

Universidade de Lisboa
Faculdade de Medicina Dentária



**Prevention of Medication-Related Osteonecrosis of the Jaw:
A Systematic Review**

Luciana Lima Cardoso

Orientadores:

Professor Doutor João Manuel Mendez Caramês

Professora Doutora Martha Alayde Alcantra Salim Venancio

Dissertação

Mestrado Integrado em Medicina Dentária

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"I can do everything through Him who gives me strength."

Resumo

Introdução

A osteonecrose da mandíbula associada à medicação (MRONJ) é uma síndrome relacionada com a utilização de fármacos antireabsortivos e antiangiogênicos, que são consideradas agentes de modificação óssea, utilizadas na terapêutica de determinados tipos de cancro, osteoporose, entre outras doenças. Descrita em 2003, a osteonecrose da mandíbula (ONJ) era decorrente do uso de bisfosfonatos, considerada uma síndrome de baixa incidência, porém grave, e que envolvia a destruição progressiva do osso na mandíbula. Descrita clinicamente como osso exposto ou osso que pode ser sondado através de uma fístula intraoral ou extra oral na região maxilofacial; que não cicatriza em 8 semanas, decorrente do uso das medicações citadas, e não tem histórico de radiação na cabeça e pescoço. Esta condição pode envolver a mandíbula ou a maxila.

Em 2014 a American Association of Oral and Maxillofacial Surgeons (AAOMS) sugeriu uma mudança na nomenclatura da síndrome, com o objetivo de unificar os critérios de diagnóstico e, devido também à associação de outros fármacos além dos bisfosfonatos. O termo que era utilizado como “osteonecrose da mandíbula relacionada com bisfosfonatos” (BRONJ) passou a ser conhecido como “osteonecrose da mandíbula relacionada com medicamentos” (MRONJ). Existe dificuldade em obter dados exatos em relação à incidência desta doença, devido à subnotificação e discrepância no reconhecimento de casos. A incidência apresenta-se maior em pacientes oncológicos, que usam altas doses de medicação intravenosa em intervalos frequentes. Em contraste com outros ossos esqueléticos, os ossos da mandíbula têm vascularidade e remodelação óssea relativamente alta em virtude do stress mecânico contínuo, que pode torná-los vulneráveis aos efeitos adversos da medicação, por essa razão curiosamente a MRONJ é principalmente limitada à região maxilofacial.

A avaliação da etiologia e patogênese da MRONJ não são completamente compreendidas, mas englobam pelo menos 3 importantes fatores de risco: medicação, fatores locais e fatores sistêmicos, que incluem: má saúde oral, procedimentos médico-dentários invasivos, traumas causados por próteses mal ajustadas, além de doenças sistêmicas como diabetes mellitus não controlada, o tabagismo e deficiência de vitamina D. Alguns estudos concluíram que a extração dentária é o fator de risco mais importante para o aparecimento de MRONJ, sendo assim, pacientes em tratamento com altas doses e sob o efeito, por período

prolongado (3-4 anos), de agentes antireabsortivos são aconselhados a evitar extrações dentárias, se possível.

A prevenção e o controlo dos fatores de risco são fundamentais para evitar a osteonecrose da mandíbula. Uma melhor perceção dos fatores de risco poderá ser útil para a prevenção e tratamento direcionado, o que também, ajudaria o clínico a identificar aqueles em risco de doença rapidamente progressiva e implementar terapia apropriada ou medidas preventivas. Vários estudos encontraram menor ocorrência de osteonecrose em grupos de pacientes onde as medidas preventivas eram aplicadas por meio de uma unidade multiprofissional. O tratamento da MRONJ é desafiante e, uma terapia eficaz e adequada que melhore substancialmente o resultado ainda precisa de ser determinada.

Antes de discutir os planos de tratamento, recomenda-se classificar o paciente de acordo com o risco. Aqueles considerados de “baixo risco” são os que seguem o tratamento com medicação via oral ou via intravenosa em baixas dosagens, como por exemplo no tratamento da osteoporose, osteopenia ou doença de Paget. Já os pacientes de “alto risco” são aqueles que se encontram em tratamento de doença oncológica, portadores de mieloma múltiplo ou com metástases ósseas, que frequentemente são sujeitos a uma terapia medicamentosa intravenosa em altas concentrações. Deve-se ter em consideração o tempo de tratamento, as comorbidades associadas, o uso de próteses removíveis, entre outros. Na gestão clínica da MRONJ, a abordagem preventiva deve prevalecer em todos os momentos.

No tratamento da MRONJ o objetivo é eliminar a dor, a infeção e conseguir o controlo da progressão da necrose óssea. A literatura apresenta diversos relatos de tratamentos bem-sucedidos em todas as fases da MRONJ, sejam estes conservadores ou invasivos. Porém, nas principais diretrizes publicadas, a escolha do tipo de tratamento está vinculada ao estadiamento clínico do paciente. A comissão especial montada pela AAOMS em setembro de 2013, propôs o uso de um sistema de estadiamento revisto para melhor orientar as diretrizes de tratamento e recolher dados para avaliar o prognóstico em pacientes que foram expostos a terapias antireabsortivos e antiangiogénicos, intravenosas ou orais (IV ou O).

Em relação a pacientes que já estão em terapia farmacológica, seja com bisfosfonatos, denosumab, ou antireabsortivos e antiangiogénicos, e que necessitam de procedimentos cirúrgicos invasivos de urgência, a literatura consultada levanta três opções: drug holiday (interrupção de medicamentos); opção terapêutica retardando o ato cirúrgico e, por fim técnicas cirúrgicas específicas que reduzam a ocorrência de MRONJ.

Nesta presente revisão sistemática teve-se o objetivo de avaliar e identificar diferentes protocolos focados na prevenção da doença, e seus resultados. De acordo com a literatura, demonstrou-se que atualmente, a osteonecrose da mandíbula associada a medicação não se pode prevenir completamente, contudo, os vários protocolos preventivos tem sido utilizados como forma de minimizar os riscos e auxiliar na prevenção.

A maioria dos estudos relatam que um controle dentário preventivo, com devidos tratamentos dentários realizados, antes a terapias antireabsortivos e antiangiogênicos, intravenosas ou orais, são métodos eficazes na redução de riscos e na prevenção da MRONJ. Outros estudos, sugerem o uso de profilaxia antibiótica associada a fechamento de ferida cirúrgica, uso de assépticos locais, higiene dental e bucal preventiva que levam a cura completa da mucosa oral, apresentando desta forma, um método também eficiente na redução de riscos e auxiliando na prevenção da doença.

Estudos utilizando terapia fotodinâmica antimicrobiana e terapia adjuvante de fotobiomodulação combinadas com laser terapia como medidas de suporte para acelerar a cicatrização de feridas após cirurgias na prevenção da MRONJ, juntamente com um protocolo dentário preventivo, em extrações cirúrgicas, apresentaram nenhuma complicação intraoperatória, além disso um processo de cicatrização correto e sem intercorrências pós-operatórias. Demonstrando assim, que o uso de terapia fotodinâmica antimicrobiana na prevenção da MRONJ, proporciona resultados satisfatórios e benéficos.

A utilização de concentrado de plaquetas autologas como, fibrinas ricas em plaquetas, plasma rico em plaquetas, como auxílio terapêutico em uma variedade de procedimentos cirúrgicos com a intenção de acelerar a cicatrização das feridas tem se tornado uma alternativa bastante popular. Um benefício específico do concentrado de plaquetas como as citadas acima, se deve ao fato de que são ricas em várias substâncias fundamentais para a promoção do processo de cicatrização, diminuindo assim o risco de recuperação tardia após um procedimento cirúrgico em pacientes fazendo uso de medicações antireabsortivos e/ou antiangiogênicos. Outro protocolo que demonstrou eficácia na prevenção da doença foi a utilização do processo de cicatrização de primeira intenção. Apresentando um atraumático e apropriado método de extração com um seguro fechamento da ferida. Estudos utilizaram uma técnica double-layered, espículas ósseas foram arredondadas com a intenção de minimizar o atrito diminuindo consequentemente feridas nos tecidos moles, retalhos mucoperiosteais foram preparados com uma incisão de alívio e suturados do lado oposto do periosteio. Estes estudos também apresentaram um protocolo eficaz em relação a prevenção da MRONJ.

Embora a MRONJ seja uma doença de difícil tratamento e ainda continue sendo um desafio para os profissionais, há uma necessidade de estudos mais completos sobre a doença e uma abordagem multiprofissional para o avanço no tratamento e prevenção. Entretanto, vários estudos confirmaram que uma preventiva intervenção oral e dentária antes de iniciar terapias antireabsortivos e antiangiogênicos, intravenosas ou orais, são métodos eficazes na redução de riscos e na prevenção da MRONJ.

O **objetivo** desta revisão sistemática foi responder à pergunta PICO: “Qual é o protocolo mais eficaz para prevenir MRONJ em pacientes recebendo tratamento com agentes antireabsortivos e / ou angiogênicos?”; fazendo uma comparabilidade entre estudos já publicados.

Materiais e métodos: Uma pesquisa bibliográfica dos bancos de dados; Medline, Cochrane Central Register of Controlled Trials (CENTRAL), estudos publicados entre janeiro de 2016 a março de 2021, foi realizada para estudos relevantes. Revisões sistemáticas, diretrizes e muitos outros artigos relacionados com a prevenção de MRONJ foram incluídos. Os registros foram importados para o www.mendeley.com. As pesquisas em plataformas digitais foram complementadas com pesquisas manuais e vínculo de referência.

Resultados: a estratégia de busca identificou 318 registros. Após uma primeira triagem dos títulos e resumos, um total de 30 artigos foram selecionados para leitura na íntegra e apresentaram potencial interesse na prevenção do MRONJ. Após a aplicação dos critérios de inclusão e exclusão, 4 artigos foram excluídos e 26 artigos foram incluídos nesta revisão sistemática.

Conclusão: Não há dados científicos publicados suficientes para apoiar uma orientação específica sobre as melhores práticas na prevenção da osteonecrose da mandíbula relacionada com medicamentos (MRONJ). Porém, alguns protocolos preventivos podem ser considerados eficazes para a prevenção e recorrência da doença.

Palavras chave: “MRONJ”, “Medication-related”, “Osteonecrosis”, “Jaw”, e “Prevention”.

Abstract

Introduction: Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse reaction of antiresorptive and antiangiogenic agents, formerly known as Bisphosphonate osteonecrosis of the jaw, is a rare but serious syndrome described in 2003, and involves the progressive that affects the maxillofacial region, causing destruction of the bone in the mandible. Furthermore, this condition can affect the quality of life of patients because it is potentially painful and debilitating. Therefore, needs to be addressed with the prime importance.

Objectives: The aim of this systematic review was to evaluate and to identify an effective protocol for adults who are under current or previous treatment for malignant diseases, and osteoporosis among other diseases associated with the use of antiresorptive or antiangiogenic drugs, and to answer the PICO question: “What is the most effective protocol for preventing MRONJ in patients receiving treatment with antiresorptive and/or angiogenic agents?”

Materials and methods: A literature search of Medline and Cochrane Central Register of Controlled Trials (CENTRAL) databases including studies published between January 2016 to March 2021, using the following key words; “*MRONJ*”, “*Medication-related*”, “*Osteonecrosis*”, “*Jaw*”, and “*Prevention*”, was conducted for relevant studies. Systematic Reviews, Guidelines and many other articles regarding prevention of MRONJ were included. Records were imported into www.mendeley.com. Electronic searches were supplemented by manual searches and reference linkage.

Results: The search strategy identified 318 records. After a first screening of the titles and abstracts, a total of 30 articles were selected for a full reading and presented potential interest in the prevention of MRONJ. After applying the inclusion and exclusion criteria, 4 articles were excluded, and 12 articles were included in this systematic review.

Conclusion: There are not enough published scientific data to sufficiently support a specific guidance regarding best practice in the prevention of medication-related osteonecrosis of the jaw (MRONJ). Although, some preventive protocols can be considered as effective for the prevention of MRONJ.

KEYWORDS: “*MRONJ*”, “*Medication-related*”, “*Osteonecrosis*”, “*Jaw*”, and “*Prevention*”.

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Abbreviations

- MRONJ** – Medication-related osteonecrosis of the jaw
- BMA** – Bone-modifying agent
- BP** – Bisphosphonate
- ONJ** – Osteonecrosis of the jaw
- Dmab** – Denosumab
- AAOMS** – American Association of Oral and Maxillofacial Surgeons
- BRONJ** – Bisphosphonate-related osteonecrosis of the jaw
- AR** – Antiresorptive agents
- IV** – Intravenous
- MASCC** – Multinational Association of Supportive Care in Cancer
- ISOO** – International Society of Oral Oncology
- ASCO** – American Society of Clinical Oncology
- O** – Oral
- RCT's** – Randomized Control Trials
- APCs** – Autologous platelet concentrates
- PRF** – Platelet-Rich Fibrin
- PRP** – Platelet-Rich Plasma
- aPDT** – Antimicrobial photodynamic therapy
- SC** – Subcutaneous
- IM** – Intramuscular
- MM** – Multiple Myeloma
- ZA** – Zoledronic acid
- Clx.** – Chlorhexidine
- PBM** – Photobiomodulation
- LLT** – low-level laser therapy
- A-PRF** – Advanced-platelet rich fibrin
- ONC** – Cancer patients
- OST** – Osteometabolic patients

1. INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a syndrome associated with the use of antiresorptive therapy (bisphosphonates), RANK-ligand inhibitors and antiangiogenic inhibitors drugs, used for the treatment of cancer and osteoporosis among other diseases. Medication-related osteonecrosis of the jaw (MRONJ), formerly known as Bisphosphonate osteonecrosis of the jaw, is a rare but serious syndrome described in 2003⁽¹⁾, and involves the progressive destruction of the bone in the mandible.⁽²⁾ It also can be defined as exposed bone or bone that can be probed through an intraoral or extra oral fistula(e) in the maxillofacial region and that does not heal within 8 weeks and that occurs in a patient who has received a bone-modifying agent (BMA) or an angiogenic inhibitor agent and has no history of head and neck radiation. The condition may involve the mandible or the maxilla.⁽¹⁾

At first, this condition was only associated with the use of bisphosphonates (BP) such as alendronate, risedronate, ibandronate, zoledronic acid or zoledronate, and reported in 2003.⁽³⁾ Subsequently, osteonecrosis of the jaw (ONJ) was also associated with individuals who took RANK-L ligand inhibitor drugs denosumab (Dmab) and antiangiogenic drugs (Sunitinib, Bevacizumab, Temsirolimus, Everolimus and other drugs).⁽¹⁾ With the purpose of unifying diagnosis criteria, the nomenclature “medication-related osteonecrosis of the jaw” (MRONJ) was adopted in 2014 by the American Association of Oral and Maxillofacial Surgeons (AAOMS) and preferred to the former term “bisphosphonate-related osteonecrosis of the jaw” (BRONJ). This change was made to accommodate the new classes of drugs (new angiogenic and antiresorptive agents) involved in osteonecrosis.⁽¹⁾

There is difficulty in obtaining exact incidence data for MRONJ because under-reporting of cases together with discrepancies in case recognition.^(4,5) It appears that the incidence is higher in cancer patients (who use high doses of intravenous medication at frequent intervals) ranging from 1%-1.2% to 15%-19%.⁽⁵⁾

The exact mechanisms underlying MRONJ remain unknown. Interestingly, MRONJ is primarily limited to the maxillofacial region. In contrast to other skeletal bones, jaw bones (the alveolar process and periodontium) have relatively high vascularity, bone turnover, and remodelling because of continuous mechanical stress, which may make them vulnerable to the adverse effects of drugs. Proposed hypotheses that attempt to explain the localisation of MRONJ exclusively to the jaws include altered bone remodelling, angiogenic inhibition, constant microtrauma, suppression of innate or acquired immunity, and possible effects of inflammation or infection.⁽²⁾

To distinguish MRONJ from other delayed healing conditions and address evolving clinical observations and concerns about under-reporting of disease, the working definition of MRONJ has been modified from the 2009 AAOMS position paper. Patients may be considered to have MRONJ if all the following characteristics are present:

- Current or previous treatment with 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 longer than 8 weeks;
- No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.⁽¹⁾

Not all patients on antiresorptive or antiangiogenic therapies develop MRONJ, it may develop spontaneously or can be induced by invasive dental procedures.⁽⁶⁾

The aetiology and pathogenesis of MRONJ is not completely understood, but several risk factors have been identified. Currently recognized risk factors for MRONJ include the type of drug used, the cumulative dose of the drug and poor oral hygiene.⁽¹⁾ Some studies have concluded that tooth extraction is the most important independent risk factor for the onset of MRONJ.^(1,7) Thus, patients being treated with high doses of antiresorptive agents (AR) are advised to avoid tooth extractions if possible.⁽¹⁾

Prevention and control of the risk factors are fundamental to avoid osteonecrosis of the jaw. Better awareness of the risk factors can be helpful for prevention and targeted treatment of MRONJ, also, it would help the clinician to identify those at risk of rapidly progressive disease and implement appropriate therapy or preventive measures.⁽⁶⁾ Several studies have found a lesser occurrence of osteonecrosis in patient groups where preventative measures were applied via a multidisciplinary unit.^(1,2,5,7-11) The treatment of MRONJ is challenging, and an effective and appropriate therapy that substantially improves the outcome remains to be identified.^(2,7)

MRONJ can cause significant pain, and reduce quality of life, and can be difficult to treat.⁽⁷⁾

1.1. Risk factors

The aetiology and pathogenesis of MRONJ have not been fully elucidated ^(1,10), however, the mechanisms of drugs' actions may explain a large part of the development of this condition. Epidemiological studies have shown that the risk of MRONJ increases with a longer duration of treatment and with higher drug doses.⁽¹²⁾ Effective measures to prevent and treat MRONJ may significantly improve the risk-benefit balance, in particular for people requiring long-term or high-dose therapy.^(2,13) Most of these drugs have a higher potency and does not get metabolised. It is the accumulation of the drug over time that predisposes patients to osteonecrosis.^(3,13)

Regarding to the mechanisms of drugs' actions:

- BPs are antiresorptive drugs, blockers of osteoclastic bone resorption that inhibit mineral dissolution. They adhere to the bone surface and are ingested by osteoclasts, altering their ability to reabsorb bone.⁽¹⁰⁾ BPs are commonly used orally or intravenously (IV) to treat diseases with high osteoclastic activity such as postmenopausal osteoporosis, breast, prostate and lung cancer, malignant hypercalcemia, bone metastases, lytic lesions in the context of multiple myeloma and Paget's disease ^(2,8) RANK-L ligand inhibitor drugs, which have Dmab as the main example, are human monoclonal antibodies that prevent the binding between the RANK receptor and the RANK-L ligand, reducing the function of osteoclasts, including their formation, differentiation and survival.⁽¹⁾ Dmab increases bone mass and density, both in cortical and trabecular bone, and is used in the treatment of postmenopausal osteoporosis, rheumatoid arthritis, androgen replacement therapy and multiple myeloma, among other conditions.⁽²⁾
- Angiogenesis or antiangiogenic inhibitors interfere in the neoformation of blood vessels by binding to various proteins and signalling molecules, which interrupt the angiogenesis-generating cascade.^(1,2) These new drugs have shown efficacy in the treatment of gastrointestinal and neuroendocrine tumours, renal cell carcinomas and other malignant neoplasms ^(1,2) and have also been related to the MRONJ.

In addition to the knowledge of the mechanisms of drugs' actions, the assessment of MRONJ aetiology encompasses at least three risk factors: drug-related factors, local factors and systemic factors. Regarding the factors related to the drugs used, the evaluation falls, in large part, on the use of bisphosphonates. This class of drugs, in addition to accounting for the

vast majority of MRONJ cases, is the one that has its best-known characteristics. The potency and route of administration of BPs are identified as major risk factors. Therefore, cancer patients who receive intravenous bisphosphonates are at an increased risk of developing MRONJ 2.7 to 4.2 times greater than cancer patients who do not use BPs.⁽⁵⁾ Local and systemic factors include, poor oral health, invasive dental procedures, ill-fitting dentures, uncontrolled diabetes mellitus, obesity and tobacco, deficiency of vitamin D.^(1,7)

Numerous studies have concluded that dental extraction and the use of IV BP for more than 3-4 years are invariably repeated as the most prevalent risk factors for the onset of MRONJ. Thus, patients being treated with high doses of AR agents are advised to avoid tooth extractions if possible.^(1,7)

1.2. Classification and treatment

Before discussing therapies, it is recommended to qualify the patient according to risk. Those at “low risk” are those who follow treatment with oral (O) BP or IV BPs in low concentrations, for osteoporosis, osteopenia or Paget's disease. The “high risk” patients, on the other hand, are those with medication for cancer, multiple myeloma and bone metastases, with IV drug therapy in high concentrations.^(2,8) It should be taken into consideration, the duration of treatment, associated comorbidities, use of removable prostheses, etc. In the clinical management of MRONJ, a preventive approach should prevail at all times.⁽¹⁾

The treatment of MRONJ is challenging, and the aim is to eliminate pain, control infection and minimise the progression of bone necrosis. The literature has several reports of successful treatments in all stages of MRONJ, whether conservative or invasive. However, in the main published guidelines, the choice of the type of treatment is linked to the patient's clinical staging. The special commission assembled by AAOMS in September 2013, proposed the use of a revised staging system to better guide treatment guidelines and collect data to assess the prognosis in patients who were exposed to antiresorptive (IV or O) or antiangiogenic therapies.⁽⁵⁾

According to MASCC/ISOO/ASCO Clinical Practice Guideline, MRONJ has been divided into four stages based on clinical symptoms, represented in table 1.

Table I - Treatment Strategies by Stage of MRONJ. ⁽⁷⁾

Staging MRONJ	Treatment Strategy
At Risk: No apparent necrotic bone in patients who have been treated with oral or intravenous bone-modifying agents.	<ul style="list-style-type: none"> - No treatment indicated - Patient education and reduction of modifiable risk factors
Increased Risk: No clinical evidence of necrotic bone, but nonspecific clinical findings, radiographic changes, and symptoms.	<ul style="list-style-type: none"> - Symptomatic management, including the use of pain medication and close scrutiny and follow up - Refer to dental specialist and follow up every 8 weeks with communication of lesion status to the oncologist - Patient education and reduction of modifiable risk factors
Stage 1: Exposed and necrotic bone, or fistulas that probe to bone in patients who are asymptomatic and have no evidence of infection	<ul style="list-style-type: none"> - Antibacterial mouth rinse - clinical follow up on every-8-week basis by dental specialist with communication of lesion status to the oncologist - Patient education and reduction of modifiable risk factors
Stage 2: Exposed and necrotic bone, or fistulas that probe to bone associated with infection as evidenced by pain and erythema in the region exposed bone with or without purulent drainage	<ul style="list-style-type: none"> - Symptomatic treatment with oral antibiotics and topical antibacterial rinse - Pain control - Debridement to relieve soft tissue irritation and infection control - clinical follow up on every-8-week basis by dental specialist with communication of lesion status to the oncologist - Patient education and reduction of modifiable risk factors
Stage 3: Exposed and necrotic bone, or fistulas that probe to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in mandible maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor	<ul style="list-style-type: none"> - Symptomatic treatment with oral antibiotics and topical antibacterial rinse - Pain control - Surgical debridement or resection for long-term palliation of infection and pain - clinical follow up on every-8-week basis by dental specialist with communication of lesion status to the oncologist - Patient education and reduction of modifiable risk factors

1.3. Prevention

Prevention is a key to reduce the incidence of MRONJ.⁽⁵⁾ In the clinical management of MRONJ, a preventive approach should prevail at all times.^(1,8) For patients with cancer who are scheduled to receive a BMA in nonurgent setting, oral assessment, that includes, comprehensive dental, periodontal, and oral radiographic evaluation, when feasible to do so, should be undertaken before initiating therapy.⁽¹⁾ As long as the patient's systemic state allows it, it will be considered to delay the use of pharmacotherapy until the patient's oral health is stabilised.⁽⁸⁾ In fact, patients who receive adequate dental care and who maintain optimal oral health over time, have a low risk of developing MRONJ.^(1,5,8)

Based on the assessment, MASCC/ISOO/ASCO Clinical Practice Guideline (2019)⁽¹⁴⁾, a dental care plan should be developed and implemented. The care plan should be coordinated between the dentist and the oncologist to ensure that medically necessary dental procedures are undertaken before initiation of BMA. Follow up by dentist should then be performed on a routine schedule (e.g., every 6 months) once therapy with BMA has commenced.^(7,9) It is known that patients who received preventive dental treatment, before starting the therapeutic regimen with antiresorptive and antiangiogenic drugs, had a 50% reduction in the risk of developing MRONJ.⁽⁵⁾

Leaving this preventive conceptual framework established, when we are faced with a patient who is already under pharmacological therapy, be it with BF, Dmab or antiangiogenic drugs, and who urgently requires an extraction, the consulted literature raises three options:

- First: drug holiday, refers to the temporary suspension of a drug in chronic patients, in order to reduce the probability of adverse side effects after a surgical act. The dentist may request evaluation and possible interruption of treatment with BP or related drugs.^(1,7)
- Second: therapeutic option, we have to delay the surgical act. The AAOMS, recommends this, especially in high-risk patients. This therapeutic possibility presents detractors, who consider that a tooth with cavities or periodontal disease that is not extracted in time is a risk factor in itself for the formation of a future osteonecrotic lesion, and an infectious focus in a systemically compromised patient.^(1,7)
- Third: follow the proposal of a line of researchers who have looked for specific surgical techniques which reduce the occurrence of MRONJ, for example, during bisphosphonate therapy, wound exposure to bacteria may be controlled by antibiotic prophylaxis, antiseptic mouthwash, or both.⁽¹⁾ The treatment plan should be

aggressive regarding the combat of infection, any source of acute infection or potential infection in the oral cavity must be completely eliminated. There is a protocol in case of oral surgery be performed, which involves, resecting or debriding until bleeding healthy bone is encountered, removing of bone spicules and smoothing of the bone edges to avoid the soft tissue to be traumatized.^(1,4,5,7)

2. OBJECTIVE

Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse reaction of antiresorptive and/or angiogenic agents, it is uncommon but serious disease, that affects the maxillofacial region. Furthermore, this condition can affect the quality of life of patients because it is potentially painful and debilitating. Therefore, needs to be addressed with the prime importance. The present systematic review aimed at evaluating and identifying different protocols for preventing MRONJ in terms of successful outcomes.

The bibliographic review research used the population, intervention, comparison, outcome (PICO) framework to develop the following focused question:

(P) Population: Adults who are under current or previous treatment for malignant diseases, and osteoporosis among other diseases associated with the use of antiresorptive or antiangiogenic drugs.

(I) Intervention: Different protocols and strategies for prevention of MRONJ.

(C) Comparison: Comparative of the different studies.

(O) Outcome: Primary outcome is to determine an effective protocol in terms of prevention of MRONJ.

“What is the most effective protocol for preventing MRONJ in patients receiving treatment with antiresorptive and/or angiogenic agents?”

3. MATERIALS AND METHODS

3.1. Search Strategy

A Medline (<https://pubmed.ncbi.nlm.nih.gov/about/>), Cochrane Central Register of Controlled Trials (CENTRAL) (<https://www.cochranelibrary.com/search>) databases were searched from January 2016 to March 2021, in English, Portuguese and Spanish language. A search was made to identify publications eligible for inclusion in the study, using the following key words: “MRONJ”, “Medication-related”, “Osteonecrosis”, “Jaw”, and “Prevention”. The reference list from the included studies were checked manually for possible further addition to the Systematic Review.

3.2. Selection of the Studies

The collected studies were assessed in order to check if they all contributed with information regarding prevention of MRONJ in patients under current or previous treatment with oral or intravenous antiresorptive or angiogenic agents. The selected studies met all inclusion criteria, and the methodological quality of the articles and suitability for inclusion in a meta-analysis was evaluated. The following types of studies were considered for inclusion in this systematic review: Meta- analysis, Systematic Reviews and Randomized Control Trials (RCT’s), Reviews, Cohorts, Case Reports, and include Controlled Clinical Trials. The inclusion and exclusion criteria studies were recorded, and it is presented in Table 2.

3.3. Inclusion and Exclusion Criteria

Table II - Inclusion and exclusion criteria adopted in the systematic review

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none">• Bibliographic reviews, prospective and retrospective studies, clinical guidelines, articles, systematic reviews, systematic reviews with meta-analysis, clinical studies, case control studies, cohort studies and RCTs studies, case series, and clinical trials	<ul style="list-style-type: none">• In vitro studies, experimental animal studies, editorials, hypothetic reviews• Redundant publications• Studies with less than 3 patients
<ul style="list-style-type: none">• Free full text	<ul style="list-style-type: none">• Paid full text
<ul style="list-style-type: none">• Studies regarding prevention of MRONJ and related studies	<ul style="list-style-type: none">• Studies not related to MRONJ or its prevention

3.4 Data Collection and Risk of Bias Analysis

The methodological parameters were recorded to evaluate the risk of bias: after analysing if the abstracts met the inclusion criteria, and reading the full text of the studies, they were divided according to the type of preventive intervention protocol used. The Variables extracted from the studies were the following: author/year (adequate if <5 years), study design, sample size (adequate if sample size >10) gender/age, drug/route, exposure/intervention, follow up period adequate if >6 months) and outcome.

Low risk-of-bias: In cases when one or more of the parameters were considered inadequate.

Moderate risk-of-bias: In cases when at least 1 unclear and no inadequate items.

High risk-of-bias: In cases when 1 or more of the parameters were considered inadequate.

4. RESULTS

The electronic search identified 313 articles in three different databases, and 5 additional articles were found by hand-searching, adding up to 318 articles (Figure 1). Reading the title and abstracts of the articles allowed the selection of 30 publications. After evaluation of the full text of these articles, and applying the inclusion and exclusion criteria, 4 articles were excluded. The final sample of the study consisted of 26 publications (Figure 2). The absence of a correlation regarding the prevention of MRONJ, was the most frequent exclusion factor.

As a result, a total of 12 articles were selected for evaluation, 5 articles about preventive oral care, 2 articles about Platelet-Rich Fibrin (PRF), 1 article about Platelet-Rich Plasma (PRP), 2 articles on primary wound closure, and 2 using antimicrobial photodynamic therapy (aPDT). Table 3 shows all data regarding general characteristics and sample features, and in table 4, shows preventive strategies, therapy characteristics, and outcome of the included studies.

After analysing all the studies for this review, it can be concluded that, preventive oral care therapy in patients under current or previous treatment with antiresorptive or antiangiogenic agents' drugs, is one of the most popular protocols suggested regarding prevention of MRONJ. ⁽¹⁵⁻¹⁹⁾

Different protocols were reported by diverse authors, reporting optimistic results. Antimicrobial photodynamic therapy for prevention of medication-related osteonecrosis was another protocol option evaluated with favourable outcomes. ^(20,21)

The use of PRF and PRP after dental extraction, also presented as an effective protocol regarding prevention of MRONJ. ^(22,23)

Studies regarding primary wound closure after dental extraction indicated to be an effective protocol as well. ⁽²⁴⁻²⁶⁾

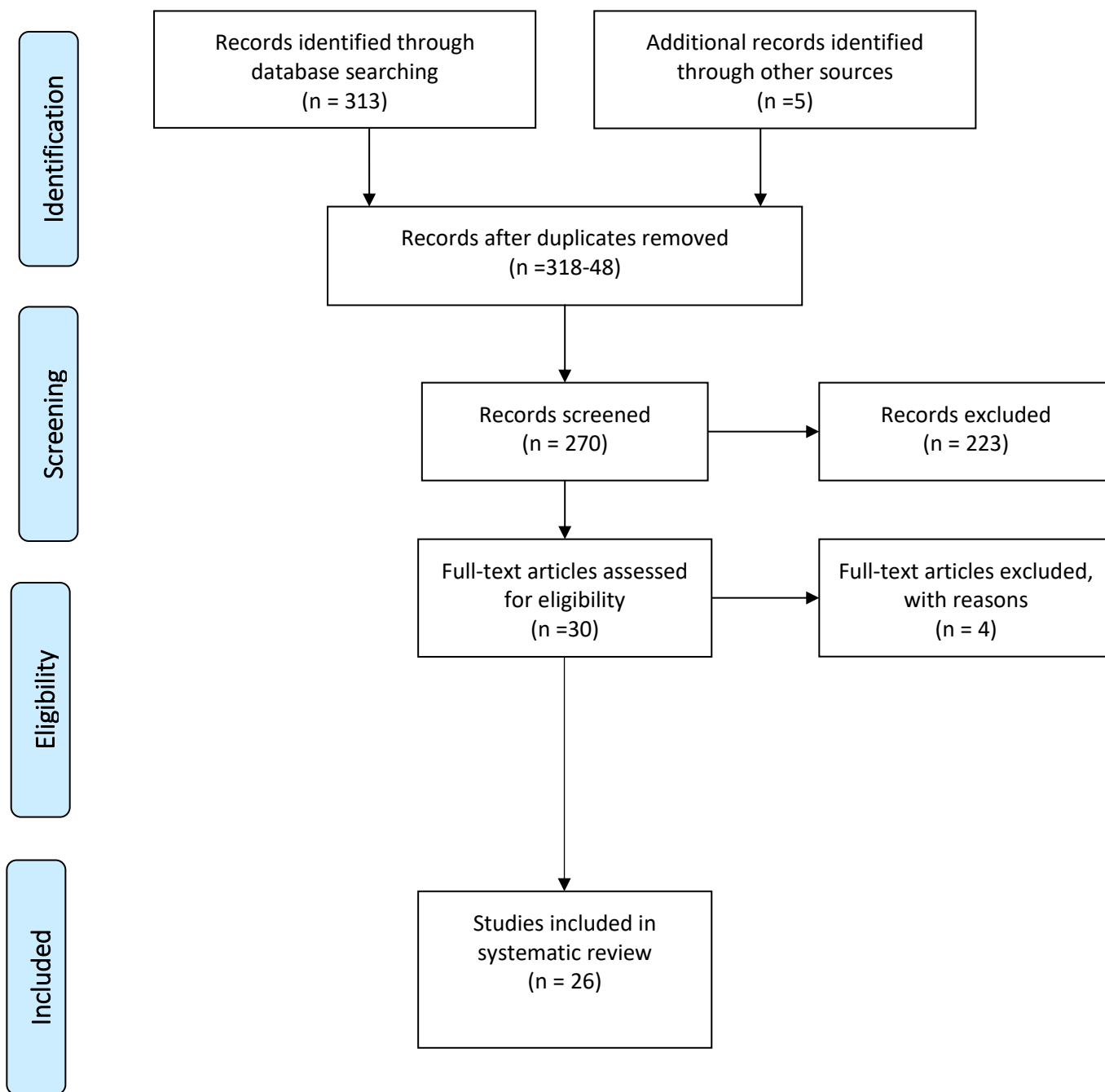


Figure 1 – PRISMA Diagram

Table III – Excluded studies

Studies	Exclusion Criteria
P. Siri et al. 2020 ⁽²⁷⁾	Animal study
O. Doppelt et al. 2020 ⁽²⁸⁾	Animal study
P. Nazeman et al. 2016 ⁽²⁹⁾	Hypothesis
A. Cucchi et al. 2016 ⁽³⁰⁾	Study with only one patient

Table IV. Sample feature of the included studies.

Study ID / Year	Study Type	Length of Study	Sample Size	Gender	Age/mean /range	Primary Cause of Disease	Drugs Administered	Drugs Route
J. A. Coello-Suanzes et al. 2018 ⁽¹⁵⁾	Single centre Clinical Study	Over 6 years	255	M=100 F=155	61.5	Cancer	Zoledronic Acid	IV
G. Catania et al. 2016 ⁽¹⁶⁾	Prospective Study	19 years	119	M=52 F=67	43-85	Multiple Myeloma (MM)	Zoledronic Acid and/or Pamidronate	IV
J. Jakiel et al. 2018 ⁽¹⁷⁾	Prospective Study	1-2 years	49	M=20 F=29	54-77	Not mentioned	BPs and Denosumab	Oral/ IV
T. Mücke et al. 2016 ⁽¹⁸⁾	Prospective Study	Over 6 years	253	M=253 F=0	46-92	Prostate cancer	Zoledronic Acid	IV
W.-S. Choi et al. 2017 ⁽¹⁹⁾	Retrospective Study	Over 5 years	130	M=74 F=57	36-76	Multiple Myeloma (MM)	Combination of Zoledronic Acid and Pamidronate	IV
N. C. Tartaroti et al. 2019 ⁽²⁰⁾	Prospective Study	3 years	35	M=02 F=33	71	Osteoporosis, Osteopenia, Breast cancer, other (Prostate cancer, MM)	BPs and Zoledronic Acid	Oral/ IV
P. P. Poli et al. 2019 ⁽²¹⁾	Prospective Study	11 months	11	M=03 F=08	65-79	Type I and type II Primary Osteoporosis	Antiresorptive Agents: Alendronate, Denosumab, and Clodronate	Oral/ SC/ IM
D. Vlad et al. 2017 ⁽²²⁾	Prospective Study	2 years	14	M=03 F=11	50-79	Osteoporosis, Neoplasia, Breast cancer, Prostate cancer, Pulmonary cancer	BPs, Zoledronic Acid and Ibandroic Acid	IV/ Oral
T. Asaka et al. 2017 ⁽²³⁾	Prospective/Retr ospective studies	2/4 years	102	M=09 F=93	24-87/33- 88	Osteoporosis or Glucocorticoid- induced osteoporosis	BPs	Oral
R. Mauceri et al. 2020 ⁽²⁴⁾	Prospective Study	2 years	20	M=04 F=16	72.35	Cancer skeletal- related events and metabolic bone disease	Zoledronic Acid	IV

A. Matsumoto et al. 2017 (25)	Prospective/Retrospective studies	3 years	19	M=06 F=13	42-85	Breast cancer, Prostate cancer, Osteoporosis.	Denosumab	SC
T. Hasegawa et al. 2017 (26)	Retrospective Study	7 years	1175	M=161 F=1014	23-102	Osteoporosis, Rheumatism, Cancer, Diabetes mellitus, Renal insufficiency including dialysis	BPs	Oral

Legend: BPs: Bisphosphonates; IV: Intravenous; SC: Subcutaneous; IM: Intramuscular; MM: Multiple Myeloma

Table V. Preventive strategies, therapy characteristics, and outcome of the included studies.

Study ID / Year	Exposure/ Intervention	Drug Holiday	Procedure Protocol			Follow up	Outcome
			Antibiotic prophylaxis	Preventive and Surgical techniques	Local measures		
J. A. Coello-Suanzes et al. 2018 ⁽¹⁵⁾	Preventive dental measures before initiation of ZA therapy	NO	Amoxicillin/clavulanic acid 875/125mg (3x daily, 2h before and for 7 days after procedure)	Patients received oral assessment and dental treatment (radiographic and clinical examination performed) After dental procedures (extractions) wounds were closed with tensionless suture	Clx. Rinses Topical application of fluoride gel	25.41 months (mean)	Positive results (preventive dental treatment prior to the initiation of ZA therapy is considered as an effective method for prevention of MRONJ)
G. Catania et al. 2016 ⁽¹⁶⁾	Preventive dental measures-together with less intensive and prolonged BP therapy	NO	Patients eligible to start BP treatment were introduced to preventive measures recommended by the AAOMS position paper	Dental visit and orthopantomogram Patients eligible to start BP treatment were introduced to preventive measures recommended by the AAOMS position paper	Patients eligible to start BP treatment were introduced to preventive measures recommended by the AAOMS position paper	47 months	Positive results (preventive dental treatment with less intensive and prolonged BP therapy are considered as an effective method for prevention of MRONJ)
J. Jakiel et al. 2018 ⁽¹⁷⁾	Preventive dental measures in patients under antiresorptive or antiangiogenic therapy	YES	Clindamycin (1 day before surgery and continued for the next 6 days) Doxycycline used until the sutures are removed	Patients received oral assessment and dental treatment (radiographic and clinical examination performed) After dental procedures (extractions) each surgical site was sutured, and the sutures were kept in place until soft tissues healed completely (after 2-4 weeks)	Clx. Rinses. Dental adhesive paste contains topical anaesthetic, policanol, and the active substance, solcoseryl, a protein free standardizes dialysate of culfblood.	Every 3 months 12-24 months	Positive results (preventive dental treatment in patients under antiresorptive or antiangiogenic therapy is considered as an effective method for prevention of MRONJ)
T. Mücke et al. 2016 ⁽¹⁸⁾	Preventive dental measures before the onset of a BP	NO	Amoxicillin/clavulanic acid 875/125mg (2x daily)	Oral examination and panoramic tomogram, dental check-up by the authors, patients received dental treatment, if necessary,	–	Every 3 months 12-24 months	Positive results (preventive dental treatment before the onset of a BP based treatment is

	based treatment			<p>dental check up until good oral condition was achieved.</p> <p>During zoledronic acid therapy if patient require dental extraction: Wounds were closed with tensionless suture, Flap after the incision of the periosteum</p> <p>Debridement and sufficient mucosal coverage Interrupted sutures were performed with resorbable suture material</p>			considered as an effective method for prevention of MRONJ)
W.-S. Choi et al. 2017 (19)	Preventive dental measures prior to initiating BP therapy	NO	Recommended by the AAOMS position paper	Recommended by the AAOMS position paper	Recommended by the AAOMS position paper	Recommended by the AAOMS position paper	Positive results (preventive dental treatment prior to initiating BP therapy is considered as an effective method for prevention of MRONJ)
N. C. Tartaroti et al. 2019 (20)	aPDT and PBM	NO	24h preoperative course of antibiotic (Amoxicillin 500mg or Ampicillin 400mg or Clindamycin orally 300mg, 8/8h) maintained for 7 days postoperatively.	<p>Patients received oral assessment and dental treatment (radiographic and clinical examination performed)</p> <p>After dental procedures (extractions) Minimum trauma, aPDT, and PBM preventive protocol (Irrigation and aspiration with saline solution, photosensitizing agent solution of 0.01% methylene blue in deionized water was applied in the dental socket for 5 min)</p> <p>Laser therapy</p> <p>Occlusive suture – dental pocket</p>	0.12% Clx. digluconate daily mouth rinse	3-36 months and 6-29 months	Positive results (aPDT and PBM therapy protocols are considered as an effective method for prevention of MRONJ)

<p>P. P. Poli et al. 2019 (21)</p>	<p>aPDT</p>	<p>YES And NO</p>	<p>3 days before procedure - Amoxicillin 1g every 8h for 20 days</p> <p>Ibuprofen 600mg every 8h for 3 days for pain relief-ice packs for 48h-soft cold diet for 72h</p>	<p>Patients underwent through clinical and radiological assessment (orthopantomography, and clinical treatment);</p> <p>Local anaesthesia (Mepivacaine hydrochloride 30mg/ml)</p> <p>After dental procedure (extractions) Full-thickness flap, minimally invasive procedures.</p> <p>Debridement</p> <p>Bony edges strictly smoothed-copious irrigation with sterile saline-aPDT application</p> <p>Periosteal releasing incisions were performed to mobilize the flap coronally</p> <p>Passive suture-single stitches using absorbable suture material</p> <p>Weekly applications of LLLT- 6 weeks</p>	<p>2 weeks before surgical procedures-rinse for 1 min with 15ml 0.2% Clx digluconate solution (2x daily for 1 month)</p> <p>Rinse with 0.9% sodium chloride solution</p> <p>0.5-ml solution of 10mg/ml phenothiazine chloride dye consisting of Methylthioniumchlorid based on methylene blue compound-left in place for 3 min</p>	<p>6-12 months</p>	<p>Partial results (aPDT protocol, might be considered as an effective method for prevention of MRONJ)</p>
<p>D. Vlad et al. 2017 (22)</p>	<p>A-PRF</p>	<p>NO</p>	<p>Antibiotic and analgic therapy only postoperatively</p>	<p>Oral examination and orthopantomography; interdisciplinary exams performed</p> <p>After dental procedures (extractions) A-PRF membranes was obtained using a Choukroun centrifuge at 1500 rpm for 14 minutes.</p> <p>After dental procedures (extractions) alveolar bone was covered with the A-PRF membranes over the gingival mucous membrane was sutured</p>	<p>Not mentioned</p>	<p>7-30 days</p>	<p>Positive results (A-PRF is considered as an effective method for prevention of MRONJ in patients who have been treated with BPs)</p>

<p>T. Asaka et al. 2017 ⁽²³⁾</p>	<p>PRF</p>	<p>YES</p>	<p>Amoxicillin 250mg every 8h or Clindamycin 150mg every 6h, for 1 week (starting from day of surgery)</p>	<p>Patients received oral hygiene instructions</p> <p>Local anaesthetics (2% lidocain)</p> <p>Delicate tooth extraction and curettage was performed-full-thickness flaps.</p> <p>PRF (blood sample centrifuged at 3000 rpm for 10 min., Erythrocytes at the bottom of the tube and acellular plasma at the top were discarded, and PRF above the erythrocytes was collected) laid directly over the bone to fill the socket</p> <p>Sutured to stabilize PRF</p> <p>Wound was not always completely closed by bone shaving and relaxation incision; a simple suture for the maintenance of PRF was conducted</p>	<p>Not mentioned</p>	<p>8 weeks</p>	<p>Positive results (PRF might be considered as an effective method for prevention of MRONJ in patients receiving oral BPs)</p>
<p>R. Mauceri et al. 2020 ⁽²⁴⁾</p>	<p>Primary wound closure and PRP</p>	<p>NO</p>	<p>Preoperative: Amoxicillin/clavulanate potassium 1g per 3x daily starting 1 day before</p> <p>Metronidazole 250mg 2x daily starting 1 day before</p> <p>Postoperative: Amoxicillin/clavulanate potassium 1g per 3x daily for 7 days</p>	<p>Clinical evaluation, tomography, CT prescription</p> <p>Ultrasonic periodontal debridement (when required) and oral hygiene instructions</p> <p>PRP preparation (centrifugation at 180g for 10 min with common bench centrifuge, then 1000g for 10 min and PPP was removed)</p> <p>Dental extraction, PRP application, Flap suture</p>	<p>Preoperative: 0.2 Clx mouthwashes 30 ml swished up to 60s, 3x daily 7 days before</p> <p>Postoperative: 0.2 Clx mouthwashes 30 ml swished up to 60s, 3x daily 10 days</p> <p>Application of sodium-hyaluronate 3x daily 10 days</p>	<p>15 days 1-3-6-12-18-24 months</p>	<p>Partial results (Preventive dental measures with PRP might be considered as an effective method for prevention of MRONJ both in ONC and OST patients)</p>

			Metronidazole 250mg 2x daily for 7 days - Patients allergic to penicillin received lincomycin (preoperative- 500mg 2x daily, 1 day preoperative/ postoperative- 500mg 2x daily for 6 days)	Suture removal and clinical control			
A. Matsumoto et al. 2017 ⁽²⁵⁾	Primary wound closure after tooth extraction	NO	IV antibiotics Penicillin 10,000,000 IU once daily or Clindamycin 600mg 3x daily in case of penicillin allergy	Teeth were extracted and all extraction sites were closed with double-layered technique. Bone edges were smoothed and the mucoperiosteal flaps were prepared with relieving incision and sutures with the other side of periosteal.	Antiseptic rinse for 6 months (for 1 patient)	Every month at least for 3 months	Positive results (Primary wound closure can be considered as an effective method for prevention of MRONJ)
T. Hasegawa et al. 2017 ⁽²⁶⁾	Primary wound closure and drug holiday	YES	Systemic antibiotics	Category A: non-surgical treatment or debridement of separated necrotic bone Category B: conservative surgical treatment, including the removal of necrotic bone only Category C: extensive surgical treatment, including removal of necrotic bone and surrounding bone (marginal mandibulectomy or partial maxillectomy)	Antiseptic mouth rinse	-	Positive results (Primary wound closure can be considered as an effective method for prevention of MRONJ)

Legend: ZA: zoledronic acid; BP: bisphosphonates; Clx.: chlorhexidine; aPDT: antimicrobial photodynamic therapy; PBM: photobiomodulation; LLT: low-level laser therapy; A-PRF: advanced-platelet rich fibrin; PRP: platelet-rich plasma; ONC: cancer patients; OST: osteometabolic patients.

5. DISCUSSION

Prevention of MRONJ should be based on qualification of patients to their appropriate MRONJ risk group, assessment of possible additional risk factors and formulating individual treatment recommendations.⁽¹¹⁾ Regardless of their MRONJ risk, all patients should be examined by a dentist and instructed about oral cavity hygiene. Furthermore, dental professionals should perform oral cavity sanitation, perform periodontal treatment and check if patients' dentures fit properly. Patients should be informed about the symptoms of MRONJ and the necessity of reporting them early, in order to avoid the progression of the disease.^(7,12,13) The recent guidelines from the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) and the American Society of Clinical Oncology (ASCO) emphasize the importance of collaboration among the cancer care team, dentists, and dental specialists.⁽⁷⁾

Currently, the osteonecrosis of the jaw as an adverse effect of antiresorptive and antiangiogenic treatment cannot be completely prevented. However, many preventive protocols have been used in order to minimize the risk and to prevent MRONJ. The following are a few interventions discussed in this systematic review: preventive dental care including completion of all necessary dental treatment before the commencement of drug therapy, or as soon as possible following commencement of drug therapy⁽¹⁵⁻¹⁹⁾; antimicrobial photodynamic (aPDT) and photobiomodulation adjuvant (PBM) therapies^(20,21); supportive measures to accelerate wound healing after surgery, such as advanced-platelet rich fibrin (A-PRF), platelet-rich fibrin (PRF), and platelet-rich plasma (PRP)⁽²²⁻²⁴⁾, and primary wound closure after tooth extraction^(25,26), the last one in particular was also presented associated with other preventive methods in different studies.^(15,17,18,21)

Four studies considered preventive dental management as a prior protocol, that influence the incidence of MRONJ related to Zoledronate therapy. According to Coello-Suanzes et al.⁽¹⁵⁾, their main finding revealed that preventive dental treatment prior to the initiation of ZA therapy in patients with metastatic bone cancer significantly reduced the MRONJ occurrence from 36% to 7.3%. When it comes to Choi et al.⁽¹⁹⁾, their study evaluated 130 Multiple Myeloma (MM) patients receiving IV BPs therapy. In some patients, the location of MRONJ and the type of dental problem coincided with the oral condition seen at the initial visit. Because they did not evaluate the patients' oral health prior to initiate BPs therapy, the majority of patients had periodontal problems. Their findings showed that the majority MM patients that received a combination of Zoledronate and Pamidronate, presented serious complication of osteonecrosis of the jaw. Clinical examinations, including panoramic

radiography, may have helped detecting dental problems and could have improved oral health before and during BFs therapy. Therefore, preventive oral care including, routine dental examinations and treatment of dental diseases should be performed prior to initiating antiresorptive and antiangiogenic therapy, in order to reduce the risk and prevent MRONJ. Another study by Catania et al.⁽¹⁶⁾, including 119 MM patients where it was evaluated the occurrence of ONJ. Patients were divided by three different groups, and the “prevention group”, who included 78 patients that started therapy only after a baseline preventive assessment and eventual dental care measures, did not present the occurrence of ONJ, in other words, revealed 0% ONJ occurrence, confirming the value of oral health preventive protocol, to minimize the risk and subsequently prevent MRONJ. Furthermore, regarding to Mücke et al.⁽¹⁸⁾, their study demonstrated that preventive measures in a high-risk population with metastatic prostate cancer can significantly reduce the risk of occurrence of BRONJ. In addition, the incidence rate for each patient of the presented study, to develop BRONJ was reduced about 82% for each year of observation. The incidence proportion for patients without any preventive treatment strategy (group A) was 23% and was significantly higher compared with 2.2% in patients receiving a close follow-up re-evaluation every 3 months. Which confirms that, a preventive oral care protocol before the onset of an antiresorptive and antiangiogenic therapy, is an effective method to reduce the risk and prevent MRONJ.

Jakiel et al.⁽¹⁷⁾, their study evaluated 49 patients receiving antiresorptive and antiangiogenic therapy, and suggested a protocol followed by an antibiotic prophylaxis together with surgical wound closure, local antiseptics and preventive dental and oral care, during the observation period, which varied from 1-2 years depending on the patient’s first visit. No signs of MRONJ were observed in the treated areas. During that period patients presented complete mucosal healing and reported no pain. Their finding shows that, a protocol based on antibiotic prophylaxis, local antibacterial mouth rinses, suturing the wounds for a prolonged period and an efficient oral hygiene, seem to reduce the risk and to be a good method for prevention of MRONJ. It is therefore suggested that atraumatic extraction, following treatment and check-ups are necessary in patients under antiresorptive or antiangiogenic therapy, or before initiating the administration.

According to the results of those studies⁽¹⁵⁻¹⁹⁾, it is clear that a protocol which presented a preventive dental and oral care, in patients receiving treatment with antiresorptive or antiangiogenic agents, presented beneficial effects on reducing patient’s risk of MRONJ and preventing the disease.

Poli et al.⁽²¹⁾, presented a study which described the use of antimicrobial photodynamic therapy (aPDT) in the prevention of MRONJ in 11 non-oncologic patients affected by type I and type II primary osteoporosis. In this study, a drug holiday period was planned before dental intervention (consisted of a 2-month drug holiday before the surgery up to the complete clinical healing of the surgical wound) in patients receiving higher cumulative doses of bisphosphonates. A total of 62 surgical extractions were performed in both jaws, including 51 natural elements and 11 dental implants. No intraoperative complications were observed. Immediate post-operative period was generally uneventful except for mild pain and ecchymosis that occurred rarely and resolved spontaneously. Healing proceeded uneventfully, with no clinical or radiological prodromal manifestations of MRONJ up to the latest follow-up visit. Together with a preventive dental and oral protocol (prior and posterior of any surgical intervention), the use of systemic antibiotic and other preventive methods have been recommended to optimize the prevention of MRONJ. Although may not be enough against complex microbial biofilm. In this respect, aPDT showed successful results when used to eliminate microorganisms associated with biofilms. Their study, suggest that the use of aPDT in the prevention and management of MRONJ may provide beneficial results in addition to the conventional treatment.

Tartaroti et al.⁽²⁰⁾, presented a study where patients treated with aPDT and PBM, combined with laser therapy and antibiotic therapy, reported relief of symptoms and oral odor in the first sessions. The study evaluated 18 patients that underwent preventive protocol, and none presented signs of MRONJ after a follow-up of at least 6 months, and 17 patients with MRONJ underwent aPDT protocol, and 16 out of 17 patients, showed total regression of lesions. On the prevention protocol, patients in need of tooth extraction received a 24h preoperative course of antibiotic prior to clinical procedure, dental extractions were performed under minimum trauma and aPDT preventive protocol was applied, which followed, immediately after the tooth extraction and saline solution irrigation/aspiration a photosensitizing agent solution of 0.01% methylene blue in deionized water was applied in the dental socket for 5 min. Then the laser irradiation was applied all over the extent of dyed dental socket using a continuous-wave diode laser. Laser application was followed by saline irrigation and aspiration. Next an occlusive suture was performed to closure dental socket. After 7 days the suture was removed and daily mouth rinsing with 0.12% chlorhexidine digluconate was prescribed. When dental socket was not healing as expected, the aPDT protocol was repeated weekly until repair. The purpose of using aPDT sessions before surgery aimed to reduce microorganism burden before surgery. Their findings assumed that aPDT and laser therapy

could diminish bacterial colonization within the biofilm layers inside bone lesions and enhance the healing process. Moreover, it can be expected that bacterial load is reduced during bone manipulation. It was also observed that multiple sessions of aPDT and PBM associated with laser therapy have better healing effect, where almost all patients healed after the combine procedure, and presented epithelization of the surrounding soft tissue and spontaneous exfoliation of the necrotic bone leaving a healthy oral mucosa.

When surgical intervention is the treatment of choice, it is important to follow a conservative/selective protocol that aim to avoid complications. The use of autologous platelet concentrates (APCs) such as platelets rich fibrin (PRF), advanced platelet rich fibrin (A-PRF), and platelet rich plasma (PRP), as a therapeutic aid in a variety of surgical procedures in different fields has become increasingly popular, especially in the treatment of osteonecrosis of the jaw, also in preventing the onset of this disease, because APCs are rich in many substances' fundamental to the promotion of healing process. Thus, lowering the risk of delayed recovery after tooth extraction in patients undergoing AR agents. It is crucial that clinicians take this into consideration prior to surgical procedures to prevent MRONJ.⁽²³⁾ Asaka et al.⁽²³⁾ evaluated the effectiveness of platelet fibrin PRF as a wound-healing accelerator in 29 patients undergoing oral BFs therapy and requiring tooth extractions, and there were no intraoperative complications, and none of the patients exhibited the onset of MRONJ, confirming that a PRF protocol is effective in preventing this disease. Another study with 14 patients, have observed relatively early epithelization of oral mucosa in most cases (85.71%), which confirms that the effects of A-PRF competed with mucosal suppression and inhibition of osteoclasts induced by bisphosphonate administration. Therefore, protecting the alveolar bone with A-PRF is an effective method of preventing the onset of MRONJ.⁽²²⁾ Mauceri et al.⁽²⁴⁾ evaluated a study which standardizes a medical-surgical protocol for dental extraction, combined with PRP application, compared with conventional protocol not combined with PRP or any other autologous platelet concentrate in cancer (ONC) and osteometabolic (OST) patients, at risk of BRONJ, and the outcome of the surgical treatment was successful in all 20 patients treated with PRP. Furthermore, two years after extraction, no patient had clinical or radiological signs of ONJ.

Primary wound closure after tooth extraction is another protocol that has the purpose of preventing MRONJ. Matsumoto et al.⁽²⁵⁾, presented a study focused on examining the appropriate tooth extraction method to reduce the risk of developing MRONJ and to investigate the association between tooth extraction with secure wound closure and the development of MRONJ. The study presented a total of 40 teeth in 19 patients under denosumab therapy.

Regarding discontinuation of the drug, no drug holiday was taken into consideration. During surgery, the teeth were extracted at first and all extraction sites were closed with double-layered technique. On the double-layered technique, the bone edges were smoothed and the mucoperiosteal flaps were prepared with a relieving incision and sutured with the other side of periosteal. Moreover, running sutures were taken at the alveolar crest. Appropriate primary wound closure could be obtained in the extraction site. The sutures were removed at 2-3 weeks after extraction. The outcome of tooth extraction was evaluated with clinical wound condition site without any signs of a fistula or exposed bone defined to be a success. All patients were followed up every month at least for 3 months, in case of uneventful healing. Thirty-seven extraction sites (92.5%) in 17 out of 19 patients (89.5%) were healed, which leads to a conclusion that tooth extraction in patients receiving denosumab can be performed in an appropriate manner and result in good outcomes. On the other hand, Hasegawa et al.⁽²⁶⁾ developed a similar study, although applying drug holiday. A total of 2458 dental extractions performed on 1175 patients receiving oral bisphosphonate therapy were investigated in the study. All patients were investigated with regard to demographics; type and duration of oral BF use; drug holiday before intervention; duration of such discontinuation; and whether any additional surgical procedures were performed. Their findings have successfully demonstrated multivariate relationships among the various risk factors for MRONJ after tooth extraction in patients receiving oral BFs. The performance of root amputation, the extraction of a single tooth, the presence of bone loss or severe tooth mobility, and an unclosed wound were all significantly associated with the development of MRONJ. Therefore, they recommend a minimally traumatic extraction technique, removal of bone edges and mucosal wound closure. The effectiveness of a short-term drug holiday was not confirmed as it has no significant impact on MRONJ incidence.

6. CONCLUSION

This presented systematic review shows and emphasizes the need and the impact of an oral and dental evaluation prior to commencement of anti-resorptive and antiangiogenic therapy. MRONJ can cause significant pain, reduce quality of life, and can be difficult to treat, therefore a Multiprofessional approach combined with efficient strategies including preventive dental appointments ensuring patients are educated on good oral hygiene, is fundamental in order to improve the quality of life for patients that suffer from this disease. There is not sufficient scientific evidence available to date on the efficacy of MRONJ prevention protocols in patients treated with antiresorptive and antiangiogenic drugs. There is a necessity of more complexes and long-term studies which could help in terms of defining the ideal protocol for preventing MRONJ, although, most studies considered that a preventive oral and dental management prior to initiating antiresorptive and antiangiogenic therapy, can be an effective protocol to reduce the risk and prevent MRONJ, specially combined with other preventive methods.

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