Content available at: https://www.ipinnovative.com/open-access-journals

Journal of Oral Medicine, Oral Surgery, Oral Pathology and Oral Radiology

Journal homepage: http://www.joooo.org

Review Article

Medication induced osteonecrosis of jaw: A detailed review

Niketan Deokisan Durge[1]*, Deepa Das[1]

[1]Dept. of Oral Medicine and Radiology, YMT Dental College & Hospital, Navi Mumbai, Maharashtra, India

Abstract

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but serious condition associated with antiresorptive and antiangiogenic drugs, commonly used in treating osteoporosis and various cancers. The pathogenesis is multifactorial, involving impaired bone remodelling, infection, reduced angiogenesis, and immune suppression. MRONJ is more prevalent among cancer patients than those treated for osteoporosis. Clinically, it presents with exposed necrotic bone, pain, swelling, and secondary infections, significantly affecting the quality of human life. Diagnosis is clinical, supported by imaging and patient history. Management includes conservative or surgical approaches, with prevention being the most effective strategy. A multidisciplinary approach involving dentists, oncologists, and oral surgeons is essential for early diagnosis and treatment planning to minimize complications and improve patient outcomes. The purpose of this review is to shed light on the road map for clinical and radiographic diagnosis, prevention, and management of medication-related osteonecrosis of the jaw (MRONJ).

Keywords: MRONJ, Osteonecrosis, Bisphosphonates, Denosumab, Jaw necrosis, Antiresorptive therapy.

Received: 24-07-2025; **Accepted:** 15-09-2025; **Available Online**: 29-09-2025

1. Introduction

The term "medication-related osteonecrosis of the jaw" (MRONJ) refers to osteonecrosis of the jaw caused by denosumab, bisphosphonates, and anti-resorptive medications.[1] Medication-related osteonecrosis of the jaw is a rare but serious and disabling condition. Its etiology is unknown, however it can have multiple causes. MRONJ is characterised by exposed bone that does not heal in patients who have a history of radiation exposure to the head and neck but who are currently using anti-resorptive or antiangiogenic drugs.[2]

In the early years of the twenty-first century, Marx documented the first instance of MRONJ in a study about nonhealing exposed bone in the craniofacial region of a patient receiving treatment with a bisphosphonate, an antiresorptive drug that influences the breakdown of the bone's mineral content.[3-8] Dental professionals and academics are still interested in bisphosphonate-related osteonecrosis of the jaw (BRONJ), which was initially described in 2003. However, independent findings of bone necrosis linked to denosumab prompted the American Association of Oral and Maxillofacial Surgeons (AAOMS) to rename BRONJ to MRONJ in 2014.[9]

Patients with medication-related osteonecrosis of the jaw (MRONJ), experience progressive bone loss in the craniofacial region. Two pharmacological agents, namely antiresorptive (such as bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors) and antiangiogenic, have the potential to cause osteonecrosis. The pathogenesis of MRONJ is not well understood. Its specific location in the jaws has been explained by a number of theories, including: infection or inflammation, micro trauma, altered bone remodelling or excessive suppression of bone resorption, inhibition of angiogenesis, toxicity of soft tissue blood products, unusual oral biofilm, terminal

*Corresponding author: Niketan Deokisan Durge
Email: niketandurge3@gmail.com

https://doi.org/10.18231/j.jooo.79495.1759120703

vascularization of the mandible, immune suppression, or a vitamin D deficiency.

2. Discussion

2.1. Epidemiology and incidence

As highlighted by Robert S. Weinstein, osteonecrosis is known by various terms such as aseptic, avascular, or ischemic necrosis, which should be considered in epidemiological research. From 1989 to 2003, its incidence increased from 1.4 to 3 per 100,000 annually, likely due to greater use of MRI for diagnosis.[10] Drescher et al. observed that glucocorticoid-induced osteonecrosis is dose and duration dependent, but may also occur after intra-articular injections or short-term high doses. Intra-articular steroids can worsen Charcot's arthropathy by masking pain and promoting joint overuse.[11] Edwards, B.J. et al, reported that in cancer patients, the incidence of MRONJ varies from 0.1% to 10%, in investigator-initiated academic research, significantly higher percentages were noted.[12]

2.2. Pathophysiology

The pathophysiology of MRONJ is multifactorial, involving the interplay of impaired bone remodelling, vascular compromise, local infection or inflammation, immune dysregulation, and genetic susceptibility.

1. Inhibition of bone remodelling: Antiresorptive agents such as bisphosphonates (BPs) and denosumab (DMB) suppress osteoclast function, reducing bone turnover. This leads to the accumulation of microdamage and necrotic bone, particularly in high-turnover areas like the jaw.[14,15]
2. Glucocorticoid effects: Glucocorticoids induce apoptosis in osteoblasts and osteocytes and disrupt the lacunar–canalicular network, impairing mechanosensing and vascular exchange. This weakens bone quality and contributes to necrosis.[16,17]
3. Infection and inflammation: Dental procedures such as extraction often occur at sites of existing periodontal or periapical infection. Inflammatory cytokines further drive bone necrosis. Animal models confirm that inflammation significantly contributes to MRONJ development.[19,20]
4. Angiogenesis inhibition: Both BPs and antiangiogenic drugs reduce local vascularity, delay healing, and contribute to ischemic bone changes, mimicking avascular necrosis.
5. Immune dysfunction: Conditions like diabetes, cancer, or autoimmune diseases impair host defenses, increasing MRONJ risk, especially in patients on immunosuppressive therapies.[18]
6. Genetic factors: Single-nucleotide polymorphisms (SNPs) in genes such as *SIRT1*, *PPARγ*, and *CYP2C8* affect bone turnover, angiogenesis, and immune response, potentially increasing susceptibility to MRONJ.[13]

2.3. Clinical manifestations and staging

Italian Society of Maxillofacial Surgery (SICMF)/Italian Society of Oral Pathology and Medicine (SIPMO) and the American Association of Oral and Maxillofacial Surgeons (AAOMS) given different classification system for the MRONJ which are as follows:

Table 1: Different bisphosphonate related osteonecrosis of the jaw staging systems[13]

Stage	Marx 2007	AAOMS 2009	SICMF-SIPMO 2012
At risk category		No evidence of exposed or necrotic bone in patients who have been treated with bisphosphonates.	
Stage 0	Subclinical damage, microscopically represented by beginner hypocellularity osteoclast apoptosis and decrease of endosteal osteoblast.	Nonspecific clinical findings and symptoms such as jaw pain or osteosclerosis but no clinical evidence of exposed bone.	
Stage 1	A: Painless exposed bone of 1 cm. B: Painless exposed bone >1 cm.	Exposed/necrotic bone in patients who are asymptomatic and who have no evidence of infection.	Focal BRONJ clinical signs and symptoms: Bone exposure, sudden dental mobility, nonhealing postextraction socket, mucosal fistula, swelling, abscess formation, trismus, gross mandibular deformity, and/or hypoesthesia/ paraesthesia of the lips. CT findings: The following symptoms may or may not accompany increased bone density restricted to the alveolar bone region (trabecular thickening and/or focal osteosclerosis). Persistent alveolar socket, cortical rupture, and/or noticeably enlarged and sclerotic lamina dura. 1a: Asymptomatic 1b: Symptomatic (pain and purulent discharge).

Table 1 Continued….			
Stage 2	A: Painful and infected single exposed bone of 2 cm. B: Painful and infected single exposed bone >2 cm.	Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage.	Diffuse BRONJ Clinical signs and symptoms: The same as Stage 1 CT findings: Diffuse osteosclerosis is characterised by increased bone density that extends to the basal bone, with or without the following symptoms: oroantral fistula, sinusitis, periosteal reaction, sequestra development, and/or prominence of the inferior alveolar nerve canal. 1a: Asymptomatic 1b: Symptomatic (pain and purulent discharge).
Stage 3	A: Multiple exposed bone areas without clinical findings of osteolysis, orocutaneous fistula, or pathological fractures. B: Exposed bone >3 cm or with clinical findings of osteolysis, or orocutaneous fistula, or pathological fractures.	Exposed/necrotic bone in patients with pain, infection, and one or more of the following: Pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border or sinus floor.	Complicated BRONJ- The same as Stage 2, with one or more of the following. Clinical signs and symptoms: Extraoral fistula, displaced mandibular stumps, nasal leakage of fluids. CT findings: Pathologic mandibular fracture, osteolysis that extends to the sinus floor, and osteosclerosis of nearby bones (hard palate, zygoma).

2.4. Radiographic finding

2.4.1. Early radiographic changes

These are often subtle and may precede clinical symptoms.

1. Widened periodontal ligament (PDL) space – earliest change
2. Thickening or sclerosis of the lamina dura
3. Loss of trabecular detail
4. Localized rarefaction of bone (early radiolucency)
5. No clear border between normal and necrotic bone

2.4.2. Intermediate/established stage

This stage presents with classic features of necrotic bone and reactive bone changes.

1. Mixed radiolucent and radiopaque areas
   a. Indicates necrotic bone (lucent) and sclerotic, non-vital bone (opaque)
2. Sequestrum formation
   a. Radiopaque dead bone fragment
   b. Surrounded by a radiolucent halo due to granulation or pus
3. Cortical disruption or irregularity
   a. Especially in mandible
   b. Persistent alveolar sockets
4. Non-healing extraction sites
5. Periosteal reaction (rare; more in younger or immunocompromised)
6. Loss of lamina dura and indistinct cortical bone margins

2.4.3. Advanced/chronic stage

Reflects extensive bone necrosis and secondary infections.

1. Large areas of bone destruction (radiolucency)
2. Diffuse sclerosis – “moth-eaten” or “cotton-wool” appearance
3. Pathological fracture may be seen in mandible
4. Sinus tract or oroantral fistula – radiolucent track extending to soft tissue
5. Bone resorption without new bone formation
6. Maxillary sinus involvement if maxilla is affected

2.5. Risk factor

There are two pharmacological substances that can cause osteonecrosis of the jaw (**Table 2**). Antiangiogenic and antiresorptive (including bisphosphonates (BPs) and inhibitors of the receptor activator of nuclear factor kappa B ligand [RANK L]).[13]

2.6. Local factors

1. Dentoalveolar operations
2. Anatomic factors
3. Concomitant oral diseases
4. Demographic and systemic factors and other medications.

Table 2: Medication-related osteonecrosis of the jaw-related medications[13]

Molecule	Category	Indication
Alendronate	Bisphosphonate	Osteoporosis
Bevacizumab	Humanized monoclonal antibody	Metastatic colorectal carcinoma, non-squamous non-small cell lung carcinoma, glioblastoma, metastatic renal cell carcinoma
Denosumab	Receptor activator of nuclear factor kappa-B-ligand inhibitors	Bone metastases osteoporosis
Ibandronate	Bisphosphonate	Osteoporosis
Neridronate	Bisphosphonate	Osteogenesis imperfecta, Paget's disease
Pamidronate	Bisphosphonate	Bone metastases
Risedronate	Bisphosphonate	Osteoporosis
Sirolimus	Mammalian target of Rapamycin pathway	Organ rejection in renal transplant
Sorafetib	Tyrosine kinase inhibitors	Hepatocellular carcinoma, renal cell carcinoma
Sunitib	Tyrosine kinase inhibitors	Gastrointestinal stromal tumor, renal cell carcinoma, pancreatic neuroendocrine tumor
Tiludronate	Bisphosphonate	Paget's disease of bone
Zoledronate	Bisphosphonate	Bone metastases osteoporosis

MRONJ Grades	Treatment
At risk:	- No treatment indicated. - Preventive patient education.
Grade 0	- Systemic management, including painkillers and antibiotics.
Grade 1	- Clinical follow-up with quarterly antibacterial mouthwashes. - Patient education and review of indications for continuous therapy with bisphosphonates.
Grade 2	- Symptomatic treatment with antibiotics. - Antibacterial mouthwash. - Pain management. - Debridement to relieve soft tissue irritation and infection control.
Grade 3.	- Antibacterial mouthwash. - Antibiotic therapy and pain management. - Surgical debridement or resection to alleviate long-term infection and pain.

Figure 1: Recommended treatments according to the grade or stage of MRONJ.[4]

Treatment strategies for medication-related osteonecrosis of the jaws:

The major goals of treatment for patients at risk of developing or who have established MRONJ are:

1. Ensuring continuation of cancer therapy
   a. For oncology patients receiving antiresorptive drugs, either alone or combined with immune modulators or antiangiogenic agents, it is crucial to maintain their treatment.
   b. These medications help manage bone pain and reduce the risk of skeletal-related events (SREs), thereby enhancing treatment outcomes.
2. Supporting bone health in non-cancer conditions
   a. Patients with conditions like osteoporosis, osteopenia, or other metabolic bone disorders gain significant benefits from antiresorptive therapy.
   b. These treatments lower the risk of fragility fractures and support long-term skeletal integrity.
3. Enhancing quality of life
   a. Key supportive measures include:
      i. Educating patients about MRONJ and addressing their concerns
      ii. Effective pain management
      iii. Prompt control of infections
      iv. Preventing the spread of necrosis and avoiding the formation of new lesion.

MRONJ Stages	Treatment
Stage 1	1. Quantification in millimeters of the exposed area. 2. If possible, stop treatment with anti-resorptive or antiangiogenic drugs. 3. Rinses with 0.12% or 0.2% chlorhexidine every 12 h for 15 days. 4. Control at 15 days: - Equal or smaller size: maintain treatment for another 15 days. - Increased exposure: apply stage 2 treatment. 5. Control at one month.
Stage 2	1. Points 1–3 as in stage 1. 2. Empirical antibiotic therapy (when no culture or antibiogram is available): - Amoxicillin/clavulanic acid 2000/125 mg, every 12 h for 15 days. - Allergic patients: Levofloxacin 500 mg every 24 h for 15 days. - Alternative: Azithromycin. 3. Administer oral nonsteroidal anti-inflammatory drugs (NSAIDs). 4. Control at 15 days: - Improvement: move to stage 1 treatment. - Equal or worse: maintain treatment for another 15 days and request computed tomography (CT). 5. Control at one month: - Improvement: move to stage 1 treatment. - Equal or worse: move to stage 3 treatment.
Stage 3	1. Point 1–3 as in stage 1. 2. Point 2 and 3 as in stage 2. 3. Under local anesthesia, eliminate bone sequestration and extraction of teeth involved if necessary, irrigation of the surgical bed with 0.12% chlorhexidine and suture with resorbable material. 4. Control at 15 days: - Improvement: maintain antibiotics, anti-inflammatories and rinses for another 15 days. - Equal or worse: maintain antibiotics, anti-inflammatories, and rinses for another 15 days. - Control at one month - Improvement: implement preventive measures and reinstate treatment with anti-resorptive or antiangiogenic drugs. - Equal or worse: new conservative surgery in serious circumstances: Pathological fracture: curettage of necrotic bone tissue and reconstruction plate (avoid grafts). Involvement of inferior border: block resection and reconstruction plate. Extraoral fistula: debridement to eliminate necrotic bone causing mucous irritation.

Figure 2: The Spanish society of oral and maxillofacial surgery (SECOM) recommends the following protocol for the treatment of MRONJ.[2]

Prevention method of medication-related osteonecrosis of the jaws:

General advice:

1. Perform dental screening before starting antiresorptive/antiangiogenic therapy.
2. Throughout treatment, practice proper oral hygiene and refrain from invasive dental procedures.
3. "Drug holidays" are controversial and not routinely recommended.

Cancer patients starting IV therapy:

1. Dental exam before treatment to eliminate infections or risky teeth.
2. Delay therapy until surgical sites heal (2–3 weeks) if needed.
3. Adjust/replace ill-fitting dentures.

Cancer patients on IV treatment:

1. Dental check-ups every 4–6 months.
2. OPG every 6–12 months to detect bone changes.
3. Prefer splinting over extraction for mobile teeth (grades 1–2).
4. Use antibiotic prophylaxis during surgery (penicillin or alternatives)

Osteoporotic patients starting oral therapy:

1. Inform about MRONJ risk, especially if treatment exceeds 4 years.
2. Promote oral hygiene and regular dental follow-ups.
3. Implants are possible, but only with informed consent.

Osteoporotic patients on oral therapy:

1. Risk increases with treatment >4 years or comorbidities.
2. Elective dental surgery is usually safe.
3. Monitor and maintain oral health.

On oral bisphosphonates:

1. <4 years, no risk factors:
   All procedures allowed. Emphasize hygiene and patient education.
2. <4 years with Risk or >4 years:
   a. Regular exams and imaging.
   b. Splint grade 1–2 mobile teeth; extract grade ≥3 with minimal trauma.
   c. Modify dentures as needed.
   d. Prefer endodontic over extraction.
   e. Implants allowed with risk disclosure.

3. Conclusion

Glucocorticoids and antiresorptive drugs like bisphosphonates and denosumab increase the risk of osteonecrosis, especially after dental procedures. IV BPs and Denosumab pose a higher and earlier risk than oral forms. Preventive dental care before and during therapy is essential. Conservative treatments like antibiotics, chlorhexidine rinses, and PRF-L membranes show promise, but more research is needed to guide prevention and management strategies.

4. Ethical Approval

Ethical approval is not required.

5. Source of Funding

None.

6. Conflict of Interest

No conflict of interest.

References

1. Laputková G, Talian I, Schwartzová V. Medication-related osteonecrosis of the jaw: a systematic review and a bioinformatic analysis. *Int J Mol Sci*. 2023;24(23):16745. https://doi.org/10.3390/ijms242316745.
2. Pardo-Zamora G, Martínez Y, Moreno JA, Ortiz-Ruíz AJ. Treatment of Stage 2 Medication-Induced Osteonecrosis of the Jaw: A Case Series. *Int J Environ Res Public Health*. 2021;18(3):1018. https://doi.org/10.3390/ijerph18031018.
3. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg*. 2003;61(9):1115–7. https://doi.org/10.1016/s0278-2391(03)00720-1.
4. Ruggiero SL. Bisphosphonate-related osteonecrosis of the jaw (BRONJ): initial discovery and subsequent development. *J Oral Maxillofac Surg*. 2009;67(5 Suppl):13–8. https://doi.org/10.1016/j.joms.2008.10.005.
5. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al.; American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. *J Oral Maxillofac Surg*. 2014;72(10):1938–56. https://doi.org/10.1016/j.joms.2014.04.031.
6. Khan AA, Morrison A, Kendler DL, Rizzoli R, Hanley DA, Felsenberg D, et al. Case-based review of osteonecrosis of the jaw (ONJ) and application of the international recommendations for management from the international task force on ONJ. *J Clin Densitom*. 2017;20(1):8–24. https://doi.org/10.1016/j.jocd.2016.09.005.
7. McGowan K, McGowan T, Ivanovski S. Risk factors for medication-related osteonecrosis of the jaws: a systematic review. *Oral Dis*. 2018;24(4):527–36. https://doi.org/10.1111/odi.12708.
8. Lerman MA, Xie W, Treister NS, Richardson PG, Weller EA, Woo SB. Conservative management of bisphosphonate-related osteonecrosis of the jaws: staging and treatment outcomes. *Oral Oncol*. 2013;49(9):977–83. https://doi.org/10.1016/j.oraloncology.2013.05.012.
9. Jung S, Kim J, Park JH, Kim KY, Kim HJ, Park W. A 5-year retrospective cohort study of denosumab induced medication related osteonecrosis of the jaw in osteoporosis patients. *Sci Rep*. 2022;12(1):8641. https://doi.org/10.1038/s41598-022-11615-9.
10. Weinstein RS. Glucocorticoid-induced osteonecrosis. *Endocrine*. 2012;41(2):183–90. https://doi.org/10.1007/s12020-011-9580-0.
11. Drescher W, Schlieper G, Floege J, Eitner F. Steroid-related osteonecrosis--an update. *Nephrol Dial Transplant*. 2011;26(9):2728–31. https://doi.org/10.1093/ndt/gfr212.
12. Edwards BJ, Gounder M, McKoy JM, Boyd I, Farrugia M, Migliorati C, et al. Pharmacovigilance and reporting oversight in US FDA fast-track process: bisphosphonates and osteonecrosis of the jaw. *Lancet Oncol*. 2008;9(12):1166–72. https://doi.org/10.1016/S1470-2045(08)70305-X.
13. Rosella D, Papi P, Giardino R, Cicalini E, Piccoli L, Pompa G. Medication-related osteonecrosis of the jaw: clinical and practical guidelines. *J Int Soc Prev Community Dent*. 2016;6(2):97–104. https://doi.org/10.4103/2231-0762.178742.
14. Johnston CB, Dagar M. Osteoporosis in older adults. *Med Clin North Am*. 2020;104(5):873–84. https://doi.org/10.1016/j.mcna.2020.06.004.
15. Black DM, Rosen CJ. Clinical practice. Postmenopausal osteoporosis. *N Engl J Med*. 2016;374(3):254–62. https://doi.org/10.1056/NEJMcp1513724.
16. O'Brien CA, Jia D, Plotkin LI, Bellido T, Powers CC, Stewart SA, et al. Glucocorticoids act directly on osteoblasts and osteocytes to induce their apoptosis and reduce bone formation and strength. *Endocrinology*. 2004;145(4):1835–41. https://doi.org/10.1210/en.2003-0990.
17. Jia D, O'Brien CA, Stewart SA, Manolagas SC, Weinstein RS. Glucocorticoids act directly on osteoclasts to increase their life span and reduce bone density. *Endocrinology*. 2006;147(12):5592–9. https://doi.org/10.1210/en.2006-0459.
18. Petek D, Hannouche D, Suva D. Osteonecrosis of the femoral head: pathophysiology and current concepts of treatment. *EFORT Open Rev*. 2019;4(3):85–97.https://doi.org/10.1302/2058-5241.4.180036.

19. Ficarra G, Beninati F, Rubino I, Vannucchi A, Longo G, Tonelli P, et al. Osteonecrosis of the jaws in periodontal patients with a history of bisphosphonates treatment. *J Clin Periodontol*. 2005;32(11):1123–8. https://doi.org/10.1111/j.1600-051X.2005.00842.x.
20. Thumbigere-Math V, Michalowicz BS, Hodges JS, Tsai ML, Swenson KK, Rockwell L, et al. Periodontal disease as a risk factor for bisphosphonate-related osteonecrosis of the jaw. *J Periodontol*. 2014;85(2):226–33. https://doi.org/10.1902/jop.2013.130017.

Cite this article: Durge ND, Das D. Medication induced osteonecrosis of jaw: A detailed review. *J Oral Med Oral Surg Oral Pathol Oral Radiol*. 2025;11(3):98–104.