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PREVENTION OF JAW OSTEONECROSIS IN PATIENTS TREATED WITH BISPHOSPHONATES: MEDICAL AND SURGICAL IMPLICATIONS

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ABSTRACT

Introduction: Medication-related osteonecrosis of the jaw (MRONJ) is a serious complication associated to Bisphosphonate therapy, especially following tooth extraction. Its prevention has become challenging due to the pathophysiology of this disease; **Objective:** This review aims to evaluate the effectiveness of medical and surgical preventive measures to reduce the risk of MRONJ in patients undergoing a dentoalveolar surgery; **Material and methods:** This systematized review was conducted through searches in the databases PubMed and MEDLINE Complete, including 18 articles of primary evidence published in the last 10 years. These studies were selected following different inclusion and exclusion criteria and evaluate the different preventive strategies and protocols used nowadays in the prevention of MRONJ; **Results:** The antibiotic prophylaxis appears effective in reducing post-operative complications and its use is recommended, whereas the use of a drug holiday is still controversial. Surgical protocols with atraumatic extraction were associated to an effective preventive action and a reduced MRONJ incidence. The arrival of new adjunctive procedures, especially with the use of autologous platelet concentrates, showed promising results by improving healing outcomes and resulting in high success rate; **Conclusion:** Prevention relies on a combined protocol approach and allows to considerably reduce MRONJ incidence. While those protocols showed high effectiveness, further studies are needed to define standardized guidelines.

KEYWORDS

Dentistry, medication-related osteonecrosis of the jaw, tooth extraction, preventive protocols.

RESUMEN

Introducción: La osteonecrosis de los maxilares asociada a medicamentos (OMAM) es una complicación grave asociada a terapia con Bisfosfonatos, especialmente tras una extracción dental. Su prevención se ha vuelto compleja debido a la fisiopatología de esta enfermedad; **Objetivo:** Esta revisión tuvo como objetivo evaluar la efectividad de las medidas preventivas médicas y quirúrgicas para reducir el riesgo de OMAM en pacientes sometidos a cirugía dentoalveolar; **Material y métodos:** Esta revisión sistematizada se llevó a cabo mediante la búsqueda en las bases de datos PubMed y MEDLINE Complete, incluyendo 18 artículos de primera evidencia publicados en los últimos 10 años. Se seleccionaron estos estudios basados en criterios de inclusión y exclusión y evalúan las diferentes estrategias preventivas y protocolos usados actualmente en la prevención de OMAM; **Resultados:** La profilaxis antibiótica aparece como efectiva en la reducción de complicación post operativas y su uso es recomendado, mientras que la suspensión de la medicación continúa siendo controvertida. Los protocolos quirúrgicos, incluyendo la extracción atraumática se asociaron a una acción preventiva efectiva y una reducción de la incidencia. La aparición de nuevos procedimientos adyuvantes, especialmente el uso de concentrados plaquetarios autólogos, ha mostrado resultados prometedores al mejorar os resultados de cicatrización y alta tasas de éxito; **Conclusión:** La prevención depende de una combinación de protocolos y permite reducir considerablemente la incidencia de OMAM. Aunque estos protocolos han demostrado una alta eficacia, se requieren más estudios para definir normas estandarizadas.

PALABRAS CLAVE

Odontología, osteonecrosis de los maxilares asociada a medicamentos, extracción dental, protocolos preventivos.

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1. INTRODUCTION

1.1. Definition

1.1.1. History and definition of Jaw Osteonecrosis

In 2007 and 2009, according to the position papers of the Association of Oral and Maxillofacial Surgeons (AOMS) osteonecrosis of the jaw (ONJ) was defined as exposed and necrotic bone related to the use of Bisphosphonates (BPs); followed by the introduction of the term: Bisphosphonates-Related osteonecrosis of the Jaw (BRONJ). Due to the appearance of the use of new medications leading to ONJ, new clinical evidences and recent studies, the AOMS decided to update this definition and adopted a more general term in 2014 : Medication-Related Jaw Osteonecrosis (MRJON) (1). Nowadays, as adopted in 2022, MRONJ is defined as "exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks" (2). It is a severe complication that implies the destruction with necrosis and lack of healing of the jaw affecting the mandibular and/or maxillary bone (3,4). This condition happens further to the administration of an anti-resorptive medications as Bisphosphonates or Denosumab; or antiangiogenic agents that inhibit the angiogenesis and the formation of new blood vessels, leading to insufficient vascularization and healing problems; but without previous or actual radiotherapy treatment (2,5,6).

1.1.2. Bisphosphonates

Bisphosphonates are anti-resorptive medications administered to treat primary diseases but are not without consequences. They act by regulating bone turnover: they modify the osteoclast activity of the bone (7). As the osteoclasts promote bone destruction, these agents inhibit these cells activity to induce their apoptosis, avoid bone resorption and increase bone density (6,8).
Also called bone-modifying agents their repercussion on the possible jaw osteonecrosis complication is real, therefore MRONJ prevention and management is essential (3).

1.1.2.1. Mechanism of action

Three generations of Bisphosphonates are nowadays available, however studies showed a link between the 3rd generation that is more potent and MRONJ (9). Bisphosphonates have a molecular structure similar to pyrophosphate, naturally present in bone, which allow them to hardly bind to bone minerals as hydroxyapatite, modify physiologic metabolic procedures and be captured by osteoclasts to suppress the osteoclastic bone resorption. This mechanism leads

to a cellular apoptosis and result in an impaired bone remodeling and a stabilization of the osseous internal structure to increase its density. However, due to a very strong affinity and high skeletal retention they lead to accumulation of toxic particles during several years and possible occurrence of MRONJ (4,9,10).

1.1.2.2. Indications

Bisphosphonates are indicated in the treatment of several diseases such as Paget disease, osteoporosis (as a treatment or prevention), cancer-associated bone involvement (6,11). Therefore, Bisphosphonates are widely used and among a large population. But depending on their dose and posology they produce a lot of adverse effects and the MRONJ risk is different (12).

Osteoporosis affects over 200 millions of people worldwide (13). It is a systemic disease affecting bones and its microarchitecture by making them fragile. This is why in the last years, Bisphosphonates and particularly Denosumab were prescribed in the treatment of osteoporosis and their use significantly increased (13,14). These medications aim to reduce fracture risk due to a low bone mass and are very effective in porous bones (15).

Bisphosphonates are nowadays introduced in various cancer treatment (breast, lungs or even prostate cancer) to improve patient's quality of life (9). They significantly reduce osseous complications and pain linked to bone metastases (16). Several recent studies showed that the use of Type III Bisphosphonates as Ibandronate or Zoledronate reduce skeletal-related events (spinal cord compressions or any bone complication) by improving the microarchitecture of the bone to stabilize the skeleton of oncologic patients (9,17,18).

Patients can also be divided in high and low risk groups, depending on the medication administration. According to the guidelines of the Scottish Dental Clinical Effectiveness Programme (SDCEP) when the duration of medication intake is > 5 years the patient is considered high risk, and when < 5 years the patient is considered low risk. The same applies with the Bisphosphonate treatment posology, depending on oral (low risk) or intravenous (high risk) administration route (19).

1.2. Epidemiology

1.2.1. Prevalence

As the dosage and posology of Bisphosphonates intake differ between the patients and the type of disease, the prevalence and incidence of MRONJ is variable.

However the prevalence is very low as this complication is rare (from 0,01% and up to 5%) but varies depending on the indication of the treatment (20,21).

Bisphosphonate therapy is considered to carry a low risk of ONJ when administered at relatively low doses, commonly prescribed in the treatment of osteoporosis. A recent meta-epidemiological analysis was conducted in 2023 to evaluate the publications bias to estimate risk of osteonecrosis of the jaw of osteoporotic patients. Over a very large population-based study, it revealed a very low incidence of 0,001% to 0,01% (22).

In contrast, the use of higher and more frequent doses of Bisphosphonates as used in cancer-treated patients are associated to a significant increase of incidence of ONJ as demonstrated in a recent retrospective study and confirmed by a large systematic review and meta-analysis (9,23). It reported that among the population receiving Bisphosphonate therapy only, the incidence of ONJ was about 2,8% rising up to 16,3% if the treatment is combined and followed by Denosumab (23).

1.2.2. Risk factors

Osteonecrosis of the jaw is associated to general risk factors as the intake of Bisphosphonates, its posology and its dose but is combined to other local risk factors linked to the clinical and mostly surgical exercise, with traumatisms affecting the bones of the maxillofacial area (6–8). One of the most common is the tooth extraction that induce MRONJ of more than 60% of the cases (4,8). A meta-analysis demonstrated the risk of ONJ increases when an extraction is performed in parallel of Bisphosphonate therapy: in an osteoporotic patient the prevalence can go up to 1,7% (24). Other trauma as implant placement, poorly adapted prothesis inducing friction or even high occlusal forces (10).

Recent studies also demonstrated a clear association between treatment indications as treatment duration and its dose with the exposition to the toxic accumulation of Bisphosphonates in the bone structure. A higher frequency of drug administration with shorter intervals leads to a higher incidence of ONJ (17,25).

1.3. Pathophysiology

The pathogenesis of the osteonecrosis of the jaw associated to Bisphosphonates is complex as it associates bone and drug metabolism but is mainly based on 2 mechanisms : the elimination of the bone turnover and angiogenesis (3). It creates a critical environment that predisposes the bone to the effects of the drugs (10).

1.3.1. Bone remodeling

As explained before, Bisphosphonates primarily act through the inhibition of osteoclastic activity to result in a diminution of bone turnover. Under normal physiological condition, the maxillary and mandibular bones experience a constant and frequent modeling and remodeling processes (6). The jaw bones have unique features: the alveolar bone suffers continuous dental microtraumas, mastication movements solicitated and transmitted by the periodontal ligament (10). This leads to a high bone turnover and more rapid than other bones. By acting on that regenerative process and due to the cumulative concentration of Bisphosphonates in the bone, it impairs the natural healing capacity of the jaws and increase susceptibility of ONJ (10,26).

1.3.2. Angiogenesis

The jaw bones are highly vascularized which promote and facilitate the cicatrization and bone healing under normal conditions. But when exposed to Bisphosphonates the blood flow is considerably decreased due to their anti-angiogenic effect, they do not allow the formation of new vessels within the bone structure (5,10). This result to a limited blood flow and low oxygen and nutriments delivery to bone cells. In consequence, tissue repair is reduced, and necrotic process may develop (10).

1.4. Clinical manifestations

1.4.1. Stages

Osteonecrosis of the jaw has been described in 5 different stages by the AAOMS according to the clinical symptoms and advanced stages in order to help clinicians to diagnose and elaborate a correct treatment plan (5).

Patient at risk is asymptomatic with actual or previous treatment with Bisphosphonates.

Stage 0 or non-exposed bone variant shows no necrotic bone exposed to the oral cavity but possible clinical findings that could lead to a future development of ONJ.

The stages 1 to 3 are characterized by visible necrotic bone or fistulous tract reaching bone; without clinical symptoms of infectious signs (Stage 1), with clinical symptoms or infection (Stage 2) or as the preceding stage with additional clinical finding as osseous fracture, cutaneous or mucous fistula, or any other osseous and sinus structures affection (Stage 3) (2).

1.4.2. Complications

When an osteonecrosis is not treated, it can lead to more severe local complication compromising the structural stability of the jaw bones or more generalized complications. Due

to the altered bone turnover and the exposed necrotic bone, the possibility of infection increases because of an easier bacterial colonization. Studies demonstrated specifically the involvement of *Actinomyces* bacteria species (27,28). Patients have to be careful and awarded of the possibility of secondary infections (2). As infections can spread in the surrounding tissues, it could affect the jaw function and cause trismus and a reduced mandibular mobility. Psychosocial complications also need to be considered as it directly impacts the patient's quality of life, anxiety and loss of self-esteem can easily be present (28,29).

1.5. Diagnosis

1.5.1. Clinical features and differential diagnosis

MRONJ diagnosis can be based on the described characteristics of the condition by the AAOMS (2). As osteonecrosis of the jaw does not always present visible necrotic bone, complementary investigations as biopsy and imaging tests are important to reach a good diagnosis, that is essential to differentiate it from other condition and type of ONJ (3,30). Any lesion that does not heal, presents signs of tissular invasion or adenopathy should require complementary tests to exclude any neoplasia. A non-healing post-extraction socket accompanied by soft tissue swelling indicates that the remodeling process is impaired and can expose the area to the oral cavity, leading to infection followed by necrosis (10,30). Dental mobility is also a valuable criteria to expose destruction of bone especially if it is not associated to a periodontal disease (31). Palpation is essential and common extraoral features can be found as cutaneous fistulas, mandibular deformation and mobile fragments that can appear in more advanced stages (5,30).

1.5.2. Radiographic features

Radiology is nowadays a fundamental tool used in the diagnosis of osteonecrosis, to evaluate the extension of the disease at the bone level and complete the clinical diagnosis with more valuable information. Radiography as Orthopantomography or CBCT analysis is the main feature to lead to an early diagnosis, as radiographic signs appear before bone exposure and clinical manifestations (5). Orthopantomography is the first-line radiographic examination realized in patients. It allows an initial assessment of the density of the bone and the presence of osteolytic radiolucency. Indeed, it can be more or less frequent and pronounced due to the altered bone remodeling process in patients receiving Bisphosphonates. It has to be carefully interpreted as they can represent early pathological signs of the disease. Computed tomography scans (CT) are

useful combined to panoramic Xray especially for differential diagnosis (5). In more advanced stages, sequestrum of bone and extensive osteolysis can be easily visualized (5,30).

With Cone Beam Computed Tomography (CBCT) more localized changes as patterns of lytic-sclerotic bone changes are easily seen thanks to the transversal cuts and the segmental analysis that can be made for more accuracy (5,28). It provides a better spatial analysis with good resolution to assess the cortical integrity and detect bone necrosis and cortical disruption (28).

Other imaging techniques as Magnetic Resonance Imaging (MRI) are used when additional imaging are required for the diagnosis. Thanks to the visualization of the soft tissues involvement and the bone-marrow alterations, it is particularly useful to differentiate osteonecrosis from other malignancies as Oral Squamous Cell Carcinoma that can have close clinical manifestations (28,30).

It also allows to look for subjacent clinical manifestations of the primary cause of Bisphosphonate therapy as jaw bone fracture in osteoporotic patients for example (30).

1.6. Treatments

The treatment of medication-related osteonecrosis of the jaw is not clearly defined, and no curative approach is currently available. Therefore, the therapeutic management is mainly symptomatic and aiming the reduction of infection and limitation of necrotic expansion of the jaws bones (29). However, the management of this disease can be stage-dependent and guided thanks to the 2022 position paper of the AAOMS where is proposed several therapeutic approaches the clinicians can follow (2).

1.6.1. Non-surgical treatments

Non-surgical treatments represent the first and most essential step in the disease management as we can directly improve patient's quality of life and pain control daily in any stage of the condition. Patient education remains the primary first-line intervention, he should be fully informed of the potential consequences of disease progression and the importance of attending regular dental follow-ups (29). Studies demonstrated the importance of local treatment of open wounds and exposed necrotic areas with antimicrobial rinses and Chlorhexidine, effective against a broader spectrum. As the presence of bacteria plays a central role in the development of MRONJ (27,32).

1.6.2. Surgical treatments

In more advanced stages and severe cases surgery has to be considered, as non-surgical treatments have limitations for the healing of the sequestrated necrotic bone or did not provide

a reduction of the disease progression. A surgical intervention that demonstrated a good effectiveness is the necrotic bone resection in both maxilla and mandible (28). The resection can be either marginal, that is more conservative and only remove necrotic bone keeping continuity of bone, or segmental, more aggressive removing an entire necrotic area disrupting bone integrity. Resections should include healthy bone surrounding the necrosis for safety margins to effectively stop of disease progression (2).

1.7. Prophylaxis

Preventive measures are essential when patients are already receiving a Bisphosphonate treatment. A primary approach would consist in controlling the local risk factors and minimize invasive procedures.

As chronic inflammation and periodontal diseases are considered contributing factors of osteonecrosis of the jaw, maintaining a good oral hygiene is the first step in MRONJ prevention. Basic oral care plays a crucial role, regular check-ups every four months are recommended including professional prophylaxis and assessment of periodontal status (5). Oral hygiene at home should be maintained through an effective tooth brushing and interdental cleaning (5,33). Patient education regarding smoking cessation is also essential, as tobacco could impair healing and contribute to tissue inflammation (5).

When oral diseases are present, an early management of infection becomes important and preventive measures should be considered. Patients may present with pulpal or periodontal conditions of microbial implication, which are identified as risk factors for MRONJ. Conservative approaches should be prioritized whenever possible to limit bone exposure (2). Studies concluded that endodontic treatment could be considered as a safer option and preferred as a less invasive procedure (34). Root canal treatment allows to minimize trauma over bone and possibly avoid an extraction while preserving the tooth; but remains controversial in the literature.

However, despite those conservative approaches, tooth extraction remains unavoidable in some clinical situations but is considered as an important triggering factor of MRONJ (4,8). Therefore, the literature focused its attention on the study and development of specific strategies adapted to that surgery.

One of the fundamental principles in prevention is the atraumatic extraction with the aim to lower bone trauma and injury. Alveoloplasty can be performed, to remove any sharp bone edge to have a stable base for an effective primary wound closure and minimize risks of mucosa breach and exposure of bone to bacteria. The mucoperiosteal flap is also a key element to allow a good tissue mobilization with a tension-free closing and a better hermetic closure avoiding bone exposition (35,36).

Perioperative antibiotic prophylaxis is also one of the main preventive strategies to manage an infection process during an extraction (4,33). No standardized regimen has been established although Amoxicillin with combined Clavulanic acid or Metronidazole are the most used (33,35). When the patient does not have an established MRONJ, drug holiday can be considered as a prophylactic measure (31,33). It is the discontinuation or interruption of Bisphosphonate administration before and after a surgical procedure. It aims to limit the cumulative dose present in the bone at the moment of the surgery. This strategy highly depends on the type of patient as the Bisphosphonate dose differ from each of them. According to the AAOMS position paper, its use is questionable but can be used prior to a surgical procedure involving bone manipulation (2).

More recently the use of Autologous Platelet Concentrates (APC) started to be extensively investigated due to their stimulating properties of angiogenesis and tissue regeneration (31). They are autologous biomaterials from the patient's own blood. Nowadays they are highly used to reduce post-extraction complications but also for the treatment and management of MRONJ. They start to be more explored in its prevention (37). A lot of preclinical studies with animal models were conducted and resulted in a favorable prevention. The ones usually used are the Platelet-Rich Plasma (PRP) that is a first-generation platelet concentrate and Platelet-Rich Fibrin (PRF), a second-generation that is cheaper and have a simpler preparation protocol (38). They are rich in platelets and leukocytes and contain different growth factors to act on cell proliferation and promote osteogenesis (37,39). They could be given with additional leukocytes to have a better infection and inflammatory control. Thanks to their properties to act on bone they are able to reduce complication risks after an extraction (38).

Other preventive strategies were developed in pre-clinical studies and demonstrated good results (33,40). Different lasers have been studied due to their minimally invasive properties. The Nd:YAG laser demonstrated bacterial decontamination properties. Other therapeutics approaches as the Photodynamic therapy (PDT), that includes an antibacterial effect, can be

very interesting in the case of infectious processes. As well as the Photobiomodulation therapy (PBM) aims to promote healing and reduce pain (40,41).
Apart from the antibiotics and antiseptics application, other techniques were developed to try to reduce even more the bacterial load as the oxygen and ozone-based therapies that could reduce complications risks (40).

They aim to lower surgical intervention and be less invasive while providing effective results. Early preventive measures remain a fundamental in the prevention of the osteonecrosis of the jaw.

1.8. Justification

As the use of Bisphosphonates in the treatment of different diseases has increased in the last years, the risk of Medication-Related Osteonecrosis of the Jaw has become a global preoccupation. Osteonecrosis of the jaw is a serious and complicated condition hardly treatable therefore studies about prevention measures became essential to demonstrate a clear clinical efficacy so they can be implemented in the daily dental practice. Tooth extraction is one of the main triggering factors and represents a high risk due to mucosa breakdown and bone exposure. This systematized review aims to synthetize actual reviews and clinical methods to prevent ONJ during that dentoalveolar surgery. Therefore, proposing medical and surgical guideline to follow, will allow to consolidate the clinical practice with patients receiving a Bisphosphonate therapy and improve their long-term health.

2. OBJECTIVE

The objective is to investigate the most recent preventive clinical guidelines and propose an evidence-based medical and surgical protocol aiming to reduce the incidence of medication-related osteonecrosis of the jaw during a dental extraction.

3. MATERIAL AND METHODS

This section outlines how the search strategy was elaborated, and the methodology used to select and identify the included studies of this review.

3.1. Pico question

P (Patient): Adults patients receiving Bisphosphonate therapy and undergoing a dental extraction procedure.

I (Intervention): Updated medical and surgical prophylactic protocols and clinical guidelines to prevent osteonecrosis of the jaw.

C (Comparison): Absence of preventive measures during a dental extraction procedure.

O (Outcomes): Effective prevention to reduce the incidence of Medication-related osteonecrosis of the jaw.

The research question is :

On adult patients receiving Bisphosphonates therapy and undergoing a dental procedure (P), how do recently published prophylactic protocols (I) compared to the absence of preventive measures (C) can affect the clinical practice during a dental extraction and guide the dentists to adapt their medical and surgical interventions to reduce the incidence of the osteonecrosis of the jaw (O).

3.2. Eligibility criteria

The following inclusion and exclusion criteria were defined:

Inclusion criteria:

- Clinical trials
- Cohort studies
- Cross-sectional studies
- Studies published in between 2016 and 2026
- Free full text available
- Articles in English
- Publications including human participants only

Exclusion criteria:

- In vivo / in vitro studies and preclinical model studies
- Systematic reviews and meta-analysis
- Articles older than 10 years
- Studies with low sample size

3.3. Source of information

This systematized review was conducted to identify and analyze recent scientific evidence about the prevention of osteonecrosis of the jaw in patients taking Bisphosphonates. Articles were

searched from the databases PubMed (National Library of Medicine, USA) and MEDLINE Complete covering articles up to 10 years.

It allowed to guide first a comprehensive study based on literature reviews with systematic reviews and meta-analysis. The following keywords were used: “Bisphosphonates”, “Bisphosphonates-related osteonecrosis of the jaw”, “BRONJ”, “Medication-related osteonecrosis of the jaw”, “osteonecrosis of the jaw”, “dental treatments”, “prevention”, “treatment”, “osteoporosis”.

3.4. Search strategy

The search equations were elaborated using key words and Boolean operators to combine them. It was used in both databases with the last search made the 22/02/26.

Search equation used on PubMed and MEDLINE:

((bisphosphonate) OR (antiresorptive drug)) AND ((osteonecrosis of the jaw) OR (Bisphosphonate associated osteonecrosis of the jaw)) AND ((tooth extraction) OR (surgical extraction) OR (platelet-rich fibrin)) AND ((prevention) OR (prophylaxis)).

3.5. Article selection process

The final articles found were downloaded in a “CSV” file to be transferred in the program “Rayyan – Intelligent Systematic Review”. This allowed to remove duplicates, screen the articles and then select the final studies included according to inclusion and exclusion criteria.

That process until the final selection of the included articles is described in the PRISMA diagram.

4. RESULTS

4.1. Selection of studies

The search performed on both databases with the search formula identified a total of 603 articles. Due to the high number of articles found, the search was narrowed from the databases by selecting in the publication date section “last 10 years” removing a total of 226 articles. The 377 articles were transferred on “Rayyan”, the duplicates were identified and removed (n=146); and the final selected articles were screened according to their title and abstract. A total of 30 articles were assessed for the revision of the full text according to the eligibility criteria described, to keep articles that meet the inclusion criteria. 18 final studies were included in this review.

This review was conducted in accordance with the PRISMA guidelines (Figure 1.) (42).

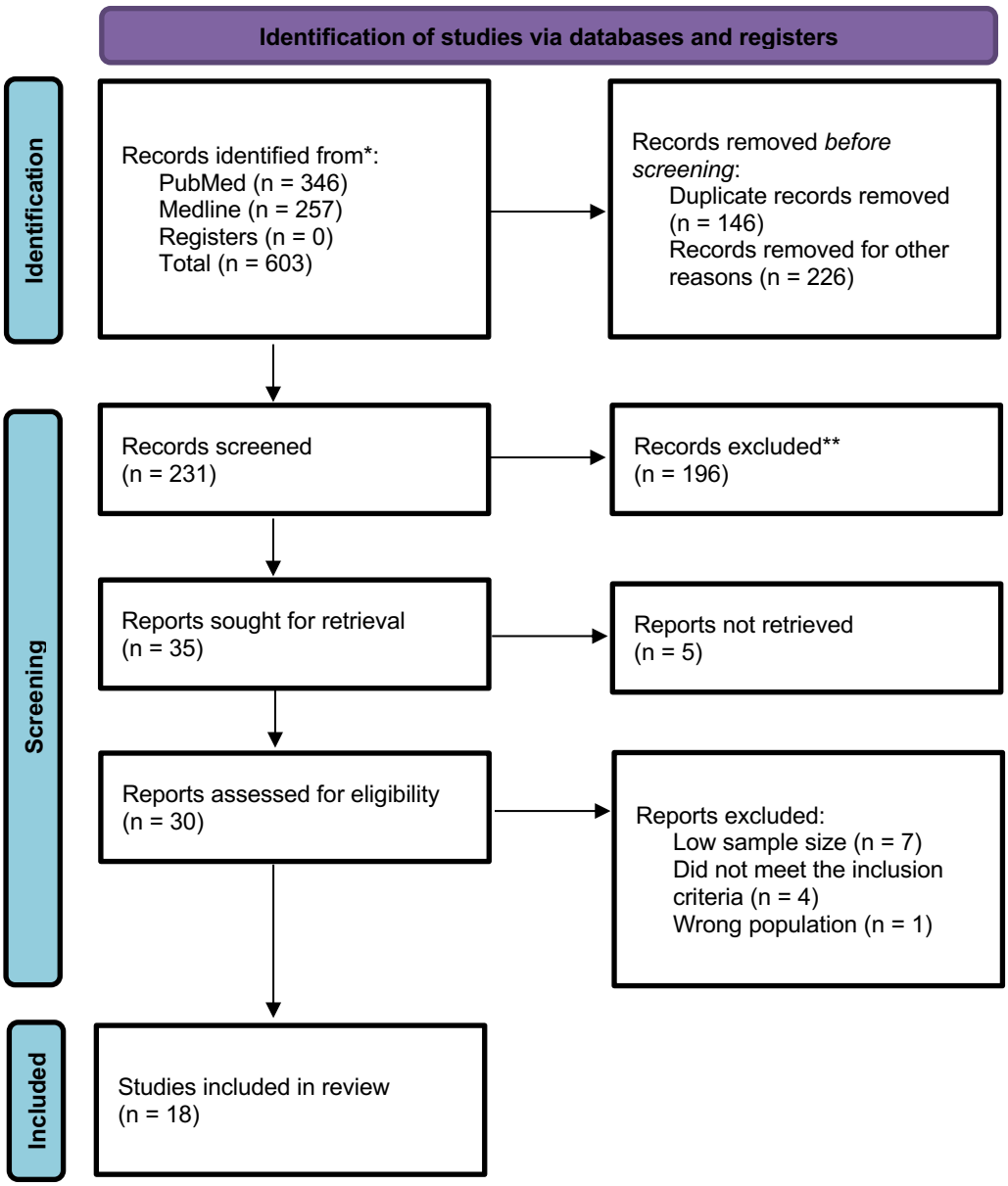


Figure 1. PRISMA flowchart diagram (42).

4.2. Synthesis of the results

Table 1. Results summary of the included articles of the review.

Reference / study design	Sample size (n)	Population studied	Preventive protocol	Comparison	Outcomes
Maracineanu et al. (43) 2025 / prospective controlled clinical study	85 patients: 46 established MRONJ; 39 high-risk (105 extractions) (PRF group n=25; control group n=14)	Osteoporotic and oncologic patients under antiresorptive and antiangiogenic medication; population at risk	Atraumatic extraction without flap Antibiotic prophylaxis the day before + placement of PRF inside socket with cross-stitched suture	Atraumatic extraction without a flap and placement of a hemostatic material inside the socket with cross-stitched suture	Complete healing in high-risk population: 96% PRF group 64,29% control group (8 weeks healing evaluation) PRF is considered as effective (p=0,03).
Asaka et al. (44) 2017 / clinical trial study	102 patients: PRF group: n=29 (52 extractions); control group: n=73 (166 extractions)	Osteoporotic patients receiving BP therapy for more than 1 year	Antibiotics administration + placement of PRF with simple suture	28/73 patients received antibiotics Standard extraction protocol with simple suture	Complete healing: 100% PRF group; with a faster epithelization 100% control group; with a delayed complete healing (8 weeks healing follow-up) PRF reduces the delayed healing (p<0,05); identified as an independent factor (p=0,02).

Besi et Pitros (39) 2024 / observational study	39 patients (63 extractions): L-PRF group: n=15; control group: n=24	Population at high and low risk	Atraumatic extraction (sharp bone edges removed) + L-PRF placement with simple suture	Atraumatic extraction and simple suture	PRF group: 100% healing and no reported case of MRONJ; control group: 5 reported cases of MRONJ (high risk patients) L-PRF may have a protective effect in a high-risk population.
Miranda et al. (45) 2021 / retrospective study	37 patients (69 extractions): PRF group: n=11; control group n=26	Patients receiving antiresorptive medication (mainly Bisphosphonates)	Antibiotic prophylaxis + no flap elevation + PRF placement with simple suture	Conventional extraction + no flap elevation with simple suture	Incidence of MRONJ: 0% in PRF group; 19,23% in control group (5 reported cases) PRF allows to prevent MRONJ onset.
Sahin et al. (46) 2020 / retrospective study	44 patients (63 extractions)	Osteoporotic and oncologic patients receiving BP therapy	Antibiotic prophylaxis + alveoloplasty + L-PRF placement in socket + Nd : YAG laser	No comparison	No MRONJ cases reported This protocol suggests favorable outcomes.

Pick et al. (35) 2021 / retrospective cohort study	104 patients (203 extractions): low risk n=66; medium risk n=18; high risk n=19	Patients under or with previous antiresorptive treatment (including BP and Denosumad)	Assess the preventive effect of antibiotic prophylaxis + atraumatic technique with primary closure and full thickness flap	No comparison	Incidence of ARONJ: 3,8% (4 patients) (8 weeks follow-up) Antibiotic prophylaxis and primary closure are considered effective preventive measures.
Lin et al. (47) 2026 / retrospective case serie	106 patients (248 extractions) Under BP: 76 patients: low risk group n=41; high risk group n=35	Patients under antiresorptive therapy > 1 year Drug holiday 3 months before	Drug holiday of 3 months pre-surgery Antibiotic prophylaxis + guided bone regeneration (alloplastic bone graft and tetracycline placement in socket) with suturing	No comparison	99,6% of success with no reported cases of MRONJ The use of a guided bone regeneration reported a successful prevention. Good healing by secondary intension.
Ristow et al. (36) 2021 / randomized clinical trial	157 patients: SPP/intervention group n=82; EPP/control group n=78	Osteoporotic and oncologic patients under or with previous antiresorptive treatment	SPP group: Atraumatic technique + primary closure with mucoperiosteal flap (subperiosteal)	EPP group: atraumatic technique + primary closure with mucosal flap (epiperiosteal)	Treatment failure: 6,3% in SPP group; 23,4% in EPP group Better treatment outcome with SPP mucoperiosteal flap for a primary closure.

Wang et al. (48) 2025 / prospective cohort study	101 patients (248 extractions)	Osteoporotic and oncologic patients receiving oral / IV BP and Denosumab (n=25)	Antibiotic therapy + atraumatic extraction + CGF placement without primary closure	No comparison	No incidence of MRONJ, good healing of the mucosa but delayed in high-risk group. (90 days follow-up) A complete protocol is effective in preventing MRONJ occurrence.
Chang et al. (49) 2025 / retrospective study	329 patients (836 extractions) BP therapy only group n=75	Osteometabolic diseases and oncologic patients	Antibiotic prophylaxis + atraumatic extraction	No comparison	5,5% incidence of MRONJ; higher in high-risk group. (8 weeks follow-up) It suggests a better individualized protocol.
Shudo et al. (50) 2018 / prospective clinical study	132 patients (274 extractions), groups based on duration of BP therapy (< 2 years n=51, 2-5 years n=41, > 5 years n=40)	Osteoporotic patients (prevention or treatment) receiving oral BP	Antibiotic prophylaxis without drug discontinuation	No comparison	No reported cases of MRONJ. Delayed healing in long-term BP use (> 5 years), related to the cumulative dose.

Karaca et al. (51) / 2023 retrospective study	51 patients (109 extractions): group with drug holiday n=31; group without drug holiday n=20	Oncologic patients receiving IV BP	Drug holiday before extraction (around 2 months) Atraumatic extraction + antibiotic prophylaxis + primary closure	No drug holiday before extraction Atraumatic extraction + antibiotic prophylaxis + primary closure	Incidence of MRONJ: 5,3% (3 patients). One of them had a drug holiday: MRONJ occurred after 1 year. No association between the use of drug holiday and incidence of MRONJ (p=0,315).
Ottesen et al. (52) 2022 / randomized clinical trial	23 patients (31 extractions): drug holiday group n=13; no drug holiday group n=10	Oncologic patients receiving IV BP (n=10) and antiresorptive medication	Drug holiday (4 months): 1 month before surgery and up to 3 months after Atraumatic extraction and antibiotic prophylaxis	No drug discontinuation Atraumatic extraction and antibiotic prophylaxis	4 cases of MRONJ in drug holiday group (only Denosumab group). No cases in patients under BP therapy. No association between a reduced risk of MRONJ onset and drug holiday in high-risk patients.

Seki et al. (53) 2022 / retrospective cohort study	40 patients (70 extractions): BP group n=31 (oral and IV administration)	Osteoporotic patients under BP or Denosumab therapy	Drug holiday of 7,7 months for oral BP and 8,8 months for IV BP	Oral vs injectable Bisphosphonate intake	No MRONJ cases reported in the BP group. The use of IV BP is associated to a higher risk of MRONJ onset than oral BP. Consider the importance of medication administration and risk of MRONJ.
Coropciuc et al. (54) 2023 / retrospective cohort study	240 patients: osteoporosis n=126; oncologic n=114	Osteoporotic patients; oncologic patients under antiresorptive agents	Atraumatic extraction + L-PRF placement + primary closure + antibiotics prophylaxis	No comparison	Incidence of MRONJ: 71 patients: 13 from osteoporosis group; 58 from oncologic group Use of L-PRF reduced the risk of MRONJ by 84% (p=0,003) Antibiotics showed good results (p=0,013) Time since last administration decreased occurrence of MRONJ (p=0,018).

Park et al. (8) 2025 / retrospective cohort study	152,299 patients	Osteoporotic patients	Time since last IV BP injection	No comparison	0,6% cases of MRONJ reported Time since last administration: <90 days: 1,3% cases >1 year: 0,4% cases Larger interval associated to lower cases.
Di Fede et al. (55) 2024 / randomized clinical trial	117 patients: intervention group n=38; control group n=79	Patients with previous or current antiresorptive therapy	Oxygen-ozone therapy injection post-extraction	Standard protocol of tooth extraction	Improved healing in the early stages: inflammatory (p=0,006 at 3-4 days) and proliferative (p<0,001 at 14 days) phases. No significant healing improvement in the late remodeling phase (p=0.230 at 6 weeks). Ozone therapy significantly improves tissue healing in the early phases.

Tenore et al. (41) 2025 / retrospective study	62 patients	Osteoporotic or oncologic patient with previous or current BP use	Antibiotic prophylaxis Photobiomodulation application: laser therapy	No comparison	Complete healing in 80,65% of the patients; MRONJ reported cases in 19,35% of the patients. Higher incidence in the patients with IV administration especially with Zoledronic acid. The photobiomodulation therapy is considered as effective in improving healing.

List of abbreviations used in the table of results (Table1.) :

BP: Bisphosphonates, IV: intravenous, PRP: Plasma-Rich Platelets, CGF: Concentrated Growth Factor, SPP= Sub-periosteal prepared flap, EPP= Epi-periosteal flap

5. DISCUSSION

This review aimed to analyze medical and surgical preventive measures as well as new adjunctive therapies and their prevention effectiveness.

5.1. Medical preventive strategies

The medical prevention mainly focuses on minimizing systemic risk factors prior to a dentoalveolar surgery.

Among the medical strategies, antibiotic prophylaxis was the most used measure across the included studies of this review but was almost always part of a combined protocol which makes its analysis difficult.

Pick et al. used antibiotics combined to primary closure and showed encouraging results, only 3,8% reported cases of osteonecrosis of the jaw. The antibiotics were administered in low and high-risk population risk until the healing of the wound (35). Similarly, Coropciuc et al. concluded that the use of antibiotics was associated to a significant reduction of MRONJ occurrence of 86% up to 93% depending on the type of population. Antibiotics were administered before and after surgery when an infectious process was present (54). This aligns with the fact that infection plays a major risk factor, and peri-operative antibiotic coverage is effective in both low and high-risk population.

Other studies also demonstrated a protective effect but with limitations especially in high-risk patients. As Shudo et al. concluded, no cases of MRONJ were reported even with the absence of drug holiday. However when Bisphosphonate administration exceeds five years, the cumulative dose increases the time of healing despite the administration of antibiotics (50). Karaca et al. also used antibiotic prophylaxis in high-risk population but cases of MRONJ were still reported (51).

Therefore, these studies support the use of antibiotics as key component of prevention. It allows to limit risk of infection and bacteria colonization with an associated reduction of osteonecrosis risk, but its effectiveness still depends on the type of population (50,54). Nowadays antibiotics are almost always included in the studies' protocols when performing an extraction in that specific population.

Another discussed medical strategy is the drug holiday. The study of Karaca et al. reported that in a high-risk population with intravenous Bisphosphonate administration, a short-term drug holiday of around two months did not demonstrate a significant preventive effect compared to

no drug discontinuation. No difference between tissue healing and drug holiday was observed neither (51). The randomized trial of Ottesen et al., in a similar population, showed that with a drug holiday of 4 months no cases were reported in the patients receiving Bisphosphonates. However they concluded that no preventive benefit were observed when comparing the two groups (52). These results emphasize the fact that in the oncologic population the preventive effect of drug holiday is still uncertain. It aligns with Shudo et al. that demonstrated any osteonecrosis reported cases with a continuous drug administration (50).

Contrary to those results, Coropciuc et al. observed that a longer interval since the last administration dose could be associated to a lower risk of MRONJ in an oncologic population (54). However, those results remain an observational association rather than a direct evaluation of the effectiveness of drug holiday.

Attention has been directed toward the benefit of a longer drug holiday. For instance, a large nationwide cohort study was elaborated in 2025 by Park et al. in a lower-risk population to conclude the effectiveness of a long drug discontinuation interval between the last intravenous administration and dental surgery from 90 days to 365 days; resulting in better results. A drug holiday <90 days resulted in 1,3% of cases whereas drug discontinuation >365 days resulted in a lower incidence of 0,4% of cases (8). This emphasizes that a drug holiday could be beneficial in a low-risk population.

The studies of this review did not show any clear preventive benefit, and results are in contradiction of each other.

5.2. Surgical preventive protocols

In addition to medical prevention, several surgical techniques have been proposed to optimize the post-extraction healing socket.

In most of the studies, the atraumatic extraction is followed by alveoloplasty (35,36,39,46). Biopsies were made in the study of Ristow et al. and revealed already non-vital bone at the time of the surgery. These findings reinforce the idea that alveoloplasty is effective in removing altered or necrotic bone surrounding the surgery site (36).

Apart from the alveoloplasty, the flap design plays an important role. The randomized clinical trial made in 2021 by Ristow et al. was conducted to evaluate which type of flap had a better outcome. The full thickness mucoperiosteal flap with primary closure resulted in lower failure rate compared to the mucosal flap (6,3% vs 23,4%). It supports the need of good management of soft tissue with an hermetic closure avoiding bone exposition (36).

The type of wound healing was also questioned. The effectiveness of alveoloplasty combined with a full thickness mucoperiosteal and primary closure as described by Pick et al. and Ristow et al., leads to improved mucosal healing and a reduction in treatment failure rates (35,36). However, in the studies of Wang et al. and Lin et al. the use of a complementary measures with secondary closure still confirmed high success rates and complete healing. They suggested that the use of socket preservation protocols did not require the need of primary intension healing (47,48).

Pick et al. who followed a standardized meticulous preventive protocol combining different surgical techniques found out an effective preventive action with an incidence of only 3,8% (35). In the study of Wang, despite the use of growth factors, good results were showed with the use of a minimally invasive extraction procedure even in a high risk population (48).
The use of surgical preventive techniques indicated favorable results and reliable outcomes in several studies. This emphasizes the need of a controlled surgical protocol for prevention success (35,36,48).

The surgical prevention is supported by high level evidence in the literature in reducing the onset of MRONJ. However, MRONJ can still occur, therefore surgical protocols although fundamental may not be sufficient and new strategies were studies to maximize its prevention as suggested by Pick et al. (35).

5.3. Adjunctive preventive therapies

Despite the application of those protocols, other adjunctive therapies were developed in the last few years to enhance prevention.

5.3.1. Autologous platelet concentrates (APCs)

In the study of Asaka et al. conducted in 2017, it concluded that a complete healing of the mucosa in the PRF group was possible with an epithelization of the tissues within 4 weeks, and faster than in the control group presenting a delayed healing (44). In the study of Sahin et al. similar results were found. An additional use of the Nd:YAG laser therapy was suggested to improve clinical outcomes. No cases of MRONJ were reported among the 44 patients and a complete tissue healing was observed at one month follow-up (46). This highly emphasizes the properties of the PRF and its tissue regeneration possibilities.

Concerning osteonecrosis incidence, encouraging results were found in other studies. The recent prospective clinical study of 2025 by Maracineanu et al. compared a study group including PRF placement with a complete healing rate of 96%, higher than the controlled group treated in a conventional way (43). Similarly, Miranda et al. reported no cases of MRONJ in the PRF group compared to 19,23% in the control group (45). The use of Leukocyte-PRF (L-PRF) was also successful; notably in the study conducted by Besi et Pitros that demonstrated high effectiveness especially in high-risk patients with no reported cases of MRONJ. Coropciuc et al. also concluded in a reduced risk of MRONJ by 84% (39,46,54).

In 2 studies, a comprehensive medical protocol combining drug holiday and prophylactic antibiotic therapy with PRF placement resulted in favorable outcomes (43,44). However, 3 other studies did not include drug holiday and reported similar results, suggesting that effective healing of the tissues without complications can be achieved with PRF placement and no drug discontinuation (39,45,46).

These therapies appear effective and minimally invasive and concluded encouraging results in both low-risk and high-risk patients.

Among studies investigating PRF, other biologically active materials demonstrated similar results as described in the study of Wang et al.; despite a complete protocol including atraumatic extraction and antibiotic prophylaxis, concentrated growth factor (CGF) was used. The study confirmed an improved healing time even so a delayed healing was noticed in the high-risk population (48).

5.3.2. Other emerging adjunctive therapies

Several new preventions techniques have been investigated with the aim of enhancing healing and lower risk of MRONJ.

The Photobiomodulation (PBM) used by Tenore et al. reported a complete healing of 80,65% of the patients treated with that protocol, but its effectiveness remains lower in a higher risk population (41). It supports the stimulating effect of the PBM on bone tissue to improve healing and lower inflammation.

Graft materials and antimicrobial agents were also investigated; Lin et al. used a guided bone regeneration technique with alloplastic and tetracycline in the socket and reported a success of about 99% (47).

The oxygen-ozone therapy was approved by Di Fede et al. in a randomized clinical trial showing significant improvement of healing. It helped the early post-extraction cicatrization by modulating cell metabolism (55).

To conclude, while adjunctive approaches, particularly PFR, appear promising, they should still be considered as a complement to a standard preventive protocol and always adapted to the patient's drug administration situation.

The other adjunctive therapies need further investigation but appear promising.

5.4. Limitations

Several limitations should be considered regarding the studies included in this review.

First, there was a significant heterogeneity in the populations studied according to the patients' characteristics (osteoporotic or oncologic population). The variability in the type of drug used, dosage, duration of therapy could influence the reported outcomes between each study.

Second, the lack of randomized clinical trials about prevention of MRONJ could limit the ability to establish a direct causal relationship between two preventive strategies. Most of the studies had a retrospective design with a limited sample size.

Also, the variability of preventive protocols in each study made the analysis of each individual therapy difficult.

Third, as described by the AAOMS in their last position paper, most of the included studies considered diagnosis of MRONJ after a follow up of 8 weeks, according to that current diagnosis criteria (2). However, in some studies the lack of a longer follow up, up to several months, could limit the ability to assess the effectiveness of the preventive measures and the onset of MRONJ.

6. CONCLUSION

This review highlights that prevention of medication-related osteonecrosis of the jaw in patients taking a Bisphosphonate therapy remains a complex and multifactorial challenge.

Medical protocols particularly antibiotic prophylaxis is associated with a reduction of postoperative complications especially in cases of infectious processes, whereas drug holiday remains controversial and is not considered as reliable.

Surgical protocols show more consistent results, with atraumatic extraction, alveoloplasty and primary closure playing a key role in reducing complications.

Adjunctive therapies such as autologous platelet concentrates expose promising results in enhancing healing but remain complementary.

Overall, MRONJ prevention relies on a combined medical and surgical protocol, adapted to each patient's individual risk factors, contributing in a reduction in incidence and improvement of postoperative outcomes.

7. SUSTAINABILITY

Social sustainability

Osteonecrosis of the jaw is a severe condition affecting the oral cavity and has a direct impact on patient's quality of life even in early stages. It is not an isolated medical problem and includes a global imbalance of the body, the patient will have pain, will not be able to sleep or eat properly and can potentially cause psychological distress.

Economic sustainability

Prevention of osteonecrosis of the jaw is an important preoccupation of dentists, not only to protect patient's health but also to lower post-surgical complications, avoid future complex treatments and reduce the overall cost associated with dental care. By reducing the need of extensive treatments, we also optimize resources and clinical efficiency.

Ethical and clinical attention

Bisphosphonate related osteonecrosis of the jaw has, these last years, raised professional concerns. The American Association of Oral Maxillofacial Surgeons' (AAOMS) proposed some position papers concerning this condition, the most recent one in 2022, to bring an ethical dimension with the aim of promoting patient's well-being. It helped to improve healthcare practices, and shows how important the preventive measures are to mostly avoid this complication and contribute actively to the patient's health.

8. REFERENCES

1. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw—2014 Update. J Oral Maxillofac Surg. octubre de 2014;72(10):1938-56. doi:10.1016/j.joms.2014.04.031

2. Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws—2022 Update. J Oral Maxillofac Surg. mayo de 2022;80(5):920-43. doi:10.1016/j.joms.2022.02.008

3. Patel N, Seoudi N. Management of Medication-Related Osteonecrosis of the Jaw: An Overview of National and International Guidelines. Br J Oral Maxillofac Surg. diciembre de 2024;62(10):899-908. doi:10.1016/j.bjoms.2024.08.008

4. Dioguardi M. Post-Extraction Complications in Patients Undergoing Oral Bisphosphonate Therapy [Internet]. INPLASY - International Platform of Registered Systematic Review and Meta-analysis Protocols; noviembre de 2022 [citado 2 de noviembre de 2025]. Disponible en: https://inplasy.com/inplasy-2022-11-0035/ doi:10.37766/inplasy2022.11.0035

5. De Cicco D, Boschetti CE, Santagata M, Colella G, Staglianò S, Gaggl A, et al. Medication-Related Osteonecrosis of the Jaws: A Comparison of SICMF–SIPMO and AAOMS Guidelines. Diagnostics. 21 de junio de 2023;13(13):2137. doi:10.3390/diagnostics13132137

6. Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O, Peter JU. Interventions for managing medication-related osteonecrosis of the jaw. Cochrane Oral Health Group, editor. Cochrane Database Syst Rev. 12 de julio de 2022;2022(7). doi:10.1002/14651858.CD012432.pub3

7. Jelin-Uhlig S, Weigel M, Ott B, Imirzalioglu C, Howaldt HP, Böttger S, et al. Bisphosphonate-Related Osteonecrosis of the Jaw and Oral Microbiome: Clinical Risk Factors, Pathophysiology and Treatment Options. Int J Mol Sci. 24 de julio de 2024;25(15):8053. doi:10.3390/ijms25158053

8. Park JH, Kong SH, Lee J, Oh J, Lee JR, Lee HJ, et al. Time since last intravenous bisphosphonate and risk of osteonecrosis of the jaw in osteoporotic patients. Nat Commun. 11 de mayo de 2025;16(1):4367. doi:10.1038/s41467-025-59718-x

9. Zhang C, Shen G, Li H, Xin Y, Shi M, Zheng Y, et al. Incidence rate of osteonecrosis of jaw after cancer treated with bisphosphonates and denosumab: A systematic review and meta-analysis. Spec Care Dentist. marzo de 2024;44(2):530-41. doi:10.1111/scd.12877

10. Tetradis S, Allen MR, Ruggiero SL. Pathophysiology of Medication-Related Osteonecrosis of the Jaw—A Minireview. JBMR Plus. agosto de 2023;7(8):e10785. doi:10.1002/jbm4.10785

11. Ahdi HS, Wichelmann TA, Pandravada S, Ehrenpreis ED. Medication-induced osteonecrosis of the jaw: a review of cases from the Food and Drug Administration Adverse Event Reporting System (FAERS). BMC Pharmacol Toxicol. 6 de marzo de 2023;24(1):15. doi:10.1186/s40360-023-00657-y

12. Jackson C, Freeman ALJ, Szlamka Z, Spiegelhalter DJ. The adverse effects of bisphosphonates in breast cancer: A systematic review and network meta-analysis. Papageorgiou SN, editor. PLOS ONE. 5 de febrero de 2021;16(2):e0246441. doi:10.1371/journal.pone.0246441

13. Kumar S, Wang M, Kim AS, Center JR, McDonald MM, Girgis CM. Denosumab discontinuation in the clinic: implications of rebound bone turnover and emerging strategies to prevent bone loss and fractures. J Bone Miner Res. 24 de agosto de 2025;40(9):1017-34. doi:10.1093/jbmr/zjaf037

14. Li M, Ge Z, Zhang B, Sun L, Wang Z, Zou T, et al. Efficacy and safety of teriparatide vs. bisphosphonates and denosumab vs. bisphosphonates in osteoporosis not previously treated with bisphosphonates: a systematic review and meta-analysis of randomized controlled trials. Arch Osteoporos. 23 de septiembre de 2024;19(1):89. doi:10.1007/s11657-024-01447-7

15. Ayers C, Kansagara D, Lazur B, Fu R, Kwon A, Harrod C. Effectiveness and Safety of Treatments to Prevent Fractures in People With Low Bone Mass or Primary Osteoporosis: A Living Systematic Review and Network Meta-analysis for the American College of Physicians. Ann Intern Med. febrero de 2023;176(2):182-95. doi:10.7326/M22-0684

16. Valachis A, Polyzos NP, Coleman RE, Gnant M, Eidtmann H, Brufsky AM, et al. Adjuvant Therapy With Zoledronic Acid in Patients With Breast Cancer: A Systematic Review and Meta-Analysis. The Oncologist. 1 de abril de 2013;18(4):353-61. doi:10.1634/theoncologist.2012-0261

17. Himelstein AL, Foster JC, Khatcheressian JL, Roberts JD, Seisler DK, Novotny PJ, et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial. JAMA. 3 de enero de 2017;317(1):48. doi:10.1001/jama.2016.19425

18. Geng CJ, Liang Q, Zhong JH, Zhu M, Meng FY, Wu N, et al. Ibandronate to treat skeletal-related events and bone pain in metastatic bone disease or multiple myeloma: a meta-analysis of randomised clinical trials. BMJ Open. junio de 2015;5(6):e007258. doi:10.1136/bmjopen-2014-007258

19. Oral health management of patients at risk of medication-related osteonecrosis of the jaw. Br Dent J. junio de 2017;222(12):930-930. doi:10.1038/sj.bdj.2017.539

20. Gehrke B, Coelho MCA, d'Alva CB, Madeira M. Long-term consequences of osteoporosis therapy with bisphosphonates. Arch Endocrinol Metab. 13 de noviembre de 2023;68:e220334. doi:10.20945/2359-4292-2022-0334

21. Ali DS, Khan AA, Morrison A, Tetradis S, Mirza RD, El Rabbany M, et al. Antiresorptive Therapy to Reduce Fracture Risk and Effects on Dental Implant Outcomes in Patients With Osteoporosis: A Systematic Review and Osteonecrosis of the Jaw Taskforce Consensus Statement. Endocr Pract. mayo de 2025;31(5):686-98. doi:10.1016/j.eprac.2025.02.016

22. Gougeon A, Granal M, Massy E, Gueyffier F, Lega JC, Lajoinie A, et al. How publication bias overestimates the risk of atypical femoral fracture and osteonecrosis of the jaw associated with bisphosphonate use: A meta-epidemiological study. Joint Bone Spine. julio de 2025;92(4):105871. doi:10.1016/j.jbspin.2025.105871

23. Brunner C, Arvandi M, Marth C, Egle D, Baumgart F, Emmelheinz M, et al. Incidence of Medication-Related Osteonecrosis of the Jaw in Patients With Breast Cancer During a 20-Year Follow-Up: A Population-Based Multicenter Retrospective Study. J Clin Oncol. 10 de enero de 2025;43(2):180-8. doi:10.1200/JCO.24.00171

24. Kostares E, Kostare G, Kostares M, Pitsigavdaki F, Perisanidis C, Kantzanou M. Prevalence of Osteonecrosis of the Jaw Following Tooth Extraction in Patients with Osteoporosis: A Systematic Review and Meta-Analysis. J Clin Med. 25 de agosto de 2025;14(17):5988. doi:10.3390/jcm14175988

25. Jung S mok, Han S, Kwon HY. Dose-Intensity of Bisphosphonates and the Risk of Osteonecrosis of the Jaw in Osteoporosis Patients. Front Pharmacol. 20 de julio de 2018;9:796. doi:10.3389/fphar.2018.00796

26. Koth VS, Salum FG, De Figueiredo MAZ, Cherubini K. Repercussions of osteoporosis on the maxillofacial complex: a critical overview. J Bone Miner Metab. marzo de 2021;39(2):117-25. doi:10.1007/s00774-020-01156-4

27. De Ceulaer J, Tacconelli E, Vandecasteele SJ. Actinomyces osteomyelitis in bisphosphonate-related osteonecrosis of the jaw (BRONJ): the missing link? Eur J Clin Microbiol Infect Dis. noviembre de 2014;33(11):1873-80. doi:10.1007/s10096-014-2160-5

28. Jiang A, Zhang Z, Qiu X, Guo Q. Medication-related osteonecrosis of the jaw (MRONJ): a review of pathogenesis hypothesis and therapy strategies. Arch Toxicol. marzo de 2024;98(3):689-708. doi:10.1007/s00204-023-03653-7

29. Byrne H, O'Reilly S, Weadick CS, Brady P, Ríordáin RN. How we manage medication-related osteonecrosis of the jaw. Eur J Med Res. 2 de agosto de 2024;29(1):402. doi:10.1186/s40001-024-01912-6

30. Mauceri R, Coppini M, La Mantia G, Seminara G, Pérez-Sayáns M, Toro C, et al. Oral squamous cell carcinoma vs. medication-related osteonecrosis of the jaw in patients assuming bone-modifying agents: a diagnostic challenge in a multi-hospital case series. Front Oral Health. 12 de junio de 2025;6:1574425. doi:10.3389/froh.2025.1574425

31. AlRowis R, Aldawood A, AlOtaibi M, Alnasser E, AlSaif I, Aljaber A, et al. Medication-Related Osteonecrosis of the Jaw (MRONJ): A Review of Pathophysiology, Risk Factors, Preventive Measures and Treatment Strategies. Saudi Dent J. marzo de 2022;34(3):202-10. doi:10.1016/j.sdentj.2022.01.003

32. Jelin-Uhlig S, Weigel M, Ott B, Imirzalioglu C, Howaldt HP, Böttger S, et al. Bisphosphonate-Related Osteonecrosis of the Jaw and Oral Microbiome: Clinical Risk Factors, Pathophysiology and Treatment Options. Int J Mol Sci. 24 de julio de 2024;25(15):8053. doi:10.3390/ijms25158053

33. Bedogni A, Mauceri R, Fusco V, Bertoldo F, Bettini G, Di Fede O, et al. Italian position paper (SIPMO-SICMF) on medication-related osteonecrosis of the jaw (MRONJ). Oral Dis. septiembre de 2024;30(6):3679-709. doi:10.1111/odi.14887

34. Zavalloni G, Spinelli A, Coppini M, Mauceri R, Campisi G, Lenzi J, et al. Endodontic treatment and management of patients under antiresorptive treatment: a scoping review on MRONJ risk. Clin Oral Investig. 19 de septiembre de 2025;29(10):466. doi:10.1007/s00784-025-06543-7

35. Pick E, Leuenberger N, Kuster I, Stutzmann NS, Stadlinger B, Valdec S. Evaluation of Preventive Treatment Protocols for Patients under Antiresorptive Therapy Undergoing Tooth Extraction at a Swiss University Clinic. Int J Environ Res Public Health. 21 de septiembre de 2021;18(18):9924. doi:10.3390/ijerph18189924

36. Ristow O, Rückschloß T, Moratin J, Müller M, Kühle R, Dominik H, et al. Wound closure and alveoplasty after preventive tooth extractions in patients with antiresorptive intake—A randomized pilot trial. Oral Dis. abril de 2021;27(3):532-46. doi:10.1111/odi.13556

37. Hajibagheri P, Basirat M, Tabari-Khomeiran Z, Asadi-Aria A. The efficacy of platelet-rich fibrin (PRF) in post-extraction hard and soft tissue healing and associated complications: a systematic review and meta-analysis of split-mouth randomized clinical trials. BMC Oral Health. 31 de mayo de 2025;25(1):869. doi:10.1186/s12903-025-06238-1

38. Liu R, Chen S, Wang P, Bi R. Using platelet concentrates to treat maxillofacial tissue lesions. Front Bioeng Biotechnol. 7 de enero de 2025;12:1523225. doi:10.3389/fbioe.2024.1523225

39. Besi E, Pitros P. The role of leukocyte and platelet-rich fibrin in the prevention of medication-related osteonecrosis of the jaw, in patients requiring dental extractions: an observational study. Oral Maxillofac Surg. 6 de enero de 2024;28(2):785-93. doi:10.1007/s10006-023-01204-z

40. De Molon RS, De Avila ED, Rodrigues JVS, Santana AP, Cunha DM, Ervolino E, et al. An evidence-guided review of preclinical strategies to counteract medication-related osteonecrosis of the jaw. What do rodent studies tell us? JBMR Plus. 3 de enero de 2026;10(1):ziaf182. doi:10.1093/jbmrpl/ziaf182

41. Tenore G, Mohsen A, Del Vecchio A, Palaia G, Rocchetti F, Borghetti L, et al. Surgical extraction with photobiomodulation as an adjunctive modality in patients at-risk for medication-related osteonecrosis of the jaw: retrospective study. BMC Oral Health. 24 de abril de 2025;25(1):627. doi:10.1186/s12903-025-05776-y

42. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 29 de marzo de 2021;n71. doi:10.1136/bmj.n71

43. Maracineanu R, Tudor A, Hum I, Urtila F, Streian F, Talpos-Niculescu S, et al. Platelet-Rich Fibrin in MRONJ Management: A Prospective Comparative Study on Its Effectiveness in Prevention and Treatment. Medicina (Mex). 28 de marzo de 2025;61(4):625. doi:10.3390/medicina61040625

44. Asaka T, Ohga N, Yamazaki Y, Sato J, Satoh C, Kitagawa Y. Platelet-rich fibrin may reduce the risk of delayed recovery in tooth-extracted patients undergoing oral bisphosphonate therapy: a trial study. Clin Oral Investig. septiembre de 2017;21(7):2165-72. doi:10.1007/s00784-016-2004-z

45. Miranda M, Gianfreda F, Raffone C, Antonacci D, Pistilli V, Bollero P. The Role of Platelet-Rich Fibrin (PRF) in the Prevention of Medication-Related Osteonecrosis of the Jaw (MRONJ). Scribante A, editor. BioMed Res Int. enero de 2021;2021(1):4948139. doi:10.1155/2021/4948139

46. Şahin O, Tatar B, Ekmekcioğlu C, Aliyev T, Odabaşı O. Prevention of medication related osteonecrosis of the jaw after dentoalveolar surgery: An institution's experience. J Clin Exp Dent. 2020;e771-6. doi:10.4317/jced.56837

47. Lin LH, Wang CH, Lu SY. Successful prevention of medication-related osteonecrosis of the jaw after dental extractions by socket preservation with alloplast plus tetracycline in patients taking antiresorptive drugs. J Dent Sci. enero de 2026;21(1):468-74. doi:10.1016/j.jds.2025.10.020

48. Wang Y, Zhang Y, Li D, Zhang W, Wang S, Zheng X, et al. Potential role of the comprehensive tooth extraction procedure in preventing medication related osteonecrosis of the jaw (MRONJ): a prospective cohort study. Orphanet J Rare Dis. 9 de diciembre de 2025;20(1):619. doi:10.1186/s13023-025-04138-9

49. Chang Y, Nanayakkara S, Yaacoub A, Cox S. Prevention of medication-related osteonecrosis of the jaw: institutional insights from a retrospective study. Aust Dent J. marzo de 2025;70(1):70-7. doi:10.1111/adj.13050

50. Shudo A, Kishimoto H, Takaoka K, Noguchi K. Long-term oral bisphosphonates delay healing after tooth extraction: a single institutional prospective study. Osteoporos Int. octubre de 2018;29(10):2315-21. doi:10.1007/s00198-018-4621-7

51. Karaca Ç, Topaloğlu-Yasan G, Adiloğlu S, Usman E. The effect of drug holiday before tooth extraction on the development of medication-related osteonecrosis of the jaw in cancer patients receiving intravenous bisphosphonates. J Korean Assoc Oral Maxillofac Surg. 30 de abril de 2023;49(2):68-74. doi:10.5125/jkaoms.2023.49.2.68

52. Ottesen C, Schiodt M, Jensen SS, Kofod T, Gotfredsen K. Tooth extractions in patients with cancer receiving high-dose antiresorptive medication: a randomized clinical feasibility trial of drug holiday versus drug continuation. Oral Surg Oral Med Oral Pathol Oral Radiol. febrero de 2022;133(2):165-73. doi:10.1016/j.oooo.2021.06.003

53. Seki K, Kaneko T, Kamimoto A, Wada M, Takeuchi Y, Furuchi M, et al. Medication-related osteonecrosis of the jaw after tooth extraction in patients receiving pharmaceutical treatment for osteoporosis: A retrospective cohort study. J Dent Sci. octubre de 2022;17(4):1619-25. doi:10.1016/j.jds.2022.03.014

54. Coropciuc R, Coopman R, Garip M, Gielen E, Politis C, Van Den Wyngaert T, et al. Risk of medication-related osteonecrosis of the jaw after dental extractions in patients receiving antiresorptive agents — A retrospective study of 240 patients. Bone. mayo de 2023;170:116722. doi:10.1016/j.bone.2023.116722

55. Di Fede O, La Mantia G, Del Gaizo C, Mauceri R, Matranga D, Campisi G. Reduction of MRONJ risk after exodontia by virtue of ozone infiltration: A randomized clinical trial. Oral Dis. noviembre de 2024;30(8):5183-94. doi:10.1111/odi.15006