenever possible (Ruggiero et al., 2022; Aparecida et al., 2018; Kim et al., 2021). However, in a survey conducted by Choi et al. (2022), none of the patients interviewed had been informed by their physician or dentist about the importance of dental appointments prior to starting therapy and about the influence of the medications on some dental procedures. This data shows that this communication is still scarce. It is also the professional's duty to evaluate the risk factors of patients who have already started therapy so that, if a surgical procedure is needed, proper planning is done in order to minimize or extinguish interurrences (Ruggiero et al., 2022; Kim et al., 2021).

However, to act in the diagnosis, treatment, and prevention of MRONJ, it is necessary that the DDS has a satisfactory knowledge of the disease and its particularities. Ozkan et al. (2021) analyzed the scenario regarding bisphosphonates and MRONJ and found that professionals that had less than 5 years of experience had more knowledge (85.5%) than those that have between 5 and 10 years of experience and those with more than 10 years of experience (76.1% and 50.6%, respectively). However, in the study by Dahlgren and Larsson (2020), the opposite was found, since more experienced professionals were found to have better knowledge than recent graduates.

Regarding BPs, in the study by Ozkan et al. (2021), only 26.8% of DDS knew the names of drugs in the BPs class. On the other hand, in the study by Arnaud et al. (2022), out of a list of four drugs, 43.9% of the participants could not identify trade

names of BPs used for oncological treatment and 36.3% could not indicate those used in rheumatological diseases. In the survey by Patil et al. (2020), although 70% of the participants knew the indications and mechanism of action of BPs, only 47.9% knew that osteonecrosis can be a side effect of medications in patients who undergo oral surgical procedures. Arnaud et al. (2022) found in their survey that only 29.7% of dentists knew about the elevated risk in patients with associated steroid therapy. In a Brazilian study by Miranda-Silva et al. (2020), only 6.96% of the participants knew how to identify the therapeutic indications of these drugs, their trade names, and their effects on the oral cavity. In that study, only 35.95% of the DDS knew how to point out preventive practices for MRONJ, such as oral hygiene maintenance and intraoral environment improvement before beginning drug therapy. However, 52.6% of the professionals knew the importance of referring patients to the DDS before the start of therapy and during the follow-up of patients with MRONJ in different stages.

Regarding the content of the anamnesis, in the research by Daron et al. (2018), only 63% of DDS asked about the use of BPs and of these, 91.5% asked about their therapeutic indication. In Han's (2021) study, it was found that 96.9% of DDS regularly document the patient's medical history, including medications, prior to dental implant placements or dental extractions, however, only 65% specifically asked the name of the medication and for how long it had been used.

The study by Daron et al. (2018) found that 84.5% of the interviewed DDSs did not feel comfortable with performing surgical procedures on patients using BPs. This result was also seen in the study by Dahlgren et al. (2020), in which only 13.1% of the participants felt confident regarding their knowledge of the management of patients on antiresorptive therapy. Patil et al. (2020) found that only 34.6% of DDS were knowledgeable about the AAOMS guideline. In contrast, Dahlgren et al. (2020) described that over 70% of participants were not aware of the AAOMS classification of MRONJ stages.

5. Conclusion

Through the systematized literature review it was possible to conclude that:

- o MRONJ is a multifactorial condition that, although rare, presents symptoms and harmful consequences.
- o The DDS must know how to recognize its symptoms, and how to treat and prevent MRONJ.
- o It is essential that dental professionals have adequate knowledge of the pathology and be able to make decisions based on updated scientific evidence to offer the best approach to the patient.

Furthermore, future research should focus on increasing the understanding of MRONJ pathogenic mechanisms to provide accurate protocols for the treatment and management of that condition, improving patients' quality of life.

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