



REVIEW ARTICLE

Medication-Related Osteonecrosis of the Jaw (MRONJ): A Review of Pathophysiology, Risk Factors, Preventive Measures and Treatment Strategies

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Received 16 August 2021; revised 3 January 2022; accepted 12 January 2022

Available online 19 January 2022

KEYWORDS

Osteoporosis;
Osteonecrosis;
Oral cancer;
Bisphosphonate

Abstract Medication-related osteonecrosis of the jaw (MRONJ) is a major problem that can occur in people taking certain medications such as bisphosphonates and denosumab. It can be used to treat osteoporosis or cancer. Bisphosphonate exposure, dental diseases and procedures, age, sex, anatomical factors, medical issues, and hereditary factors are all variables that enhance the risk of MRONJ. Even though MRONJ and antiresorptive medications have a close association, the pathophysiology of MRONJ is unknown. Careful dental preparation and oral hygiene instructions significantly minimize the risk of osteonecrosis of the jaw (ONJ). It is ideal to start antiresorptive treatment after the completion of required dental treatment; it is not contraindicated and carries low risk in patients who are on oral antiresorptive medications for less than three years. Drug holidays are one proposed solution to address MRONJ. However, there is still inadequate evidence to support their effectiveness. The objectives of this literature review are to recognize the main diagnostic principles and risk factors and to review the pathophysiology, protective procedures and treatment modalities related to MRONJ.

The following topics are covered in the review: epidemiology, diagnostic criteria, risk factors, pathogenesis and mechanism, MRONJ staging and symptoms, clinical and radiographic findings, treatment strategies, prevention and drug holiday.

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1. Introduction

According to the American Association of Oral and Maxillo-facial Surgeons (AAOMS), the definition of medication-related osteonecrosis of the jaw (MRONJ) is a serious complication that can arise in patients who took or is taking antiresorptive or antiangiogenic agents, leading to visible bone or a fistula that continues for more than eight weeks, without any history of radiotherapy. In 2014, and due to increasing number of patients with osteonecrosis of the jaw related to nonbisphosphonate treatments, the condition was renamed MRONJ instead of “bisphosphonate-related osteonecrosis of the jaw” (BRONJ) by the AAOMS (Ruggiero et al., 2014). In a 2003 research paper regarding unhealed bone exposure in the jaw area of a patient taking bisphosphonates, Marx reported the first recorded incidence of MRONJ. (Khan et al., 2017; Lerman et al., 2013; Marx, 2003; McGowan et al., 2018; Ruggiero, 2009; Ruggiero et al., 2014). Both denosumab and bisphosphonates are typically used in osteoporosis patients to minimize the incidence of bone fractures. On the other hand, antiangiogenic drugs will facilitate the inhibition of new blood vessel formation, which in the end could increase the possibility of ONJ by means of ischemia and hypoperfusion (Khan et al., 2017; Lombard et al., 2016). The prevalence of bisphosphonate prescriptions is very high; globally, it is expected that more than 190 million prescriptions for oral bisphosphonates have been given (AAOMS, 2007).

2. The Prevalence of MRONJ

2.1. In osteoporosis cases taking oral Bisphosphonates:

The prevalence varies among countries: it is currently 0.001% in Canada, 0.004% in Scotland and 0.00038% in Germany (Khan et al., 2011; Malden and Lopes, 2012; Hansen et al., 2013). The prevalence in the United States is quite high, ranging from 0.1% to 0.2% in patients who receive oral bisphosphonates for a period that exceeds four years (Lo et al., 2010).

2.2. In cancer cases taking intravenous Bisphosphonates, subcutaneous denosumab and bevacizumab (Angiogenesis Inhibitor)

The prevalence of intravenous bisphosphonates in cases with malignancies ranges from 0% to 0.186%. (Khan et al., 2011; Yamazaki et al., 2012). The incidence among patients with malignancies who are treated with subcutaneous denosumab is between 0.7% and 1.9% (Ruggiero et al., 2014). The risk of ONJ with bevacizumab as monotherapy is 0.2%, which increases to 0.9% when it is combined with bisphosphonates (Guarneri et al., 2010). However, some studies reported no association between bevacizumab and the development of MRONJ when it was used as a single therapy (Tzermpos et al., 2016; McArthur et al., 2008). In a more recent study performed in Brazil, the prevalence of MRONJ was three percent among 134 female patients undergoing treatment with intravenous bis-

phosphonates (Soares et al., 2020). Sim et al. reported that the overall incidence was 2.7% in patients who received antiresorptive drug therapy for cancer (Sim et al., 2015). Hallmer et al. reported that the incidence of MRONJ is 6.6% in denosumab-treated cases with breast cancer (Hallmer et al., 2020).

2.3. In cases treated with sequential antiresorptive Drugs:

In a recent *meta-analysis* by Srivastava et al., it was found that there is a higher prevalence of MRONJ when it is associated with sequential antiresorptive drugs (ARDs) in comparison to single ARDs. It was ranged between 10% and 19% based on different ARDs, while bisphosphonates only was 5% and denosumab only accounted for 4% (Srivastava et al., 2021). Van Cann et al. found that the total MRONJ incidence was 11.1% in patients who were treated with ARDs. (van Cann et al., 2018).

3. Diagnostic Criteria

To diagnose patients with MRONJ, patients must be met.:

- Previous or ongoing management with antiresorptive or antiangiogenic medications.
- Visible bone or a deep fistula to the bone that has continued for more than eight weeks.
- There was no history of radiotherapy in the maxillofacial region (Ruggiero et al., 2014).

The AAMOS classified MRONJ into three stages determined by how severe the signs and symptoms were, with extraoral fistula being one of the characteristic signs of stage 3 MRONJ (Bennardo et al., 2020a).

Numb chin syndrome (NCS) is a condition that is happened due to sensory neuropathy along the distribution of the inferior alveolar nerve or mental nerve, which could include numbness of the teeth, chin, lower lip and gingiva. Fortunato et al. found 29 cases who presented with NCS as their first symptom, and all of them had paresthesia, anesthesia or hypoesthesia of the lower lip and chin. Among those patients, 13 (44.8%) presented with NCS as their first symptom of MRONJ (Fortunato et al., 2018).

It was proposed that the ability to measure bone turnover markers (BTM), such as serum C-terminal telopeptide of type I collagen (CTX), could be used as a forecaster of MRONJ as well as a prognostic factor (Marx et al., 2007; Kim et al., 2014). C-terminal telopeptide cross-linking (CTX) is a consequence of bone remodeling that can be measured in blood. It was suggested before that serum levels of CTX decrease gradually with antiresorptive treatment and return to the normal level after the treatment stops. Thus, it can be used to predict osteonecrosis (Marx et al., 2007). Although there is a need for a reliable predictor for MRONJ, The American Academy of Oral Medicine stated that there is insufficient evidence to justify use CTX in predicting chance of MRONJ (Bugueno and Migliorati, 2017).

4. Risk Factors

4.1. Bisphosphonate and Denosumab Exposure

There is a greater incidence of ONJ in patients taking IV bisphosphonates than in those taking bisphosphonates orally, since IV forms of bisphosphonates are more potent. Zolen-

dronate is noted to be the most superior bisphosphonate in potency (Dimopoulos et al., 2006; Woo et al., 2006; Corso et al., 2007; Durie et al., 2005). The rate of MRONJ among patients suffering from osteoporosis who are taking IV bisphosphonates is 0.017%, with no increase in this percentage even with more than four years of therapeutic duration (Ruggiero et al., 2014). Anagnostis et al. reported that the chance of developing MRONJ for cases on IV bisphosphonates can reach up to 0.35% (Anagnostis and Stevenson, 2015). Meanwhile, oral bisphosphonates have a 0.02–0.1% chance of causing MRONJ, which can increase to as much as 0.21% when the course of treatment exceeds four years (Ruggiero et al., 2014). Although denosumab has several advantages over bisphosphonates, such as its superior prevention characteristics of skeletal-related events, subcutaneous management instead of intravenous administration without any dose adjustment in cases of renal impairment (Loyson et al., 2018). On the other hand, some studies have shown that the administration of denosumab will lead to a higher chance of developing MRONJ when compared with zoledronic acid (Limonet et al., 2020).

4.2. Dental Diseases and Procedures

Another known risk factor is previously existing inflammatory dental conditions, including periodontal and periapical disease (Yamazaki et al., 2012; Tsao et al., 2013). A previously remaining inflammatory oral disease was a factor in 50% of cancer patients with MRONJ (Yamazaki et al., 2012; Saad et al., 2012). Additionally, listed as contributing factors are the use of dentures, the existence of dental abscesses and inadequate dental hygiene (Durie et al., 2005; Hoff et al., 2008; Kyrgidis et al., 2008). McGowan et al. reported that among 4106 cases of MRONJ, dental extraction was the most common dental risk factor (45%), followed by periodontal disease (Natto et al., 2017; McGowan et al., 2018; Alharthi et al., 2019; Natto, 2020). Dental implants are also considered to be risk factors for MRONJ (McGowan et al., 2018; Marx et al., 2005). However, another study by Lesclous et al. found no difference in bone and mucosal healing in patients receiving bisphosphonate treatment following optimal dental extraction procedures compared to patients not receiving bisphosphonate treatment (Lesclous et al., 2020).

4.3. Age and Gender

The occurrence of MRONJ is higher in both female and older patients (Kalra and Jain, 2013; Ruggiero et al., 2014). According to Jeong et al., among 320 osteoporotic patients, 11 patients developed MRONJ, and all 11 patients were above the age of 65 years old (Jeong et al., 2017).

4.4. Anatomical Factors

The occurrence of MRONJ is more likely in the mandible (73%) than in the maxilla (22.5%), although it can also occur simultaneously in both (4.5%) (Saad et al., 2012). Jeong et al. reported that in 651 extracted teeth, three out of 365 maxillary tooth extractions (0.82%) caused the patient to develop MRONJ, while 15 out 286 mandibular tooth extractions (5.24%) caused the patient to develop MRONJ, and this difference was statistically significant (Jeong et al., 2017).

4.5. Medical Factors

Medical comorbidities tend to be essential risk factors that raise the likelihood of developing MRONJ (Mucke et al., 2016). The most often reported medical risk factors were chemotherapy, corticosteroids and smoking (McGowan et al., 2018). The duration of malignancy, duration of bone metastasis and certain types of cancer are likely to be related to a higher chance of developing MRONJ (Hoff et al., 2008). Breast cancer, prostate cancer, and multiple myeloma are the most common cancers in which ONJ is found (Abu-Id et al., 2008). An elevated risk of MRONJ has been substantially linked with renal dialysis, erythropoietin therapy, diabetes and hypothyroidism (Jadu et al., 2007; Khamaisi et al., 2007; Thumbigere-Math et al., 2009). Diabetes mellitus (DM) was found in 17% (33/191) of those with ONJ in a case-control study, compared to 11% (63/573) of the control subjects (Barasch et al., 2011).

4.6. Genetic Factors

To date, all genome-wide association studies (GWAS), candidate gene studies (CGS), and recently whole genome/whole exome studies (WGS/WES) have not succeeded in showing any single gene associated with the risk for developing MRONJ. Many genes have shown the possibility of increased or decreased association (Sandro Pereira da Silva et al., 2019). Matrix metalloproteinase 2 was hypothesized to be a possible gene responsible for an elevated risk of developing MRONJ caused by bisphosphonates (Lehrer et al., 2009).

5. Pathogenesis and Mechanism

5.1. Bisphosphonates

Among the primary antiresorptive medications are bisphosphonates (Shibahara, 2019; Aljohani et al., 2017). These drugs work at a cellular level, targeting osteoclasts and disturbing their activity (Shibahara, 2019; Aljohani et al., 2017). Depending on the strength, bisphosphonates can be given intravenously or orally. They are classified into nonnitrogen-containing or nitrogen-containing bisphosphonates (Shibahara, 2019; Ruggiero, 2009; Ruggiero et al., 2014). They are very effective at decreasing the possibility of fractures caused by osteoporosis as well as inhibiting the activity of osteoclasts. They work by inhibiting the remodeling mode and increasing the bone density.

Bisphosphonates have a high bone attraction, and interacting with hydroxyapatite crystals. As suggested by multiple studies, these drugs function by prohibiting resorptive activity and inducing apoptosis of osteoclasts (Lombard et al., 2016; Favia et al., 2018; Kuroshima et al., 2019a). Furthermore, they can have secondary effects, such as acting indirectly on osteoblasts by prohibiting differentiation. This effect is seen in the reduction caused by osteoclast cytokines that inhibit the capability of bone healing (Shibahara, 2019). The half-life of bisphosphonates can continue for or exceed a decade because of the great connection with bone crystals, although 95% of the drug is excreted within a few hours (Lombard et al., 2016; Favia et al., 2018).

The cytokine receptor activator of nuclear factor kappa B (RANK) and its ligand (RANKL), which are released by osteoblasts, are also used to control bone remodeling activity. This approach will increase resorption of bone or osteoprotegerin (OPG), enabling the prevention of resorptive bone action through inhibiting RANK/RANKL binding (Favia et al., 2018).

5.2. Denosumab

Denosumab is a recently developed antiresorptive drug. It acts on OPG produced by osteoblasts and is considered to be an anti-RANKL antibody (Shibahara, 2019). It functions to reduce the resorption of bone by inhibiting RANKL/RANK binding, thereby dysregulating the formation, differentiation, and osteoclast survival rate (Shibahara, 2019).

Denosumab has a short effect on bone, unlike the effects of bisphosphonates, because of its short half-life. Such RANKL inhibitors do not bind with bone and are generally eliminated within six months of cessation of treatment (Ruggiero et al., 2014).

Time of incidence is a major differentiating factor between BRONJ and denosumab-related osteonecrosis of the jaws (DRONJ). BRONJ can occur within 33 months (orally) and within 48 months (intravenously) (Shibahara, 2019). However, DRONJ often occurs soon after administration (McGowan et al., 2018).

Bisphosphonates have a direct effect by inducing osteoclast apoptosis, while denosumab indirectly prevents the maturation of osteoclast differentiation. Regardless of the mechanism, both cause delayed osseous healing (Kuroshima et al., 2016).

5.3. Angiogenesis Inhibitors or Antiangiogenic Drugs

These monoclonal antibodies medications target receptors of vascular endothelial growth factor (VEGF). VEGF inhibitors (e.g., bevacizumab) or tyrosine kinase inhibitors (e.g., sunitinib) are considered to be the most common antiangiogenic drugs (Kuroshima et al., 2019a; Kuroshima et al., 2019b).

Antiangiogenic drugs will inhibit the development of new blood vessels, which can result in ONJ through ischemia. These drugs are given to prevent cancer metastasis across the blood vessels and lymph nodes because angiogenesis by definition is the action on the formation of blood vessels by endothelial cell differentiation. This action can induce tumor diffusion through blood vessels and related lymph nodes, leading to tumor metastasis (Khan et al., 2017; Lombard et al., 2016). However, some studies have found that there is not enough knowledge regarding the pathophysiology of ONJ caused by angiogenesis inhibitors (Kuroshima et al., 2019a, 2019b).

5.4. Drugs Other Than Antiresorptive Drugs and Antiangiogenic Drugs

In addition to antiresorptive drugs and antiangiogenic drugs, some therapies, such as anti-interleukin-6-receptor (tocilizumab), have been used in the management of rheumatoid arthritis (RA), and there are few reports about MRONJ development in patients undergoing tocilizumab. However, all of these patients have a history of use of antiresorptive drugs and radiopharmaceuticals (Radium 223) in bone metastases

management. Based on current reports, the chance of MRONJ incidence in patients receiving radium 223 therapy is low and is considered to have an additive effect with antiresorptive drugs and mammalian target of rapamycin inhibitors (temsirolimus) in the treatment of advanced cases of renal cell carcinomas. There have been several articles about MRONJ incidence in patients treated with temsirolimus, but only one case of temsirolimus used medication alone. Selective estrogen receptor modulators (raloxifene) are used in the breast cancer management, and only one report has described MRONJ development in patients undergoing raloxifene therapy, but the patient also has a history of oral bisphosphonate (Bennardo et al., 2020b; King et al., 2019; Bindakhil and Mupparapu, 2018; Ebker et al., 2013; Fusco et al., 2016; Kim et al., 2013; Baur et al., 2015; Xie et al., 2016).

5.5. Infections and Inflammations

Infections and inflammation are associated with the pathogenesis of ONJ and are considered to be susceptible risk factors. The proinflammatory cytokine IL-36 α has a key role in the MRONJ incidence and is associated with remarkable upregulation, which is found in the infected periodontal tissue and gingival crevicular fluid. Notably, IL-36 α and TGF- β have

been proven to engage in crosstalk in these signaling pathways (Kim et al., 2017).

6. MRONJ Staging and Symptoms, Clinical and Radiographic Findings, and Treatment Strategies

MRONJ staging system and treatment strategies adopted by the AAOMS (Ruggiero et al., 2014) is as follows in Table 1.

6.1. Prevention

Because ONJ treatment is regarded as being difficult, efforts are focused on the prevention of ONJ with a multidisciplinary approach. Before starting antiresorptive therapy, patients should have a full oral examination with oral hygiene instructions, and educated about the chance of developing ONJ, the signs and symptoms, and the risk factors for developing ONJ (Khosla et al., 2007). Any necessary dental treatment, especially invasive procedures such as extractions, should be done before antiresorptive therapy starts (Ruggiero et al., 2009; Bagán et al., 2007). Careful dental preparation and oral hygiene instructions significantly reduce the risk of ONJ (Dimopoulos et al., 2009). The prescribing provider should be contacted before dentoalveolar surgery in cases on antire-

Table 1 MRONJ staging system and treatment strategies. Republished with permission from (Ruggiero et al., 2014); permission conveyed through Copyright Clearance Center (CCC), Inc.

MRONJ staging	Symptoms, clinical and radiographic findings	Treatment strategies
At risk category No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates		<ul style="list-style-type: none"> • No treatment indicated • Patient education
Stage 0 No clinical evidence of necrotic bone, but nonspecific clinical findings, radiographic changes, and symptoms	<p>Odontalgia/Dull, aching bone pain in the body of the mandible/Sinus pain/Altered neurosensory function/Loosening of teeth not explained by chronic periodontal disease/Periapical/periodontal fistula/Alveolar bone loss or resorption/Changes to trabecular pattern—dense woven bone and persistence of unremodeled bone in extraction sockets/Regions of osteosclerosis involving the alveolar bone and/or the surrounding basilar bone/Thickening/obscuring of periodontal ligament</p>	<ul style="list-style-type: none"> • Systemic management, including the use of pain medication and antibiotics
Stage 1 Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection	May also present with radiographic findings mentioned for Stage 0 which are localized to the alveolar bone region	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Clinical follow-up on a quarterly basis • Patient education and review of indications for continued bisphosphonate therapy
Stage 2 Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	Typically, symptomatic/ May also present with radiographic findings mentioned for Stage 0 that are localized to the alveolar bone region.	<ul style="list-style-type: none"> • Symptomatic treatment with oral antibiotics • Oral antibacterial mouth rinse • Pain control • Debridement to relieve soft tissue irritation and for infection control
Stage 3 Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following findings in the next column:	<ol style="list-style-type: none"> 1- Exposed necrotic bone extending beyond the region of alveolar bone, i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla 2- Pathologic fracture 3- Extraoral fistula 4- Oral antral/oral nasal communication 5- Osteolysis extending to the inferior border of the mandible or sinus floor 	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Antibiotic therapy and pain control • Surgical debridement/resection for longer term palliation of infection and pain

sorptive therapy for more than three years to discontinue antiresorptive medication for two months before oral surgery (i.e., a drug holiday). Intravenous antiresorptive therapy and ongoing cancer therapy are absolute contraindications for any dental surgery including implant placement (Hwang and Wang, 2006). Fortunato et al. stated that the application of autologous platelet concentrates could be helpful in the prevention of MRONJ due to their local immunomodulatory properties and possible angiogenesis acceleration (Fortunato et al., 2020).

6.2. Management

According to the AAOMS, the management of ONJ ranges from conservative to surgical therapy based on severity Table 1. For stage I and II, conservative treatment was recommended; however, in stage III and in case of no response to conservative therapy in stage II, surgical debridement was recommended.

Bennardo et al. diagnosed eight patients with stage 3 MRONJ with facial cutaneous sinus tract. Those patients underwent medical and surgical treatment in combination with platelet-rich fibrin (PRF) injections once a week for one month starting from the same day of the surgical procedure. This study suggests that when (PRF) is combined with successful surgical and medical care, it can improve the healing of the facial sinus tract secondary to MRONJ (Bennardo et al., 2020a). According to a recent systematic review, the effectiveness of PRF in the treatment of MRONJ is still insufficient (Fortunato et al., 2020). Moreover, autofluorescence-guided surgery did not add any beneficial value compared with conventional surgical techniques regarding healing process and quality of life (Giudice et al., 2018).

6.3. Drug Holiday

It is still uncertain whether the discontinuation of antiresorptive therapy is effective for the prevention or reduction of ONJ. Studies vary regarding the considered effect of drug cessation from no effect to minimal effect or based on the staging condition. The AAOMS suggested interrupting oral bisphosphonate treatment for three months prior to invasive dental surgical procedures and three months after to decrease the possibility of ONJ (Ruggiero et al., 2009). This information was last revised in 2009. However, because there is not enough evidence to support the drug holiday's efficacy, this decision should be made in consultation with the prescribing physician (Yamashita and McCauley, 2012). Another option could be treating patients with lower cumulative doses (two years) of bisphosphonates or denosumab and continuing treatment during surgical dental procedures. This approach was suggested by the ADA Council on Scientific Affairs after reviewing their previous recommendations on drug holidays (Hellstein et al., 2011). Until now, there has been much controversy and no clear evidence regarding drug holidays (Lee et al., 2015). However, recently, some studies concluded that a 50% reduction in ONJ incidence was observed when a drug holiday was applied to a minipig model (Otto et al., 2020).

6.4. Conclusion

Regardless of the association between jaw necrosis and antiresorptive/ antiangiogenic medications, the pathophysiology and mechanism of medication-related osteonecrosis of the jaw is not fully understood. Bisphosphonates, on the other hand, have been used to treat several bone disorders and cancers. Moreover, many patients are taking bisphosphonates as part of their therapy. The most common group consists of postmenopausal females as a treatment for osteoporosis. A collaborative approach including dentists, physicians, and pharmacists is deemed to be critical to preventing the development of MRONJ.

Acknowledgements

All persons who have made substantial contributions to the work reported in the manuscript (e.g., technical help, writing and editing assistance, general support), but who do not meet the criteria for authorship, are named in the Acknowledgements and have given us their written permission to be named. If we have not included an Acknowledgements, then that indicates that we have not received substantial contributions from non-authors.

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