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Surgical treatments for medication-related osteonecrosis of the jaws: advantages and limitations

Tratamentos cirúrgicos da osteonecrose dos maxilares relacionada a medicamentos: vantagens e limitações

Tratamientos quirúrgicos de la osteonecrosis de los maxilares relacionada con medicamentos: ventajas y limitaciones

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Abstract
Objective: The purpose of this paper is to discuss the surgical methods available for the treatment of MRONJ, pointing out their advantages and limitations. *Methodology:* An integrative review of the literature was performed by searching the PubMed virtual database using the MeSH term "bisphosphonate associated osteonecrosis of the jaw/surgery" and including 26 publications. *Results:* Surgical intervention is presented as a treatment option in an attempt to reduce disease progression with the recognition that this early intervention may predict beneficial outcomes for the patient. Surgical approaches confer superior treatment outcomes over conservative treatments, with success rates of 80-90% and 10-62%, respectively. To establish treatment, consideration should be given to therapy for removing nonhealing exposed bone, which can be accomplished through curettage, sequestrectomy, and surgical resection. When approaching soft tissue, different flaps can be performed, according to their indications. *Conclusion:* Surgical treatment has shown maintenance of mucosal coverage, improved quality of life, and quick resumption of antiresorptive therapy for all stages of the disease, with high rates of therapeutic success. However, continued efforts should be encouraged to investigate the best treatment for this pathology.
Keywords: Bisphosphonate-associated osteonecrosis of the jaw; Oral surgical procedures; Osteonecrosis; Jaw diseases.

Resumo
Objetivo: O objetivo deste trabalho é discutir os métodos cirúrgicos disponíveis para o tratamento da OMRM, apontando suas vantagens e limitações. *Metodologia:* Foi realizada uma revisão integrativa da literatura, através de busca conduzida na base de dados virtuais PubMed, a partir do termo MeSH em inglês “bisphosphonate associated

osteonecrosis of the jaw/surgery" e inclusão de 26 publicações. *Resultados:* A intervenção cirúrgica é uma opção de tratamento que busca reduzir a progressão da doença, na qual, a intervenção precoce pode predizer resultados benéficos para o paciente. As abordagens cirúrgicas conferem resultados superiores aos regimes terapêuticos conservadores, com taxas de sucesso de 80-90% e 10-62%, respectivamente. Para estabelecer o tratamento, deve-se levar em consideração a remoção do osso necrótico que pode ser realizada através de curetagem, sequestrectomia e ressecção cirúrgica. Já para abordagem dos tecidos moles, podem ser realizados diferentes retalhos de acordo com as indicações**.** *Conclusão:* O tratamento cirúrgico demonstrou manutenção da cobertura da mucosa, melhora da qualidade de vida e retomada rápida da terapia antirreabsortiva para todos os estágios da doença, apresentando elevadas taxas de sucesso terapêutico. Entretanto, devem ser estimulados esforços contínuos de investigação do melhor tratamento para esta patologia.
Palavras-chave: Osteonecrose da arcada osseodentária associada a difosfonatos; Procedimentos cirúrgicos bucais; Osteonecrose; Doenças maxilomandibulares.

Resumen
Objetivo: El objetivo de este trabajo es discutir los métodos quirúrgicos disponibles para el tratamiento de la MRONJ, señalando sus ventajas y limitaciones. *Metodología:* Se realizó una revisión integradora de la literatura mediante una búsqueda realizada en la base de datos virtual PubMed, utilizando el término MeSH "bisphosphonate associated osteonecrosis of the jaw/surgery" e incluyendo 26 publicaciones. *Resultados:* La intervención quirúrgica es una opción de tratamiento que busca reducir la progresión de la enfermedad, y que puede predecir resultados beneficiosos. Los abordajes quirúrgicos confieren resultados superiores a los regímenes terapéuticos conservadores, con tasas de éxito del 80-90% y del 10-62%, respectivamente. Para instaurar el tratamiento, debe tenerse en cuenta la eliminación del hueso necrótico, realizada mediante curetaje, sequestrectomía y resección quirúrgica. Para el abordaje de los tejidos blandos, pueden realizarse diferentes colgajos. *Conclusión:* El tratamiento quirúrgico demostró el mantenimiento de la cobertura de la mucosa, la mejora de la calidad de vida y el rápido retorno de la terapia antirreabsortiva para todos los estadios de la enfermedad, presentando elevadas tasas de éxito terapéutico. Por lo tanto, se deben estimar los esfuerzos de investigación del mejor tratamiento para esta patología.
Palabras clave: Osteonecrosis de los maxilares asociada a difosfonatos; Procedimientos quirúrgicos orales; Osteonecrosis; Enfermedades maxilomandibulares.

1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is defined as a pathological condition affecting the lower or upper jaw, associated with treatment with antiresorptive and antiangiogenic agents for regulating bone remodeling (Nisi *et al.*,2020).

It was first described in 2003 by Robert Marx, who reviewed 36 cases of painful bone exposure in patients with a history of zoledronate and pamidronate usage, resorptive drugs used at the time, in the treatment of metastatic breast cancer and multiple myeloma (Palla *et al.*, 2021).

The American Association of Oral and Maxillofacial Surgeons (AAOMS) published its first position paper on this form of osteonecrosis of the jaws in 2007, using the nomenclature bisphosphonate-related osteonecrosis of the jaws (Palla et al., 2021).

After seven years, AAOMS suggested changing the nomenclature from Bisphosphonate-induced osteonecrosis of the jaws (BIONJ) to Medication-related osteonecrosis of the jaw (MRONJ) to include the increasing number of osteonecrosis cases, involving the maxilla and mandible, and associated with other antiresorptive and antiangiogenic therapies (Nisi et al., 2018).

The prevalence of MRONJ varies between 0% and 20% depending on the route of administration of the medication and the type of bisphosphonate used (Rothweiler et al., 2021). Furthermore, this pathology is more common in the mandible than in the maxilla in a 3:1 ratio (Aljohani et al., 2019). However, the exact mechanism surrounding the pathophysiology leading to the onset of MRONJ still needs to be elucidated (Nonnenmühlen et al., 2019).

It can be observed that in patients who use these drugs, oral surgical procedures, associated with poor oral hygiene, periodontal infections, abscesses and ill-fitting dental prostheses, have been recognized as risk factors for MRONJ. Advanced age, smoking, corticotherapy and coexisting pathological conditions are considered to be systemic factors that favor the

development of MRONJ (Nisi et al.,2020).

The clinical aspect of MRONJ, described in 2022, by the AAOMS, is defined as the presence of nonhealing exposed bone or bone that can be probed through a fistula in the maxillofacial region, persisting for more than 8 weeks and occurring in patients being treated with antiresorptive agents and no history of radiotherapy or obvious metastatic disease of the jaws (Ruggiero et al., 2022).

Although antiresorptive and antiangiogenic therapies increase the life expectancy of patients with neoplastic diseases, they may also negatively affect their quality of life, since there is a risk of occurrence of MRONJ, which is often characterized by pain, purulent discharge with halitosis, edema and risk of pathologic fracture (Favia et al., 2018).

The AAOMS proposed a staging of MRONJ based on the clinical aspects of the disease. Considering the disease's stages, conservative therapy was suggested as the best for early stages (stages 0 and 1). Radical surgical procedures such as an en bloc resection or continuity resection of the mandible are suggested only for severe cases (stages 2 and 3) and depend on the general condition of the patient (Lemound et al., 2018; Ruggiero et al., 2022).

Some authors have reported that surgical approaches generate superior treatment outcomes compared to conservative treatments (Aljohani et al., 2019; Caldroney et al., 2017; Favia et al., 2018). However, the treatment strategy for MRONJ is controversial, and there is no consensus as to which approach is the best choice. Therefore, a clear and unanimous surgical guideline has not yet been established. In addition, the prognosis after surgical procedures is uncertain.

The adequate management of MRONJ is still a controversial and under-researched topic. Thus, the objective of this article is, by means of an integrative review of the literature, to discuss the surgical methods available for the treatment of MRONJ, pointing out their advantages and limitations.

2. Methodology

This study is characterized as an integrative literature review, which seeks to synthesize the available research on a specific theme and directs the practice based on scientific knowledge (Souza, et al., 2010; Whittemore & Knafl, 2005). An integrative literature review was performed by a search conducted on the PubMed virtual database in June 2022.

For the search to be conducted on the aforementioned platform, the Health Science Descriptors (DeCS) were identified and indexed. Subsequently, their corresponding Medical Subject Headings (MeSH), controlled vocabulary terms, were used on the advanced search associated with Boolean operators.

The search key was defined with the MeSH term "bisphosphonate associated osteonecrosis of the jaw/surgery", in which "surgery" is a qualifying term (Major Topic). Through the Boolean operator "AND" a filter was added for publications listed in the last five years. This search model generated a total of 77 results.

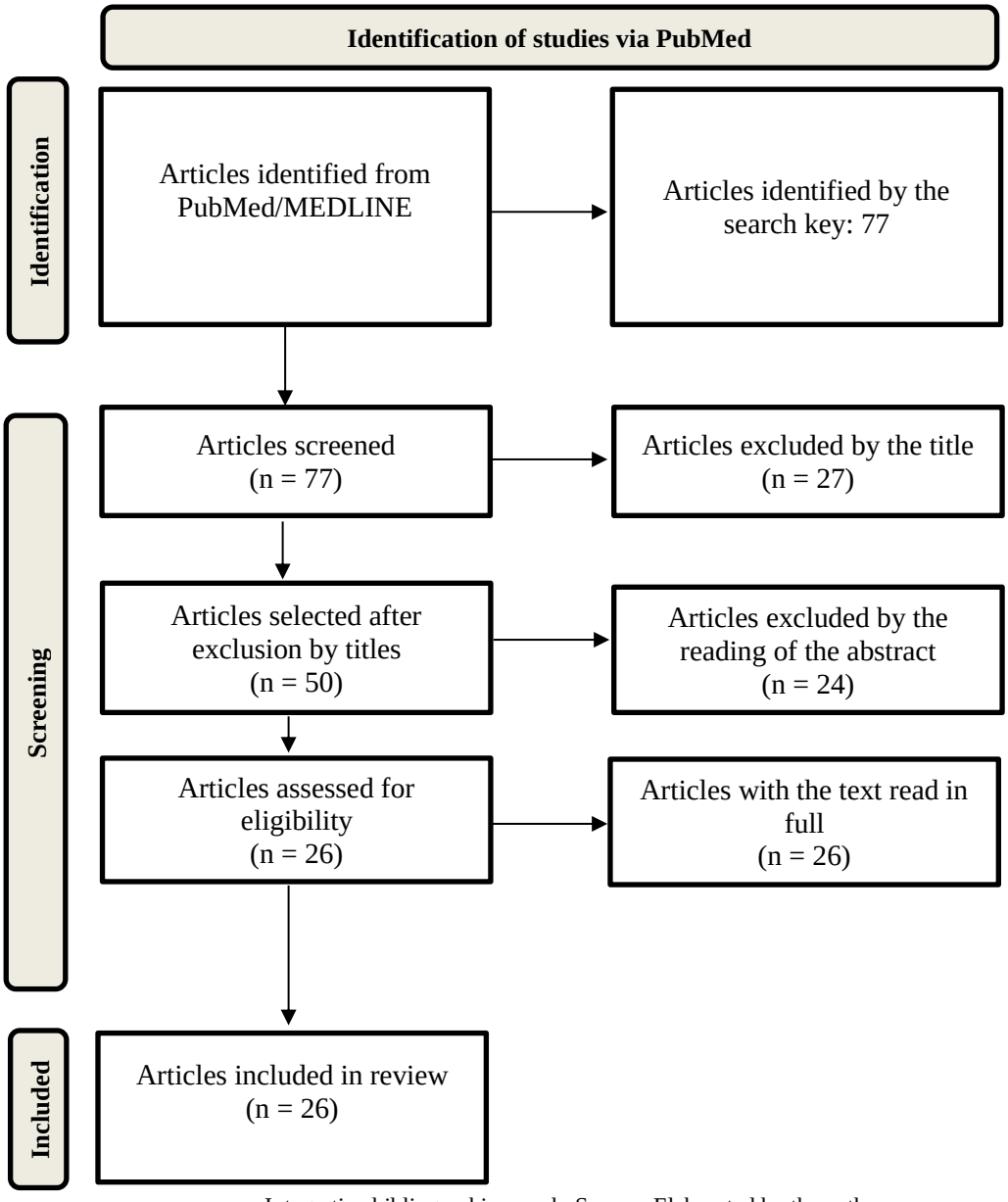
As inclusion criteria, articles published in the last five years, from 2017 to 2022, in their complete versions, in English and that had drug/bisphosphonate-related osteonecrosis of the jaws and surgical therapy as their main topic, were included.

It was established that publications that presented any of the following criteria should be excluded from the analysis: articles published in a different time interval than the one determined, publications in letter format, in a language other than English or that did not have their abstract available, articles that addressed other classes of medications or another pathology (such as osteoradionecrosis), and articles that were off-topic or had as their main focus the analysis of adjuvant therapies to the surgical treatment of osteonecrosis of the jaws.

After defining the inclusion and exclusion criteria, the titles of all 77 results found in the search were read and analyzed, which led to the exclusion of 27 articles that were not related to the topic or did not fit the criteria previously established. Of the 50 articles selected by title, after reading the abstracts, 26 were selected.

All 26 articles included in the research were read in full and data extraction was performed by two authors and compared for concordance. The methodological path applied in this study for the selection of the scientific articles is schematized in Figure 1.

Figure 1 - Selection of articles in the literature.



Integrative bibliographic search. Source: Elaborated by the authors.

3. Results

After selecting the articles that matched the inclusion criteria, the 26 articles resulting from the search and screening were used as the scientific basis for this paper. Table 1 below shows the selected articles and the main features they presented.

Table 1 - Summary of research of the articles selected after screening.

	Features	References
Definition of MROJ	Patients should be considered to have MRONJ if they present all of the following characteristics: current or previous use of antiresorptive or antiangiogenic agents; exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than eight weeks; and no history of radiation therapy to the jaws or obvious metastatic disease to the jaws.	**Favia et al. (2018)** **Sacco et al. (2021)**
Preconize conservative treatment	According to the AAOMS guidelines, MRONJ treatment is stage-dependent, and stages 1 and 2 benefit from conservative therapies, while stage 3 should be treated with surgery, including debridement or resection of the infected mandible. The AAOMS also recommends that MRONJ should be treated as conservatively as possible because the surgical treatment causes bone exposure and therefore interferes with the goal of disease prevention.	**Oteri et al. (2018)** **Ruggiero et al. (2022)**
Preconize surgical treatment	The surgical therapy aims to keep mucosal closure without bone exposure and infection and depends on the possibility of removing necrosis by limiting surgical trauma, smoothing the bone edges, controlling the progress of infection, promoting blood supply at the affected site, and achieving primary wound closure without soft tissue tension. It achieves a shorter healing period, better predictability and a higher success rate even in advanced stages. It should be indicated as an early treatment to prevent complications and lesion progression. Moreover, a key advantage of the surgical treatment is the histopathological analysis of the removed bone tissue to exclude the presence of metastases, especially in cancer patients.	**El-Rabbany et al. (2019)** **El-Rabbany et al. (2022)** **Giudice et al. (2020)** **Hayashida et al. (2017)** **Moll et al. (2021)** **Palla et al. (2021)** **Rothweiler et al. (2021)**
Early surgical intervention	The prognosis of surgical treatment, even at less advanced stages, is better than the conservative treatment. What can be seen in the literature is that surgical approaches have better treatment outcomes compared to conservative therapies, with success rates of 80-90% and 10-62%, respectively. There is also data that indicated 100% disease resolution for all stage 2 lesions and 83.3% disease resolution for stage 3.	**Caldroney et al. (2017)** **Choi et al. (2020)** **Nisi et al. (2018)** **Nisi et al. (2020)**
Necrotic bone removal	To establish the treatment, one should take into consideration the therapy for removing the necrotic bone that can be performed through curettage, sequestrectomy, and surgical resection.	**Guo & Guo (2021)** **Hallmer et al. (2018)** **Kagami et al. (2018)** **Kim et al. (2017)** **Sacco et al. (2018)**
Soft tissue flaps	Soft tissue flaps are made to promote complete coverage of exposed bone after removal of necrotic bone, and coverage is imperative to prevent recurrence and progression of the disease. There are a few sort of soft tissue flaps that can be employed, such as: *mucoperiosteal flap* in which the periosteum remains intact and the alveolar process is not visible; *buccal fat pad flap* that presents great blood supply, proximity to the surgical site, high yield, easy access, mechanical stability, low failure rate, and minimal donor site morbidity; *mylohyoid muscle flap* that provides an additional vascularized layer on top of the resected or debrided bone, it is a fast technique with a low complication rate and very predictable results, and *free flaps* that can be of various types, such as the *fibula, iliac crest* and *scapula flap* and the *nasolabial flap*. They enable single-stage surgery with composite vascular grafting.	**Aljohani et al. (2019)** **Hauer et al. (2020)** **Jose et al. (2022)** **Lemound et al. (2018)** **Nonnenmühlen et al. (2019)** **Ristow et al. (2018)**

Source: Elaborated by the authors.

Medication-related osteonecrosis of the jaw (MRONJ) is a severe condition that affects both the maxilla and the

mandible, with a preference for the latter, in patients exposed to specific drugs. It has been described most frequently in association with bisphosphonates (BP), however, it has now been observed associated with other drugs, such as Denosumab and antiangiogenic drugs (Nisi et al.,2020).

In 2003 this pathology was described by Marx, who reported cases of painful bone exposure in patients undergoing intravenous bisphosphonate therapy (Palla et al., 2021). Since then, the number of case reports of osteonecrosis of the jaw associated with other antiresorptive and antiangiogenic drugs has increased in the literature (Nisi et al., 2018). For this reason, the American Association of Oral and Maxillofacial Surgeons (AAOMS) used the term "Medication-related osteonecrosis of the jaw" (MRONJ) in its 2014 position paper.

The most recent AAOMS position paper, from 2022, states that patients should be considered to have MRONJ if they present all of the following characteristics shown in Table 2 (Favia et al., 2018; Ruggiero et al., 2022; Sacco et al., 2021).

Table 2 - Characteristics present in the diagnosis of medication-related osteonecrosis of the jaw (MRONJ).

1)	Current or previous use of antiresorptive or antiangiogenic agents.
2)	Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than eight weeks.
3)	No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.

Source: Adapted from Favia *et al*. (2018); Ruggiero *et al*. (2022) and Sacco *et al.* (2021).

It is possible to see from the table above that for a patient to be diagnosed with this disease, he needs to present these three highlighted characteristics.

Antiresorptive and antiangiogenic agents are mainly used in the treatment of malignant diseases as well as bone metastases, but they have also been used in osteoporosis cases, Paget's disease and hypercalcemia (Sacco et al., 2021). Thus, they are associated with improved quality of life in patients who use them, but they are also related to a higher probability of occurrence of MRONJ cases.

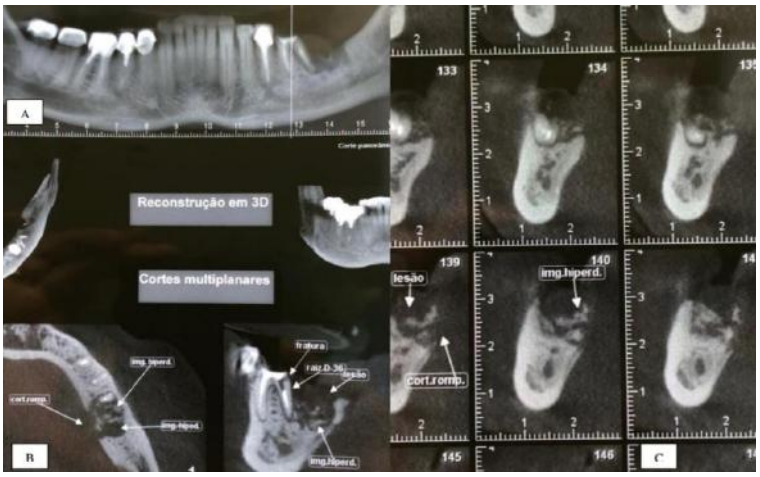
The exact mechanism around the pathophysiology that leads to the onset of MRONJ still needs to be elucidated (Nonnenmühlen et al., 2019). The pathogenesis of MRONJ is probably multifactorial and has not yet been fully clarified. None of the known etiopathogenic factors is able to explain the appearance of these lesions. The main related mechanism is a drug-induced disruption of bone homeostasis caused by altered cells of a monocyte-macrophage lineage (Hauer et al., 2020). It is hypothesized that the suppression of osteoclast activity plays a central role in the pathogenesis of necrosis caused by bisphosphonates and Denosumab ingestion (Nonnenmühlen et al., 2019).

Although the pathological mechanism is still unclear, some risk factors have been recognized when these drugs are being taken, which contribute to the development of MRONJ, such as dental extractions, implant placements and periodontal surgery, associated with poor oral hygiene, periodontal infections, abscesses and ill-fitting dental prostheses. In addition, advanced age, smoking, corticotherapy, and coexisting pathological conditions are considered to be systemic factors that favor the development of MRONJ (Nisi et al.,2020).

Once such risk factors are acknowledged, there are also potentially modifiable factors to reduce the risk of MRONJ, including: performing high-risk surgical procedures before starting drug therapy, pre- and postoperative antibiotic use, use of oral antimicrobials, and good oral hygiene. Improving the patient's overall health is always indicated, as is smoking cessation and diabetes management (Ruggiero et al., 2022).

Treatment planning for patients at risk of developing MRONJ should include the complete examination of the oral cavity and radiographic imaging or CT scan evaluation, when indicated (Figure 2). It is important to identify both acute infection and potential sites of infection to prevent future sequelae, which may be exacerbated, when drug therapies begin (Ruggiero et al., 2022).

Figure 2 - Cone-Beam Computed Tomography for evaluation of a case of medication-related osteonecrosis of the jaw.



Source: Personal archive. Panoramic View (A), Multiplanar View (B) and Coronal View (C).

The Cone-Beam Computed Tomography (CBCT) shows a mixed lesion with hyperdense foci (arrows), that appear as "moth-eaten" in the left mandibular alveolar region, in direct contact with the distal root of the left mandibular first molar. On the cuts it is possible to observe that the lesion breaks through the alveolar and lingual cortices, without compromising the inferior alveolar canal.

The classification and staging system is based entirely on the clinical presentation of MRONJ and should guide treatment. Therefore, the AAOMS has proposed the following stages as shown in Figure 3.

Figure 3 - Staging of medication-related osteonecrosis of the jaw according to Clinical Findings.

At risk	Stage 0	Stage 1	Stage 2	Stage 3
No apparent necrotic bone, asymptomatic patients treated with intravenous or oral antiresorptive therapy.	No clinical evidence of necrotic bone and nonspecific symptoms or radiographic findings.	Exposed and necrotic bone or fistula(e), asymptomatic patients without evidence of infection/ inflammation.	Exposed and necrotic bone or fistula(e), with evidence of infection/ Inflammation, symptomatic patients.	Exposed and necrotic bone or fistula(e) and presence of infection beyond the region of the alveolar bone; Pathological fracture; Extraoral fistula; Oral-antral/oral-nasal communication; Osteolysis extending to the lower border of the mandible or sinus floor.

Source: Adapted from Ruggiero et al. (2022) and Sacco et al. (2020).

In Figure 3, it can be seen that the disease has a pre-threshold phase, which consists of the risk of the patient developing the disease. It is only after stage 1 that symptoms begin to appear, which evolve in severity until stage 3.

Considering the stages of the pathology that may affect patients, MRONJ treatment goals are to eliminate pain, control soft tissue infection and minimize the progression or occurrence of bone necrosis (Hayashida et al., 2017).

Therefore, according to the AAOMS guidelines, MRONJ treatment is stage-dependent, and states that stages 1 and 2 benefit from conservative therapies, while stage 3 should be treated with surgery, including debridement or resection of the infected mandible (Oteri et al., 2018).

A wide variety of treatments have been proposed, ranging from non-surgical treatments to surgical therapy. Non-surgical approaches include strengthening the oral hygiene, frequent oral health care, chlorhexidine oral rinses, low level laser therapy, hyperbaric oxygen therapy, pentoxifylline, teriparatide, and antibiotic therapy, while surgical management consists of the removal of necrotic bone (El-Rabbany et al., 2019; Favia et al., 2018).

Therefore, when conservative treatment is not indicated, some surgical interventions can be suggested, such as curettage, sequestrectomy, debridement, saucerization, and surgical resection (El-Rabbany et al., 2019).

In the latest position papers, the AAOMS recommended that MRONJ should be treated as conservatively as possible because the surgical treatment causes bone exposure and therefore interferes with the goal of disease prevention (Ruggiero et al., 2022). What is observed is that several treatment options have been described since the first case of MRONJ was reported.

Although early stages of MRONJ appear to respond relatively well to conservative treatments or limited bone debridement, if conservative treatment fails, treatment for stage 3 lesions remains controversial (Sacco et al., 2018).

However, recent studies show that the prognosis of surgical treatment, even at less advanced stages, is better than the conservative treatment. Some authors have reported that surgical approaches have better treatment outcomes compared to conservative therapies, with success rates of 80-90% and 10-62%, respectively (Caldroney et al., 2017; Choi et al., 2020).

Thus, to date, the treatment of MRONJ is described as challenging, with no current standard of care and no consensus in the literature. However, the promising results of surgical therapy in the care of MRONJ have encouraged studies regarding the techniques to be employed in this type of treatment, being a viable option with high success rates for all stages of the disease (Ruggiero et al., 2022).

According to Hayashida et al (2017), surgical treatment should be the first choice because it allows complete healing of lesions, unlike recommended non-surgical treatments.

Therefore, surgical success is defined as maintaining mucosal closure without bone exposure and infection (Palla et al., 2021) and depends on the possibility of removing necrosis by limiting surgical trauma, smoothing the bone edges, controlling the progress of infection, promoting blood supply at the affected site, and achieving primary wound closure without soft tissue tension (El-Rabbany et al., 2019; Giudice et al., 2020).

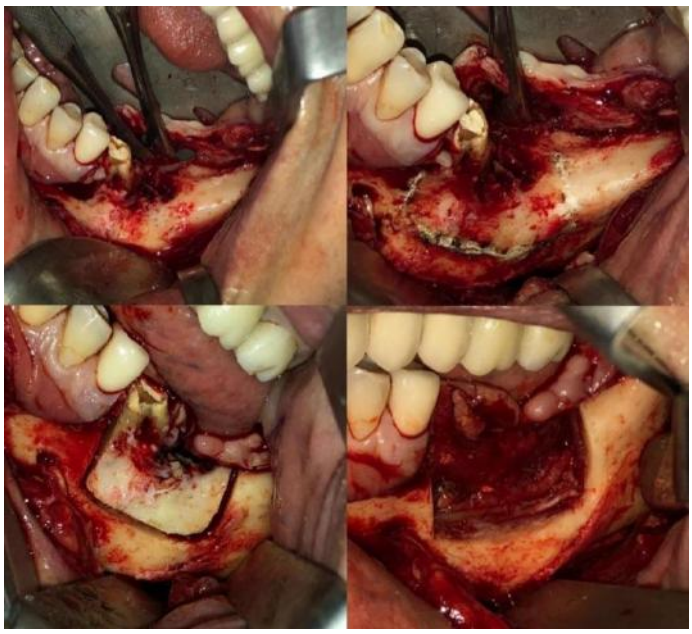
As advantages, surgical therapy generally achieves a shorter healing period, better predictability and a higher success rate even in advanced stages. It should be indicated as an early treatment to prevent complications and lesion progression (Favia et al., 2018; Hauer et al., 2020). Moreover, a key advantage of the surgical treatment is the histopathological analysis of the removed bone tissue to exclude the presence of metastases, especially in cancer patients, with a primary neoplastic disease (Giudice et al., 2020).

However, surgical techniques are not yet standardized and depend mainly on the skill and experience of the surgeon (Hauer et al., 2020). To establish the treatment, one should take into consideration the therapy for removing the necrotic bone that can be performed through curettage, sequestrectomy, and surgical resection (Kagami et al., 2018). For soft tissue approach, different flaps can be performed according to their indications.

Segmental or marginal resection of the mandible and partial maxilectomy are effective methods in controlling MRONJ. This approach can be applied to patients with all stages of MRONJ. These resections require margins beyond the edges of necrotic bone to an area of vital, bleeding bone (Figures 4 and 5) (Ruggiero et al., 2022). With regard to en bloc

resection, the overall improvement rate reported by Hallmer et al. (2018) was 92.5%.

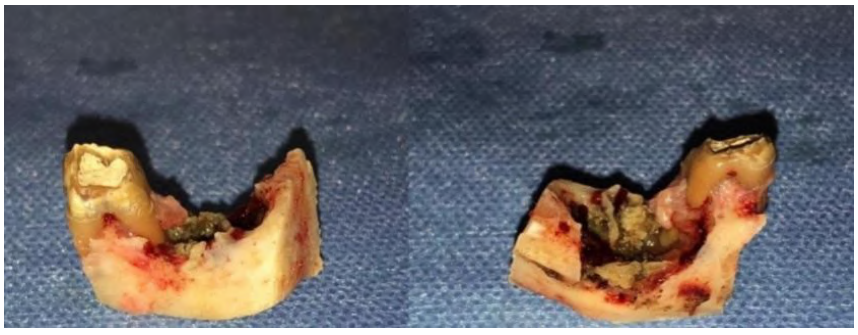
Figure 4 - Segmental resection of the mandible for removal of necrotic bone.



Source: Personal archive.

Transoperative sequence of marginal mandibular resection as treatment for removal of necrotic bone caused by the use of venous Zometa® are presented in Figure 4. An intraoral incision was made at the distal of the left maxillary second premolar and mucoperiosteal detachment was performed to access the surgical site. Resection was planned with a safety margin of 1 cm from the lesion.

Figure 5 - Necrotic bone in the alveolar bone region after marginal resection of the mandible.



Source: Personal archive.

It is observed in Figure 5 the macroscopic specimen of marginal resection of the mandible (Figure 4). It is possible to see the exposed and necrotic bone on the piece. The lesion is limited to the alveolar bone region, breaking through the alveolar and lingual córtices.

Soft tissue flaps are made to promote complete coverage of exposed bone after removal of necrotic bone, and coverage is imperative to prevent recurrence and progression of the disease (Jose et al., 2022). The flaps that can be employed are described in Table 3.

Table 3 - advantages of the types of soft tissue flaps.

Mucoperiosteal Flap	Periosteum remains intact and the alveolar process is not visible. It represents a fast and simple method, suitable for MRONJ stage 1 and 2 lesions.
Buccal Fat Pad Flap	It presents great blood supply, proximity to the surgical site, high yield, easy access, mechanical stability, low failure rate, and minimal donor site morbidity. Moreover, fat grafts have stem cells that can promote tissue healing, including bone tissue
Mylohyoid Muscle Flap	It provides an additional vascularized layer on top of the resected or debrided bone. It is a fast technique with a low complication rate and very predictable results, indicated for defects in the mandible region.
Free Flap	They can be of various types, according to the case in question, some examples are the fibula, iliac crest and scapula flap and the nasolabial flap. They enable single-stage surgery with composite vascular grafting, reconstruction of large defects in the oral cavity, and restoration of facial shape and function (including dental rehabilitation).

Source: Adapted from Aljohani et al. (2019); Caldroney et al. (2017); Hauer et al. (2020); Jose et al. (2022); Lemound et al. (2018); Nonnenmühlen et al. (2019); Ristow et al. (2018) and Sacco et al. (2018).

The above mentioned table provides a general view of the soft tissue flaps that can be used as a treatment for the pathology, as well as their respective characteristics.

4. Discussion

There is no consensus in the literature if surgical therapy is the most appropriate strategy to address MRONJ. Questions prevail about its advantages, disadvantages and whether surgical treatment is, in all cases, the best option (Hayashida et al., 2017). In addition, surgical techniques are not yet standardized and depend mostly on the skill and experience of the surgeon (Hauer et al., 2020; Kagami et al., 2018).

However, it is generally agreed that decisions about surgical versus nonsurgical therapy should be patient-specific and tailored to individual needs. The risk-benefit ratio, including quality of life with current symptomatology, ability to perform good wound care to prevent infection and spread of disease, morbidity of a major surgical procedure, as well as oral function or dental rehabilitation after marginal or segmental resection should be taken into consideration (El-Rabbany et al., 2019; Giudice et al., 2020; Ruggiero et al., 2022).

Given that the treatment goals for patients with MRONJ are to eliminate pain, control soft tissue infection, and minimize the progression or occurrence of osteonecrosis (Hayashida et al., 2017), it has been observed that conservative therapy leads to complete cure in only a modest percentage of cases (18-23%) and has a very low probability of resolution of these lesions, especially in advanced stages (El-Rabbany et al., 2019; Favia et al., 2018; Hauer et al., 2020; Hayashida et al., 2017).

Thus, although the MRONJ treatment options are under debate, and some authors still recommend surgical treatment only for the most severe, symptomatic stages of the disease or in case of failure of a conservative therapy (Ruggiero et al., 2022; Sacco et al., 2021), studies have shown that surgery seems to be effective for the treatment of MRONJ at any stage of the disease (Hauer et al., 2020).

Palla et al. (2021) reported in their study a surgical success rate for stage I MRONJ of 100%, 71.4% in stage 2 and 60.0% in stage 3. For Nisi et al. (2020) their data indicated 100% disease resolution for all stage 2 lesions and 83.3% disease resolution for stage 3.

Hayashida et al. (2017) stated that complete healing was achieved in 25.2% of patients who underwent a non-surgical therapy and in 76.7% of those who underwent surgical treatment. They also observed that extensive surgery is superior to conservative surgery and non-surgical therapy in the treatment of patients with MRONJ, in which 86.8% of patients who underwent extensive surgery achieved complete healing.

The results of El-Rabbany et al. (2019) on the other hand, showed that the overall rates of disease resolution between the surgical and non-surgical groups were 70% and 36%, respectively. That is, the surgical group seems to have a higher average proportion of patients with resolution when compared to the nonsurgical group.

Both the study by Moll et al. (2021) and the study by El-Rabbany et al. (2022) evaluated the impact of surgical therapy on the quality of life of patients affected by MRONJ, and in both studies, the authors stated that operative treatment is not only associated with disease resolution, but also with significant improvement in the impact factor on patients' oral health and quality of life.

These positive results of the surgical treatment are due to the fact that this approach offers the best condition for cure, due to the shorter healing period, better predictability and success rate even in advanced stages of the disease, and ability to reduce its progression (Hauer et al., 2020; Ruggiero et al., 2022; Sacco et al., 2018).

Moreover, active surgical intervention can greatly improve the patient's quality of life by shortening hospitalization periods and allowing early reconstruction of the oral environment (Choi et al., 2020). Furthermore, Giudice et al. (2020) concluded that early surgery can prevent the possibility of silent disease progression by minimizing the period that the antiresorptive medication is not being used.

Therefore, surgery should be indicated as an early treatment to prevent complications and progression of lesions. However, surgery for osteonecrosis is not a simple approach and includes various techniques such as curettage, sequestrectomy, and mandibulectomy (Kagami et al., 2018), in addition to the various possibilities of soft tissue flaps.

According to Kim et al. (2017), sequestrectomy was the most common surgical procedure in their study. However, after surgery, 30% of patients did not recover completely and required additional surgical treatment. Those who underwent curettage under local anesthesia had a worse prognosis after surgery and required another surgery. It has been found in the literature that curettage is poorly effective for the treatment of MRONJ (Guo & Guo, 2021).

Hallmer et al. (2018) reported an improvement rate of 80.0% in patients undergoing sequestrectomy. The overall improvement rate was 92.5% for en bloc resection. In addition, the authors stated that even more radical surgical approaches, with oroantral communication closure using the buccal fat pad or in the mandible, using a myofascial flap, may yield a higher success rate in combination with na en bloc resection.

According to Sacco et al. (2018) the most frequent type of resection in their work was the subtotal (32.53%), followed by the segmental (26.50%) and the partial (2.40%).

In their systematic review, Sacco et al. (2021) confirmed that a segmental resection, without microsurgical reconstruction is a viable alternative for surgery, with promising results, a significantly low recurrence rate, fewer postoperative complications and less comorbidity than with microvascular reconstruction.

Oteri et al. (2018), meanwhile, stated that marginal resection showed successful results with resolution of acute infection and pain and should be indicated for osteoporotic patients with early-stage, symptomatic MRONJ.

The association of different techniques is also an option for the treatment of patients with MRONJ. In the study by Guo and Guo (2021), a new surgical approach, based on curettage with cortical perforations of adjacent healthy bone, was established. The perforations were performed to reach the medullary cavity and allow blood infiltration adjacent to the surgical site.

With regard to soft tissue flaps for the treatment of MRONJ, in the retrospective study by Nonnenmühlen et al. (2019)

it was shown that the single, more invasive surgical treatment in terms of preparing a full thickness flap may be particularly more promising than using the minimally invasive option in terms of a partial thickness flap. This is because the mucoperiosteal technique offers a better view of the operative field than the mucosal flap.

In the cases reported by Aljohani et al. (2019), 46 of the lesions that were covered with mucoperiosteal flap healed completely, indicating a 76.6% success rate.

The recurrence rate of MRONJ after the use of free flaps found by the systematic review by Sacco et al. (2018) was 6.02%. Only one case of recurrence was found in vascular reconstruction, so the overall success rate of the free flap was 96.39%.

The 16 cases presented in the experimental group of the study by Lemound et al. (2018) had a success rate of 68.8% with the nasolabial flaps. The control group with local gingival flaps had favorable results in 18.7% of cases, indicating superior results with the use of the nasolabial flap.

However, a limited number of studies have proposed free flaps for MRONJ lesions, mainly mandibular lesions, with poor vascularization and large soft tissue defects (Jose et al., 2022; Lemound et al., 2018).

Furthermore, Sacco et al. (2021) stated that free transfer of vascularized bone tissue and/or free osteo-fasciocutaneous flap as treatment for patients in stages 2 and 3 of MRONJ may increase sequelae and complications. These could decrease the quality of life and increase hospital admissions and costs.

As for a buccal fat pad flap, the success rate noted by Jose et al. (2022) was 100%, therefore, consistent with similar studies available in the literature, which state that success rates ranged from 85.7 to 100% with the use of buccal fat pad flaps for MRONJ cases. For Aljohani et al. (2019), the success rate for the surgical treatment of MRONJ with the use of the buccal fat pad flap was 85.7%.

Ristow et al. (2018) stated that 93.1% of patients in the buccal fat pad flap group presented mucosal integrity. With regard to the mylohyoid muscle flap, 88.0% of the patients showed mucosal integrity.

Therefore, it is observed in the literature that the use of the buccal fat pad and mylohyoid muscle flaps have high success rates. This is possible due to the region's great blood supply, proximity to the surgical site, high yield, ease of access, mechanical stability, low failure rate, minimal donor site morbidity, low complication rate, and highly predictable outcomes (Aljohani et al., 2019; Hauer et al., 2020; Jose et al., 2022).

Although the buccal fat flap is very reliable, it has its own disadvantages, with trismus, facial edema, and ecchymosis being the most common complications (Jose et al., 2022). Ristow et al. (2018) considered that the flattening of the mouth floor because of the millohyoid muscle flap is a tolerable but less pronounced adverse effect due to the reduction in alveolar bone height attributable to the need of prior necrosis removal.

In terms of surgical treatments, Kagami et al. (2018) believe that the efficacy variation may be partly due to the lack of standardized surgical procedures. Added to this, necrotic and unhealthy bone must be removed; however, it is not easy to distinguish unhealthy bone from healthy bone simply by macroscopic appearance.

There is a lack of well-designed, prospective, randomized clinical trials and no protocol-based guidelines. There is no robust evidence from clinical trials, as treatment recommendations come mainly from expert opinions and are therefore characterized by a low level of evidence. Therefore, research in the area should be encouraged in an attempt to establish standardized guidelines for the treatment of medication-related osteonecrosis of the jaw and to reach a consensus on the indication of surgical treatment and conservative therapy.

5. Conclusion

Although there are controversies between surgical and non-surgical therapies for the treatment of MRONJ, surgical treatment demonstrated maintenance of mucosal coverage, improvement in quality of life, and quick resumption of the antiresorptive therapy for all stages of the disease, showing high rates of therapeutic success.

The proposed treatment should ultimately aim to improve the patient's quality of life and be tailored to individual needs. Although more invasive surgical approaches have high success rates, they should be reserved for patients who do not have major comorbidities and systemic alterations.

Continued efforts should be encouraged to investigate the best treatment for this pathology, so that standardized protocols, with proven scientific evidence, are established and are used to guide professionals. In this context, this study recommends that new methodologies be carried out to evaluate and compare the applicability, adherence by professionals, and results of the existing surgical techniques for the treatment of medication-related osteonecrosis of the jaw. Through these data, it is expected that it will be possible to assemble a guideline, which will help to establish the best standard of care for the treatment of this disease.

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