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# Medication-Related Osteonecrosis of the Jaw – 2024 Update

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## ABSTRACT

*As the global number of patients with osteoporosis and malignant diseases such as breast cancer, multiple myeloma, and prostate cancer increases every year, there is an associated rise in the use of antiangiogenic medications and antiresorptive medications. With increasing frequencies in the use of antiangiogenic and antiresorptive medications, there is an associated increase in the number of medication-related osteonecrosis of the jaw (MRONJ) cases reported from patients. MRONJ has emerged as a significant comorbidity in cancer patients treated with antiangiogenics or high doses of potent antiresorptive agents, such as bisphosphonates (BPs) or denosumab. MRONJ first emerged from BP-treated cancer patients who presented with a spectrum of dental problems, including delayed wound healing following a dental extraction or oral surgery, exposed bone, soft tissue infection and inflammation, anesthesia, paresthesia, odontalgia, sinus pain, and aching bone pain in the mandible, which continues to be a significant source of problems for dentists, physicians, and patients today. A significant number of MRONJ cases secondary to osteoporosis have also been reported in osteoporotic patients receiving antiresorptive medications. The American Association of Oral and Maxillofacial Surgeons (AAOMS) has established diagnostic standards for MRONJ based on pharmacological history, clinical signs, and radiographic findings. However, as the expertise and knowledge base for MRONJ continues to evolve, revisions and refinements for MRONJ pathogenesis and treatment strategies are necessary to reflect the current research status of the disease correctly. This review highlights current scientific information associated with MRONJ to identify and summarize preventative measures, and treatment interventions for reading the impact of this debiliating disorders.*

## Keywords

Malignant diseases, Osteonecrosis, BP.

## Background

As the global number of patients with osteoporosis and malignant diseases such as breast cancer, multiple myeloma, and prostate cancer increases every year, there is an associated rise in the use of antiangiogenic medications and antiresorptive medications. With increasing frequencies in the use of antiangiogenic and antiresorptive medications, there is an associated increase in the number of medication-related osteonecrosis of the jaw (MRONJ) cases reported from patients [1]. MRONJ has emerged as a significant comorbidity in cancer patients treated with high doses of potent antiresorptive agents, such as bisphosphonates (BPs) or denosumab [1-3]. The first case of MRONJ was in BP-treated cancer patients in 2003 [4] who presented with a spectrum of dental problems, including delayed wound healing following dental extraction or oral surgery, exposed bone, soft tissue infection and inflammation, anesthesia, paresthesia, odontalgia, sinus pain, and aching bone pain in the mandible; which continues to be a significant source of problems for dentists, physicians, and patients today [3,4]. A notable number of MRONJ cases secondary to osteoporosis have also been reported in osteoporotic patients receiving antiresorptive medications (e.g., BPs and denosumab).

MRONJ significantly deteriorates the overall oral health-related

quality of life, hinders the attainment of ideal dental treatment, and diminishes the ability to perform everyday activities. This is primarily attributed to impaired chewing functionality and jawbone defects resulting from surgical intervention(s) and/or the progressive advancement of MRONJ [2,3,5]. Unfortunately, there is limited scientific knowledge about the underlying causes and definitive treatment options for MRONJ. While various therapies have been attempted, the current methods need more scientific evidence to establish their effectiveness [3]. The American Association of Oral and Maxillofacial Surgeons (AAOMS) has established diagnostic standards for MRONJ based on pharmacological history, clinical signs, and radiographic findings. However, as the expertise and knowledge base for MRONJ continues to evolve, it is crucial to understand the exact mechanisms and develop effective treatment strategies for MRONJ to reflect the current research status of the disease correctly [2,5]. This manuscript aims to comprehensively review current scientific information associated with MRONJ to determine all causative agents and summarize the latest preventative measures, diagnostic standards, and treatment interventions for MRONJ.

## Summaries and Updates

Each subheading below begins with a short paragraph discussing the state of knowledge for that area as published in the literature through 2020. This is followed by published updates to this information from 2021 through the time of publication of this review.

### *Diagnostic Criteria and Stages of MRONJ*

According to the American Academy of Oral and Maxillofacial Surgeons (AAOMS), a patient must meet all the following elements of the case definition of MRONJ to establish a correct MRONJ diagnosis [3]:

1) Previous or current use of antiangiogenic or antiresorptive medications alone or in combination with antiangiogenic medications or immune modulators;
2) More than eight weeks of persistent oral bone exposure that can be probed through a maxillofacial extraoral or intraoral fistula; and
3) No history of jaw radiation therapy or metastatic disease to the jaw.

Ruggiero et al. [3] developed the MRONJ staging system in 2006, which was introduced and adopted by the AAOMS in their 2009 MRONJ position paper, which was then updated in the AAOMS' 2014 MRONJ position paper [4]. The 2014 AAOMS staging system has proven to be a straightforward and valid system that successfully stratifies the different stages of MRONJ. As a result, the AAOMS has chosen to keep the current classification system in place with no changes [3,4]. The classification of MRONJ (2014 AAOMS staging system) is as follows:

- Patients at risk: Those treated with oral or intravenous bisphosphonates but do not show any apparent necrotic bone.
- Stage 0: No clinical signs of necrotic bone, but there may be nonspecific clinical findings, radiographic changes, and symptoms.
- **Stage 1:** Asymptomatic patients with exposed and necrotic bone or fistulas that probe to the bone but with no evidence of infection.
- **Stage 2:** Infection is present, as indicated by pain and redness in the area of exposed bone, along with exposed and necrotic bone or fistulas probing the bone. Purulent drainage may or may not be present.
- **Stage 3:** Patients experience pain infection and have one or more of the following: exposed and necrotic bone extending beyond the alveolar bone area (such as the inferior border and ramus in the mandible, the maxillary sinus, and the zygoma in the maxilla) causing pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor [3].

### Imaging

To assess patients with MRONJ or suspected cases, orthopantomography is crucial and should be the initial investigative method. A general overview of the whole mandible and maxilla can be visualized and observed through orthopantomographic, panoramic examination. Radiographic characteristics such as sclerotic bone, or a combination of radiopaque and radiolucent lesions, along with the presence of a nonhealing extraction socket, are commonly present in the early stages of MRONJ. The orthopantomogram (Figure 1) shows osteosclerosis in the body of the left mandible with diffuse radiolucency, indicating a change in bone mineralization [6]. The radiographic presentation in advanced stages of MRONJ may including sequestrum formation, lamina dura thickening, and pathological fractures [7,8]. For a more thorough examination, digital imaging techniques such as computed tomography (CT) and cone-beam CT (CBCT) can produce high-quality tomographic images that reveal the presence of MRONJ lesions [7,9]. Signs such as diffuse osteosclerosis, bone resorption, degeneration of cortical bone, periosteal reaction, and bone fistulas can indicate the spread and extent of the lesion [7].

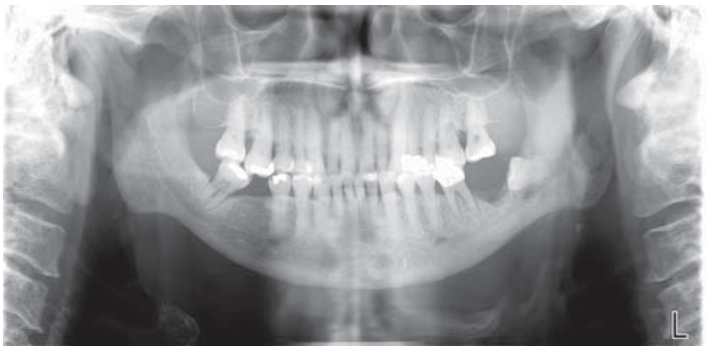

**Figure 1:** The Radiographic Presentation of MRONJ.

Panoramic radiograph of MRONJ. Focal osteosclerosis is observable in the posterior body of the left mandible with diffuse radiolucency. Reprinted from "Medication-Related Osteonecrosis of the Jaw: Update and Future Possibilities," by J. L. Borke, 2018, *Journal of the California Dental Association, Vol. 46* (Issue 5), pages 301-305. Copyright 2018 by the Journal of the California

Dental Association. Reprinted with permission [6].

CT imaging has become the standard method for detecting the most common characteristics of MRONJ, which include osteolysis and osteosclerosis [10,11]. Due to its ability to visualize a larger area than what can be seen clinically, CT can accurately determine the extent of the lesion(s) [10]. Unlike panoramic radiographs, CT is also effective in detecting MRONJ signs such as changes in trabecular bone density and bone sequestrum/sequestra [10,11]. In a clinical trial involving 28 MRONJ patients [12], CT showed a higher sensitivity in detecting MRONJ at 96%, compared to 54% for panoramic radiographs and 92% for MRI [10]. For staging purposes, CT imaging is highly recommended [10,11].

As such, a secondary-level examination is sometimes necessary for suspected cases of MRONJ to provide further comprehensive diagnostic imaging to confirm suspected MRONJ diagnoses. CT imaging achieves this by visualizing images with radiological findings that are generally more comprehensive than orthopantomography and serves as a conclusive component of the overall radiological assessment [4]. Advanced investigations (e.g. MRI and PET) are typically reserved for unclear cases or to differentiate MRONJ from other conditions, such as distant solid malignant bone metastases [4]. However, MRI's diagnostic effectiveness in detecting MRONJ has yet to be fully established [7].

### *New insights into the pathogenesis of MRONJ*

The exact pathogenesis of MRONJ remains unclear [1,3]. However, there are several proposed hypotheses for MRONJ pathogenesis from researchers, which are associated with the over-suppression of bone resorption, soft tissue BP toxicity, constant microtrauma, inhibition of angiogenesis, suppression of innate or acquired immunity, vitamin D deficiency, alterations in bone remodeling, and infection or inflammation [1,3,13]. Thus, it is critical to develop a more scientifically sound understanding of the pathogenesis of MRONJ to assist in the development of future MRONJ treatment interventions [14].

## *Antiresorptive Drugs and MRONJ*

### Bisphosphonates

An essential component of the pharmacology of BPs is that they have a high affinity for bone, especially for bone with high rates of bone remodeling, such as alveolar bone in the mandible [15,16]. BPs have a high affinity to bone tissue rather than other types of tissue because they are site-specific and naturally bind to hydroxyapatite crystal binding sites that are predominantly abundant in skeletal sites with active bone remodeling, such as the alveolar regions of the mandible [15,16]. The significant factors required for high BP-bone retention are high rates of bone turnover and the amount of bone surface available.

The bioavailability of BPs is a significant feature that governs its pharmacology [1,17,18]. BPs can be given as intravenous infusions, or they can be taken orally. However, oral BPs have an intestinal absorption rate of only <1-3%, with only 50% of the absorbed drug selectively retained by the skeleton and the remainder excreted out of the body as urine [1,17,18]. This is because BPs are polar with a negative charge, which prevents them from paracellular transportation between the cells of the intestinal epithelia. In addition, BPs are lipophilic, so they cannot perform transcellular transport through the intestinal epithelial cell membranes [1,17,18]. This inhibition of both methods of intestinal diffusion based on the properties of BPs may explain the drug's poor absorption rate and limited bioavailability when taken orally. In contrast, approximately 50% of intravenously administered BPs are readily bioavailable to bind to their bone target cells compared to the minuscule <1% bioavailability seen in orally administered BPs. This is in line with the clinical finding that MRONJ occurs most in individuals who receive intravenously administered BPs.

BPs can only bind to bone hydroxyapatite crystal binding sites in a neutral pH environment [19-21] and are rendered inactive until activation through acidic milieus. These aforementioned pharmacological mechanisms take place physiologically where BPs locally accumulate, which is in Howship's lacunae of bone; during osteoclastic bone resorption, an increase in pH value has been reported to cause the release and activation of BPs that allows for the exertion of the drug's effects [19-21]. This mechanism between BPs and their method of activation through acidic milieus has not been associated with MRONJ until recently [19]. It may play a substantial role in the multifactorial etiology of MRONJ manifestation and its localization to the jawbone. Sato and colleagues [20,22] justified these BP activation claims through acidic milieus in their rat model experiments. These activating, acidic conditions occur most often in the jawbone due to the oral cavity's high susceptibility to apical infections, marginal infections, and dento-alveolar surgeries (post-op infections); especially regarding dental extractions [19]. These different types of infections, whether individually present or all present, all result in the same effect: the local acidification of jaw bone areas that leads to the release and activation of BPs to possibly even toxic levels that lead to MRONJ [20]. With a dental extraction-induced, acidic-infectious environment of the jaw with localized soft tissue toxicity (from locally concentrated BPs), antiangiogenic BP effects, BP-induced osteoclastic inhibition, and even further local accumulation of BPs targeting and binding to more and more alveolar bone with high rates of bone remodeling in the jaw, there is a resulting multifactorial cascade of processes that each may cumulatively contribute to explain why the jawbone is exclusively targeted by MRONJ.

### Denosumab

Denosumab is a commonly used alternative antiresorptive agent that is a fully humanized antibody against RANKL and inhibits osteoclast function and its associated bone resorption process [3,23,24]. RANKL is secreted by bone marrow stromal cells and osteoblasts, and under normal conditions, RANKL binds to the RANK receptor on osteoclasts and promotes osteoclast differentiation and activity [25]. However, denosumab blocks the binding of RANKL to RANK on osteoclasts by having RANKL bind to denosumab directly rather than RANKL binding to RANK

receptors, which inhibits and slows osteoclast resorption [3]. Denosumab is administered subcutaneously every six months to reduce the risk of hip, vertebral, and non-vertebral fractures for individuals diagnosed with osteopenia or osteoporosis [3,26]. In contrast to BPs, RANK ligand inhibitors do not bind directly to bone, and their bone remodeling effects diminish within six months of treatment cessation [3,26,27]. In addition, Limones et al. [1] reported that the incidence of MRONJ is significantly greater with denosumab than with ZA.

### *Antiangiogenics and MRONJ*

Angiogenesis is the formation of new of new blood vessels [28]. Angiogenesis inhibitors (antiangiogenic medications) such as human monoclonal antibodies, vascular endothelial growth factor (VEGF) inhibitors, thalidomide, mTOR inhibitors, and tyrosine kinase inhibitors interfere with the formation of new blood vessels by binding to various signaling molecules that disrupts the angiogenesis-signaling cascade [28]. These novel medications have demonstrated efficacy in treating gastrointestinal tumors, renal cell carcinomas, and neuroendocrine tumors. However, exposure to antiangiogenic medications is associated with an increased risk of the manifestation of exposed maxillofacial bone that leads to MRONJ [3,28].

### *New Insights into Mechanisms Underlying the Development of MRONJ*

#### Local Factors

In a retrospective study with 240 MRONJ patients [29], it was found that dental extractions preceded the development of MRONJ in 40% of the cases. When analyzing the combined data from three phase III trials that resulted in the approval of denosumab for preventing skeletal-related events (SREs), it was observed that a dental extraction had occurred prior to the onset of MRONJ in 61.8% of the cases [29]. It has also been observed that denture usage increases the likelihood of developing MRONJ. Patients with pre-existing oral conditions such as periodontal disease or periapical pathology are at a heightened risk of developing MRONJ [29]. Observational data from real-world studies on the use of zoledronic acid in cancer patients has revealed that undergoing an invasive dental procedure is linked to a 4.67-fold increased risk of developing MRONJ (95% CI, 1.75-12.42; p=0.002) [29,30]. Patients with concomitant oral conditions, such as periodontal disease or periapical pathology, are predisposed to a heightened risk of developing MRONJ [31].

#### Systemic Factors

Prolonged use of BPs is correlated with a higher risk of MRONJ, especially when taken for over four years [32,33]. The risk of MRONJ is also elevated with the simultaneous use of steroids and BPs [34], which may weaken immunity and hinder wound healing [19,35]. Furthermore, MRONJ has been associated with older age, particularly individuals over 65 years old [34,36], and the presence of diabetes mellitus [37].

### *New Recommendations for the Prevention of MRONJ*

The AAOMS panel suggests a collaborative approach involving dental and medical professionals who prescribe the related medications to prevent ONJ effectively. It is crucial to prioritize overall health optimization, specifically focusing on dental health. Educating patients about the potential risks of medication therapy and the impact of compromised oral health is essential at all stages of care. Prior to initiating antiresorptive treatment, it is recommended to address any existing periapical or periodontal inflammation to reduce the likelihood of future extractions or other bone trauma [3,38].

Different preventative approaches have been used in cases where dentoalveolar surgery is necessary after starting antiresorptive therapy, such as minimal access surgery, perioperative antibiotics, antimicrobial rinses, and closing extraction sites. The level of evidence supporting the "drug holiday" concept is limited, and therefore, the AAOMS panel has not reached a consensus on its recommendation [3,38]. There is currently no validation for using bone turnover markers to determine the optimal timing for dentoalveolar surgery in patients using antiresorptive agents. Recently, biomarkers associated with angiogenesis, VEGF activity, endocrine function, and PTH have been identified. However, these biomarkers are still in the exploratory phase and have not yet been validated for clinical use [3].

### *New Management and Treatment Options for MRONJ*

MRONJ treatment options and management strategies include operative and nonoperative therapies. Both operative and nonoperative therapies are viable and accepted management forms for all MRONJ stages. In the context of reducing MRONJ-associated acute inflammatory signs, infection, and pain in the early asymptomatic stages of MRONJ, the literature supports the non-invasive/nonoperative treatment approaches, especially in MRONJ patients with risky comorbidities that prevent the option of operative therapy [39]. Nonoperative therapies for MRONJ include patient reassurance, patient education, and the management of pain and secondary infections [3,40]. Other forms of the conservative management of MRONJ include hyperbaric oxygen therapy [41] and ozone therapy [42] to stimulate the proliferation of new cells and soft-tissue healing required to ameliorate MRONJ pain. Low-level laser therapy (LLLT) is a form of nonoperative/noninvasive therapy that has been reported [43-45] to have positive biostimulatory effects on the reparative process of MRONJ by increasing inorganic bone matrix, increasing osteoblastic mitotic index, and stimulating blood and lymphatic capillary growth [46]. Systemic antibiotics (metronidazole penicillin or clindamycin), antimycotic agents (nystatin, fluconazole, or ketoconazole) [47], and oral rinses (hydrogen peroxide or chlorhexidine gluconate) are used to treat patients with MRONJ bone exposure [3,45]. MRONJ patients are generally advanced in age and have risky comorbidities such as cancer that require chemotherapy [48], which compromises the health status of these patients and renders them unable to bear the side effects associated with a prolonged or permanent antibiotic schedule. In many cases with patients with late-mid stage MRONJ (e.g., Stage II Refractory – Stage III) or reoccurring MRONJ, surgical management of MRONJ

is recommended [3]. Surgical management of MRONJ includes surgical resection or debridement in combination with antibiotic therapy, high-level laser surgery (when antibiotic therapy and LLLT fail), and an autofluorescence-guided surgical approach performed with Er:YAG laser [3,49].

## Conclusion

There is a strong correlation between bisphosphonates, antiresorptive medications, and antiangiogenic drugs and jaw necrosis. As the elderly population is predicted to double by 2050, the usage of these medications, and hence the associated side effects, are expected to rise. Prevention is an essential factor in managing MRONJ. Consequently, determining a suitable and effective treatment for MRONJ is yet to be determined.

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