

## Medication-related osteonecrosis: Literature review

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### Abstract

**Objective:** The aim of this study is to determine the most likely medication to develop osteonecrosis of the jaw, the route of administration, dose and treatment time that carry the greatest risk, and to establish appropriate prevention strategies in order to provide new knowledge for the management of patients who are at risk or that are developing medication-related osteonecrosis of the jaw.

**Materials and methods:** Literature review of the last 5 years in the databases PubMed, ScienceDirect and Springer Link, using the following terms: osteonecrosis in dentistry, osteonecrosis of the jaws and drug related osteonecrosis of the jaws.

**Results:** A total of 20,662 articles were obtained from the three digital databases; after applying exclusion and inclusion criteria, 51 articles were selected for the literature review.

**Conclusion:** MRONJ is a rare but potentially serious condition associated with prolonged use of antiresorptive and antiangiogenic agents. However, because of the heterogeneity of evidence, the administration route of greatest risk has not been accurately determined.

**Keywords:** Antiangiogenic agents; Antiresorptive; Bisphosphonates; Denosumab; Drug-related osteonecrosis; Osteonecrosis of the jaws; Intravenous route; oral route

### 1. Introduction

Medication-related osteonecrosis of the jaw, or MRONJ, is a rare but potentially serious condition that can occur after exposure to high doses of agents used to modify bone metabolism, such as bisphosphonates (BP), denosumab and angiogenesis inhibitors (1) (2) (3).

Both bisphosphonates and denosumab are drugs primarily used to reduce the risk of skeletal complications in patients with bone loss who have received long-term treatment for cancer, osteoporosis, and malignant bone diseases (1) (38).

Bisphosphonates are a group of inorganic pyrophosphate derivative drugs. According to their mechanism of action, they are divided into two large groups: first generation (non-nitrogenous) such as etidronate, clodronate and tiludronate; second and third generation (nitrogenous): alendronate, risedronate, ibandronate, pamidronate and zoledronic acid (1) (2) (20).

These drugs are composed of molecules that bind to hydroxyapatite binding sites on bone surfaces; at the same time, they bind to the farnesyl pyrophosphate synthase of the osteoclast's enzyme (osteoclast: cells responsible for the reabsorption of the bone matrix by releasing hydrolytic enzymes) which lead to their apoptosis. Without osteoclasts,

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there is no signal for bone matrix apposition by osteoblasts or angiogenesis stimuli, consequently the bone tissue becomes acellular and avascular with necrosis risk when exposed to the oral environment (1) (2) (16).

The bisphosphonates attachment to the bone structure leads to their high concentration, especially in areas of greater bone remodeling such as the maxillary and mandible bones, this is the reason why the apoptotic rate of osteoclasts is higher in these areas, increasing the risk of drug-associated osteonecrosis (2) (9).

Although BPs are the main pharmacological causes of osteonecrosis in the jaw, there are other frequently used drugs; called anti RANKL monoclonal antibodies that can cause the same adverse effect. One of these agents is Denosumab, a highly specific human IgG2 monoclonal antibody against receptor activator of nuclear factor  $\kappa$  B ligand (RANKL), which inhibits osteoclast activity, reduces resorption and increases bone density (1) (20) (10). In addition, MRONJ may also be associated with anticancer agents, including classical chemotherapy agents, angiogenesis inhibitors, and biologic immunomodulators (1) (4) (5).

The clinical symptoms are variable, from an asymptomatic process to local pain, presence of fistulas, ulceration, inflammatory reaction of soft tissues, dental mobility and exposure of necrotic bone; pain and infectious symptoms being the most frequent reported by patients (2).

For the diagnosis of MRONJ, the following aspects should be considered:

- Current or previous treatment with bisphosphonates, denosumab, or antiangiogenic therapy.
- An area of exposed bone or bone that can be probed through an intraoral or extraoral fistula and has persisted for more than 8 weeks.
- No history of mandible radiotherapy or metastatic disease of the maxillary bones (3) (11).

Once the diagnosis of MRONJ is confirmed, the AAOMS classification and staging system is used as a management guide (Table 1) (2) (51).

**Table 1** Classification and Staging of the Advancement of Necrosis

| Stage | Necrosis advance                                                                                                                                                                                                                                           |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0     | Without clinical evidence of necrotic bone but with the presence of nonspecific clinical symptoms and radiographic changes or symptoms.                                                                                                                    |
| 1     | Necrotic bone exposure without symptoms of infection                                                                                                                                                                                                       |
| 2     | Necrotic bone exposure, accompanied by infection, pain, erythema with or without purulent exudate in the region of the exposed bone                                                                                                                        |
| 3     | Necrotic bone exposure with pain, infection, and one or more of the following aspects: Necrotic bone exposure causing pathologic fractures, extraoral fistula, oral sinus fistula, or osteolysis extending to the edge of the mandible or maxillary sinus. |

The pathogenesis is multifactorial and implies a synergistic effect between local infection/trauma and decreased bone replacement after exposure to these agents. For this reason, the objective of this literature review is to establish the drugs that have a greater probability of developing osteonecrosis of the jaw, the route of administration, dose and treatment time that carry a greater risk, and to establish adequate prevention strategies in order to provide new knowledge for the management of patients who are at risk or are developing medication-related osteonecrosis of the jaw.

## 2. Material and methods

### 2.1. Inclusion criteria

- Articles with a publication range 2018-2022.
- Full text availability.
- Articles available on databases in English, Portuguese and Spanish.
- Articles focused mainly on osteonecrosis of the jaws.

## 2.2. Exclusion criteria

- Case reports, books, magazines and documents
- Articles based on therapeutic options.
- Articles focused on osteoporosis.
- Duplicate articles.

## 2.3. Literature research

This literature review is based on the analysis of the existing bibliography of the last 5 years. The databases used for the research were PubMed, ScienceDirect and Springer Link with the use of terms derived from previous reading of scientific articles, because the different search strategies were: OSTEONECROSIS IN DENTISTRY, OSTEONECROSIS OF THE JAWS AND DRUG RELATED OSTEONECROSIS OF THE JAWS (Table 2).

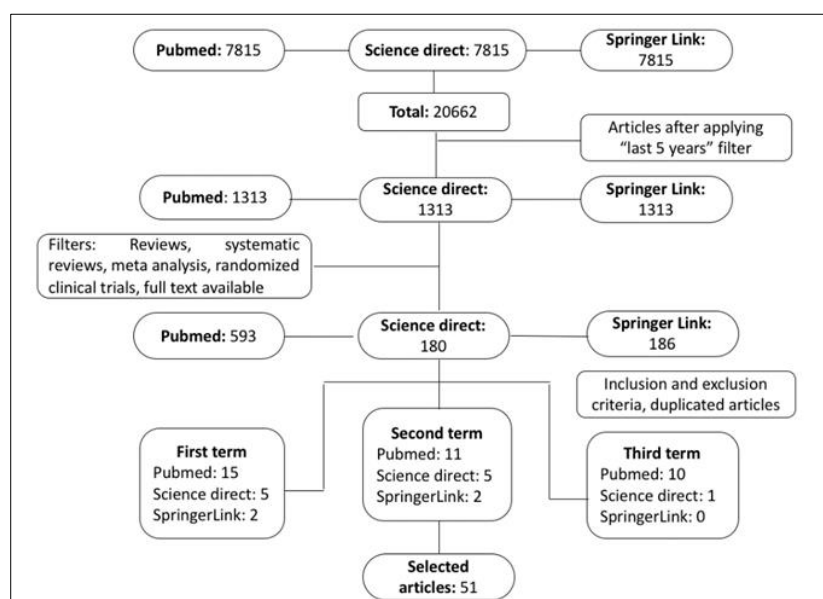
**Table 2** Search strategies

| First search strategy: Osteonecrosis in dentistry | Second search strategy: Osteonecrosis of the jaws | Third search strategy: Drug-related osteonecrosis of the jaws |
|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------------------|
| PubMed: 2147                                      | PubMed: 4475                                      | PubMed: 1196                                                  |
| ScienceDirect: 2180                               | ScienceDirect: 2523                               | ScienceDirect: 1297                                           |
| SpringerLink: 1487                                | SpringerLink: 4725                                | SpringerLink: 635                                             |

## 3. Results

### 3.1. Data collection

There were 7 815 articles obtained from PubMed, 6 000 from ScienceDirect, and 6 847 from SpringerLink. After applying the filter “5 last-years”, 2630 articles remained in PubMed, 1313 articles in ScienceDirect, and 3608 in Springer Link. At the same time, different filters were applied such as: reviews, systematic reviews, meta-analyses, randomized controlled clinical trials, full text availability, and articles written in English, Spanish or Portuguese, from which 592, 180 and 200 articles were obtained respectively. When reading the titles, abstracts, applying inclusion, exclusion and duplicate articles criteria, 51 articles were selected for the literature review. Figure 1 illustrates the article selection diagram and results in Table 3.



**Figure 1** Literature Search Flow Chart

**Table 3** Summary of the studies selected for literature review

| Author                                                                                                                                                    | Article title                                                                                                                                            | Year | Principal results                                                                                                                                                                                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ourania Morten, Rui Mendes, Carla Ripamonti, Sally Hope, Lawrence Drudge-Coates, Daniela Niepel, Tim Wyngaert                                             | Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment.                                      | 2018 | MRONJ is a rare adverse event associated with high cumulative doses of bisphosphonates or denosumab, prophylactic dental treatment decreases the risk of developing it.                                          |
| Paweł Nieckula, Anna Stempniewicz, Monika Tubaja                                                                                                          | Prophylaxis of osteonecrosis in the case of patients treated with bisphosphonates: A review paper                                                        | 2018 | Discontinuation of bisphosphonate therapy before dental procedures does not decrease the risk of osteonecrosis but should be considered as well as antibiotic prophylaxis.                                       |
| Kün-Darbois, F. Fauvel                                                                                                                                    | Medication-related osteonecrosis and osteoradionecrosis of the jaws: Update and current management                                                       | 2020 | A tooth extraction is often found to be a trigger for MRONJ.                                                                                                                                                     |
| Cesar Augusto Migliorati                                                                                                                                  | Oral Complications in Cancer Patients–Medication-Related Osteonecrosis of the Jaw (MRONJ).                                                               | 2022 | The exact mechanism leading to MRONJ formation is not yet known, it is a multifactorial process.                                                                                                                 |
| Kununya Pimolbutr, Stephen Porter , Stefano Fedele                                                                                                        | Osteonecrosis of the Jaw Associated with Antiangiogenics in Antiresorptive-Naïve Patient: A Literature Review                                            | 2018 | The mean duration of intravenous and oral antiangiogenics was 6.5 and 16.72 months, respectively, and the most frequent risk factor was dental extraction.                                                       |
| Roberto Sacco, Julian Woolley, Julian Yates, Monica Diuana Calasans-Maia, Oladapo Akintola, and Vinod Patel                                               | The role of antiresorptive drugs and medication-related osteonecrosis of the jaw in nononcologic immunosuppressed patients: A systematic review          | 2021 | The most common trigger for MRONJ was tooth extraction and with a high frequency of postoperative complications after treatment.                                                                                 |
| Hitesh Bansal                                                                                                                                             | Medication-related osteonecrosis of the jaw: An update                                                                                                   | 2022 | MRONJ is a relatively rare complication of antiresorptive and antiangiogenic medication, its prevention is key to its management.                                                                                |
| H Kagami                                                                                                                                                  | Issues with the surgical treatment of antiresorptive agent related osteonecrosis of the jaws                                                             | 2018 | It is essential to develop less invasive therapies to prevent MRONJ progression and maintain patient's quality of life and alleviate symptoms.                                                                   |
| George Bullock , Cheryl A. Miller , Alasdair McKechnie ,Vanessa Hearnden                                                                                  | A Review into the Effects of Pamidronic Acid and Zoledronic Acid on the Oral Mucosa in Medication-Related.                                               | 2022 | BPs reduce cell viability, reduce proliferation, and increase apoptosis in oral keratinocytes and fibroblasts, thus leading to reduced wound healing.                                                            |
| Akanksha Srivastava, María E. Cabanillas, Graciela M. Nogueras González, Aung Naing, Jeffrey Myers, Yimin Geng, Yisheng Li, Alexander Ganó, MarK Chambers | Prevalence of medication related osteonecrosis of the jaw in patients treated with sequential antiresorptive drugs: systematic review and meta-analysis. | 2020 | There was a higher prevalence of MRONJ associated with sequential antiresorptive therapy for administration of pamidronate-zoledronate and denosumab bisphosphonate compared with single antiresorptive therapy. |
| J. Chang, A. E. Hakam, L. K. McCauley                                                                                                                     | Current Understanding of the Pathophysiology of Osteonecrosis of the Jaw                                                                                 | 2018 | The definitive pathophysiology is still unclear.                                                                                                                                                                 |

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|-----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Minju Song                                                                                                                  | Dental care for patients taking antiresorptive drugs: A literature review                                                        | 2019 | MRONJ is rare but untreatable; therefore, physicians and dentists should be aware of the importance of preventing the development of ONJ.                                                                                                                  |
| K McGowan, T McGowan, S Ivanovski                                                                                           | Risk factors for medication-related osteonecrosis of the jaws: A systematic review                                               | 2017 | MRONJ has been reported to occur in multiple myeloma, breast cancer, prostate cancer, and osteoporosis.                                                                                                                                                    |
| Ali Aboalela, Fathima Farook, Amerah Alqahtani, Mandlin Almousa, Rehab Alanazi, Duaa Almohammadi.                           | The Effect of Antiresorptive Drug Holidays on Medication-Related Osteonecrosis of the Jaw: A Systematic Review and Meta-Analysis | 2022 | Withholding antiresorptive therapy for a period does not minimize the risk of MRONJ.                                                                                                                                                                       |
| António Marques, Carlos Polis-Yanes, Maria Seminario-Amez, Enric Jané-Salas, Jose López-López                               | MRONJ associated with implant and regenerative treatments: Systematic review.                                                    | 2019 | The risk of developing osteonecrosis associated with the regeneration/placement of implants in patients with benign bone diseases is low if the duration of treatment with BP is greater than 3 years and with administration of systemic corticosteroids. |
| Camila Foncea, Kristine Von, Cristian Teuber, Hernan Ramírez, Ignacio Goñi, Cesar Sánchez, Ignacio N. Retamal, Alex Vargas. | Drug-associated osteonecrosis of the jaw: Literature review and proposal for prevention and management                           | 2020 | The most effective way to prevent MRONJ is thorough dental, clinical, and imaging evaluation before starting therapy.                                                                                                                                      |
| Mustafa Mian Subhashaan Sreedharan, Ricky Kumar.                                                                            | Osteonecrosis of the jaws associated with protein kinase inhibitors: a systematic review                                         | 2020 | The evidence related to MRONJ associated with protein kinase inhibitors is of low quality. There are many different clinical features of MRONJ associated with antiresorptive therapy.                                                                     |
| Madhumati Singh, Giriraj Sandeep Gonegandla.                                                                                | Bisphosphonate-Induced Osteonecrosis of the Jaws (BIONJ)                                                                         | 2019 | Currently, there is no way to predict which people taking bisphosphonates are at higher risk of developing MRONJ.                                                                                                                                          |
| Álvaro Limones, Luis Miguel Sáez-Alcaide, Pedro Molinero-Mourelle.                                                          | MRONJ in cancer patients treated with denosumab VS. zoledronic acid: A systematic review and meta-analysis                       | 2020 | The use of denosumab is associated with a significantly increased risk of developing MRONJ compared with zoledronic acid.                                                                                                                                  |
| Mampeï Kawahara, Shinichiro Kuroshima, Takashi Sawase                                                                       | Clinical considerations for medication-related osteonecrosis of the jaw: a comprehensive literature review                       | 2021 | Dentists should perform appropriate dental treatment to prevent MRONJ in patients before or when receiving medications that can induce MRONJ.                                                                                                              |
| Aya Alsali, Annica Dam, Anna Truedsson                                                                                      | Medication-Related Osteonecrosis of the Jaws Initiated by Zoledronic Acid and Potential Pathophysiology                          | 2021 | Current findings show negative effects after ZA administration, leading to prolonged wound healing, chronic inflammation, and impaired bone remodeling.                                                                                                    |
| Benjamin Palla, Egon Burian, Andrew Deek, John Anderson, Nicholas Callahan, Eric R. Carlos.                                 | Comparing the Surgical Response of Bisphosphonate-Related Versus Denosumab-Related Osteonecrosis of the Jaws                     | 2020 | The surgical success rate for secondary MRONJ to denosumab was 80.0%, similar to that reported for bisphosphonates of 85 to 95%.                                                                                                                           |
| Asier Eguía, Leticia Bagan, and Francisco Cardona                                                                           | Review and update on drugs related to the development of osteonecrosis of the jaw                                                | 2019 | To prevent new cases of MRONJ, it is essential that all dentists are trained on etiopathogenic aspects.                                                                                                                                                    |

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|------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lina He, Xiangyu Sun, Yumei Niu.                                                                                                         | Pathogenesis and multidisciplinary management of medication-related osteonecrosis of the jaw                                 | 2020 | BP accumulation in the jaw can be competitively inhibited, this may be an effective method to prevent osteonecrosis of the jaw in the future.             |
| Hiromitsu Kishimoto, Kazuma Noguchi, Kazuki Takaoka                                                                                      | Novel insight into the management of bisphosphonate-related osteonecrosis of the jaw (BRONJ)                                 | 2019 | The presence of exposed bone in patients treated with BP does not necessarily cause BRONJ.                                                                |
| Kun-Jung Hsu, Szu-Yu Hsiao, Chun-Ming Chen.                                                                                              | Investigation of the Effectiveness of Surgical Treatment on Maxillary MRONJ: A Literature Review                             | 2021 | To prevent and control MRONJ, all elderly patients were suggested to maintain a proper oral hygiene routine and have a periodic dental examination.       |
| S Bernardi, M Di Girolamo, S Necozone, M A Continenza, T Cutilli                                                                         | Antiresorptive drug-related osteonecrosis of the jaws, literature review and 5 years of experience                           | 2018 | A surgically conservative strategy appears to be the best way to ensure a good life quality for patients adversely affected by this condition.            |
| Olga Fede, Vera Panzarella, Rodolfo Mauceri, Vittorio Fusco, Alberto Bedogni, Lorenzo Muzio, Sipmo Board, Giuseppina Campisi.            | The Dental Management of Patients at Risk of Medication-Related Osteonecrosis of the Jaw: New Paradigm of Primary Prevention | 2018 | A multidisciplinary approach should be adopted among physicians involved in treating patients at risk of MRONJ and increasing the patient's life quality. |
| Raiza Querrer, Nathália Ferrare, Nilce Melo, Cristine Miron, Paula Diniz, Carla Moreira, Gabriel Borges, André Ferreira, Paulo Tadeu.    | Differences between bisphosphonate-related and denosumab-related osteonecrosis of the jaws: a systematic review              | 2022 | BP-related ONJ and AMDb-related ONJ manifest imaging features that are significantly more frequent in one condition than in the other.                    |
| Camila Foncea, Kristine Bischoffshausen, Cristián Teuber, Hernán Ramírez, Ignacio Goñi, Cesar Sánchez, Ignacio N Retamal, Alex Vargas    | Osteonecrosis of the jaws                                                                                                    | 2020 | The most effective way to prevent MRONJ is complete dental, clinical, and imaging evaluation before starting therapy.                                     |
| Weidong Zhang, Ling Gao, Wenhao Ren, Shaoming Li, Jingjing Zheng, Shasha Li, Chunmiao Jiang, Shuying Yang, Keqian Zh                     | The Role of the Immune Response in the Development of Medication-Related Osteonecrosis of the Jaw                            | 2021 | These results suggested that impaired immunity plays an important role in the development of MRONJ.                                                       |
| Sven Otto, Suad Aljohani, Riham Fliefel, Sara Ecke, Oliver Ristow, Egon Burian, Matthias Troeltzsch, Christoph Pautke, Michael Ehrenfeld | Infection as an Important Factor in Medication-Related Osteonecrosis of the Jaw (MRONJ)                                      | 2021 | They conclude that local infection plays a key role in the pathogenesis of MRONJ.                                                                         |
| Aloizio Premoli Maciel, Reyna Aguilar Quispe, Lázara Joyce Oliveira Martins, Rogério Jardim Caldas, Paulo Sérgio da Silva Santos         | Clinical profile of individuals with bisphosphonate-related osteonecrosis of the jaw: an integrative review                  | 2020 | BRONJ had a higher prevalence in women and the mandible was the most affected region with a moderate stage of BRONJ.                                      |
| Akanksha Srivastava, Graciela M Noguera Gonzalez, Yimin Geng, Alexander M Won, Jeffrey Myers, Yisheng Li, Mark S Chambers                | Medication-Related Osteonecrosis of the Jaw in Patients Treated Concurrently with Antiresorptive and Antiangiogenic Agents:  | 2021 | High-quality representative studies with larger sample sizes are needed for an accurate estimate of the relative risk of MRONJ.                           |

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|--------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                              | Systematic Review and Meta-Analysis                                                                                                                     |      |                                                                                                                                                                             |
| Akanksha Srivastava, Graciela M Noguera, Gonzalez, Yimin Geng, Alexander M Won, Maria E Cabanillas, Aung Naing, Jeffrey N Myers, Yisheng Li, Mark S Chambers | Prevalence of medication related osteonecrosis of the jaw in patients treated with sequential antiresorptive drugs: systematic review and meta-analysis | 2021 | Higher prevalence of MRONJ associated with sequential ARD therapy for pamidronate-zoledronate and bisphosphonate-denosumab administration compared with single ARD therapy. |
| Masaya Akashi, Junya Kusumoto, Daisuke Takeda, Takashi Shigeta, Takumi Hasegawa, Takahide Komori                                                             | A literature review of perioperative antibiotic administration in surgery for medication-related osteonecrosis of the jaw                               | 2018 | Oral and maxillofacial surgeons mostly prefer penicillin-based antibiotics plus $\beta$ -lactamase inhibitor or metronidazole for MRONJ surgery.                            |
| Raed Al Rowis, Abdulmalik Aldawood, Mohammed Alotaibi, Essam Alnasser, Ibrahim Alsaif, Abdullah Aljaber, Zuhair Natto.                                       | Medication-Related Osteonecrosis of the Jaw (MRONJ): A Review of Pathophysiology, Risk Factors, Preventive Measures and Treatment Strategies            | 2022 | A collaborative approach involving dentists, physicians, and pharmacists is considered essential to prevent the development of MRONJ.                                       |
| Aristilia Tahara, Vitor Hugo Ferreira, Rafael Mobile, Thais Brandao, Laurindo Sassi, Amanda Zarpellon, Paulo Braz-Silva, Juliana Schussel.                   | Risk factors for medication-related osteonecrosis of the jaw and salivary IL-6 IN cancer patients-                                                      | 2022 | There was no association between salivary IL-6 levels and MRONJ stages.                                                                                                     |
| Nobuyuki Kaibuchi, Keika Hoshi, Ayame Yamazaki, Noriko Miyamoto-Sangu, Yuichi Akagi, Toshihiro Okamoto.                                                      | The progress of medication-related osteonecrosis of the jaw with conservative initial treatment: A 12-year retrospective study of 129 patients.         | 2021 | The results showed that the cure rate did not decrease in patients with MRONJ.                                                                                              |
| Guang Yang, Sonal Singh, Yiqing Chen, Issam Hamadeh, Taimour Langaee, Caitrin McDonough, Shannon Holliday, Jatinder Lamba, Jan S.Moreb, JosephKatz, YanGong  | Pharmacogenomics of osteonecrosis of the jaw                                                                                                            | 2019 | Researchers believe that genetic factors play an important role in the development of MRONJ.                                                                                |
| Estee L.George<br>Yi-LingLin<br>Marnie M.Saunders                                                                                                            | Bisphosphonate-related osteonecrosis of the jaw: a mechanobiology perspective.                                                                          | 2018 | Multiple factors, including blood pressure, load, and inflammation, act on multiple cell types to cause a defect in bone remodeling.                                        |
| Saad Hajeri, Yasir Alturkistany                                                                                                                              | Medication-related osteonecrosis of the jaw after dental clearance: Prevalence in an oncology cent                                                      | 2022 | The prevalence of MRONJ in this study was within the average range reported in the literature, which is higher with the intravenous administration.                         |
| Devie Falinda Nicholas Malden                                                                                                                                | Case series: Osteonecrosis of the jaw related to denosumab preceded by bisphosphonates in cancer and osteoporotic patients.                             | 2022 | The potentially cumulative effect of BP and DSB on the development of MRONJ with tooth extraction is the main trigger.                                                      |
| Susan Diaz, Luis Naval-Gíaz, Mario Munoz-Guerra, Jesús                                                                                                       | Management of osteonecrosis of the jaw associated with the use of medications by virtue of its                                                          | 2018 | A dental check-up is necessary before the administration of antiresorptive drugs to                                                                                         |

|                                                                                                                 |                                                                                                                                         |      |                                                                                                                                                       |
|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sastre-Pérez, Francisco Rodríguez y José Gil-Diez                                                               | clinical stage: Analysis of 19 cases.                                                                                                   |      | reduce the risk of the appearance of OMAM.                                                                                                            |
| Lieselotte De Bruyn, Ruxandra Coropciuc, Wim Coucke, Constantinus Politis                                       | Microbial population changes in patients with medication-related osteonecrosis of the jaw treated with systemic antibiotics             | 2018 | Our findings suggest that the total bacterial level in MRONJ patients is higher even when treated with systemic antibiotics.                          |
| Coline Daron, Christophe Deschaumes, Martin Soubrier, Sylvain Mathieu.                                          | Viewpoints of dentists on the use of bisphosphonates in rheumatology patients                                                           | 2018 | The guidelines also reported that annual IV administration of BP is weakly associated with the onset of ONJ.                                          |
| Tormod B. Krüger, Bente B. Herlofson, Aina M. Lian, Unni Syversen, Janne E. Reseland                            | Alendronate and omeprazole in combination reduce angiogenic and growth signals from osteoblasts                                         | 2021 | The combination of alendronate and omeprazole appeared to exaggerate the negative effects of each drug on human gingival osteoblasts and fibroblasts. |
| Seung Hun Lee, Choi tan jowen†, Min-Su Bae y Tae-Geon Kwon                                                      | Characteristics of patients with osteonecrosis of the jaw with oral versus intravenous bisphosphonate treatment                         | 2021 | IV administration of BP causes a severe inhibition of bone remodeling and could result in a higher degree of inflammation.                            |
| P.J.Voss, D. Steybe, P. Poxleitner, R. Schmelzeisen, C. Munzenmayer, H. Fuellgraf, A. Stricker & W. Semper-Hogg | Osteonecrosis of the jaw in patients transitioning from bisphosphonates to denosumab treatment for osteoporosis                         | 2018 | They suggested that it was not necessary to stop oral BPs before dental procedures.                                                                   |
| Kelly McGowan, Robert S. Ware, Caroline Acton, Saso Ivanovski & Newell W. Johnson                               | Both non-surgical dental treatment and extractions increase the risk of medication-related osteonecrosis of the jaw: case-control study | 2019 | Preventive dental care should be seen as an important factor in ensuring patients to take their antirheumatic medications safely.                     |
| Mampei Kawahara, Shinichiro Kuroshima & Takashi Sawase                                                          | Clinical considerations for medication-related osteonecrosis of the jaw: a comprehensive literature review                              | 2021 | Before initiating potent antiresorptive therapy, a good oral status should be provided by a comprehensive dental evaluation.                          |

#### 4. Discussion

The risk of MRONJ varies from low to high cumulative dose, duration of treatment, and frequency of administration of antiresorptive agents. Therefore, according to several studies, cancer patients who receive high doses of antiresorptive drugs have a greater risk of suffering from it. Patients receiving BP or Denosumab therapy for the treatment of bone metastases and multiple myeloma receive monthly doses of BP intravenously and Denosumab subcutaneously. While patients with osteoporosis or other disease such as Paget's require antiresorptive therapy at lower doses (zoledronic acid 5mg IV once a year and alendronic acid 10mg orally once a day) (Denosumab 60mg every 6 months, zoledronic acid 5 mg every 1 to 5 years) (17) (2) (40). In fact, Eguía A. et al shown that the risk is low for those patients who take oral bisphosphonates or denosumab for those with osteoporosis and who do not suffer from other pathologies. However, this risk increases considerably after the fourth year of treatment and is much higher in those patients who receive intravenous administration of bisphosphonates (23).

According to Granate et al, the majority of patients treated for osteoporosis receive intravenous or oral BP. The average duration of this treatment was 38 months in patients receiving intravenous therapy and approximately 50 months in patients receiving oral BP administration, demonstrating that the majority of patients who developed MRONJ are associated with oral alendronate use (15) (47). However, the risk of osteonecrosis due to intravenous therapy with bisphosphonates must be evaluated since some authors mention that the BPs administered by this route have a high bioavailability and take more than 10 years to be metabolized and simultaneously eliminated in the bone tissue (16) (46).

On the other hand, Díaz S et al. mention that the risk of developing MRONJ by oral therapy is lower than its intravenous or subcutaneous administration in the case of denosumab, as evidenced in the results of this review in which 89% of patients were administered with this medication intravenously. Zoledronic acid (intravenous) is the drug most

frequently associated with MRONJ, followed by denosumab (subcutaneous) and alendronate (oral). Furthermore, this drug causes a delay in the elimination of the cartilage matrix, which negatively affects bone development (17) (44) (28).

Despite the above, Rowis R. et al, have shown that the administration of denosumab will lead to a higher probability of developing MRONJ compared to zoledronic acid (37).

McGowan K et al, Premoli A et al, Kaibuchia N et al, Lee S, affirm that the location with the greatest tendency to develop MRONJ is the mandible in the posterior sector, specifically in the molar area, which could be attributed to the decreased vascularity of the mandible (13) (33) (44) (48). However, Falinda et al, determined that the region with the greatest involvement of MRONJ was the maxilla, contrasting with the information expressed in previous studies. Such affirmations are supported by the following information: 4 of the 8 cases analyzed were associated with dental surgical procedures exclusively in the maxilla, from this it is argued that the literature to reach this conclusion is still scarce, however all the procedures that involving manipulation of bone tissue, must be performed accurately, quickly, and atraumatically (43) (33).

Regarding gender, several authors established that women are the most affected with MRONJ, since it may be related to the administration of BP after menopause and with the high incidence of breast cancer and osteoporosis (13) (33).

According to the studies by McGowan et al, in the dental field, the procedure with the highest risk of developing MRONJ is extraction. For this reason, it is considered to suspend the antiresorptive drug if the extraction of a tooth is unavoidable (13) (15) (19).

Most authors agree that the risk is closely related to the patient's condition as it depends on the primary disease, duration and frequency of treatment with antiresorptive agents, however, the suspension of these drugs at high doses remains uncertain in term of effectiveness in reducing the risk of MRONJ since Nieckula P et al, verify that the interruption of treatment with bisphosphonates for 3 months has little impact since they remain incorporated into the bone in a high percentage for many years after therapy, since it is estimated that alendronate can remain in the body for 10 years, even after a single dose. However, antiresorptive and antiangiogenic therapy should not be started before the mucosa has healed because it can recover if the effect of these drugs is reduced (2) (25).

With respect to risk factors, Zheng J et al and Otto S et al mention that part of the success of prevention is a correct anamnesis, since patients who are going to receive medications associated with the development of osteonecrosis should not present oral infectious processes and their oral health must be optimal. Evidence shows that dental care prior to starting treatment with bisphosphonates prevents the development of MRONJ (31) (32); information corroborated by Srivastava A et al, who emphasize that the treatment of dental caries, periodontal disease, and extraction of teeth infected or at risk of developing infection must be carried out at least 4 weeks before therapy with antiangiogenic and antiresorptive drugs (24) (34).

During treatment, invasive procedures should be avoided in high-risk patients, unless there are infectious processes that cannot be treated with conservative therapies. Extractions can be performed in patients with a low risk of developing osteonecrosis of the jaw in the primary care setting (17).

According to Galitis O et al, the risk of developing MRONJ can be reduced by antibiotic prophylaxis; the selection of the drug depends on individual factors of each patient (1). On the other hand, Nieckula P et al, do not recommend prior prophylactic therapy in all patients, they affirm that antibiotic prophylaxis should only be applied to high-risk patients such as systemic and cardiovascular diseases (2).

However, in recent years, various updates on the MRONJ have determined that there is no effective prevention protocol, therefore, it is necessary to implement more reliable evidence to reach a consensus (44) (45).

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## 5. Conclusion

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but potentially serious adverse event that is associated with the prolonged use of antiresorptive and antiangiogenic agents, this is the reason why we conclude that dental professionals should be aware of the risk factors associated with MRONJ development at the time of performing any dental procedure. It has not been possible to accurately determine the route of administration with the highest risk, due to the heterogeneity of evidence and dependence on the individual characteristics of each patient. It is essential to emphasize the importance of communication between the treating physician and the dentist to prevent these events,

highlighting the preventive scope prior to the start of treatment with bisphosphonates, antiresorptive, and antiangiogenics.

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## Compliance with ethical standards

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### *Disclosure of conflict of interest*

The authors declared that they had no conflicts of interest with respect to the research, authorship and/or publication of this article.

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