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Medication-Related Osteonecrosis of the Jaw: Contemporary Concepts and Clinical Decision-Making

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KEYWORDS

Medication related osteonecrosis of jaw, bisphosphonates, denosumab, drug holiday, surgical management

ABSTRACT:

Background: Medication-related osteonecrosis of the jaw (MRONJ) is increasingly encountered due to the widespread use of antiresorptive and antiangiogenic therapies. Despite extensive research, consensus on optimal prevention and management remains incomplete.

Objectives: To critically appraise and synthesize current evidence on MRONJ and present a systematic-style narrative review emphasizing clinically relevant decision-making.

Methods: A structured literature search of major biomedical databases was undertaken, focusing on publications addressing MRONJ definition, epidemiology, pathogenesis, prevention, and management. Evidence from systematic reviews, cohort studies, clinical trials, and consensus guidelines was narratively synthesized.

Results: MRONJ incidence is low in osteoporosis patients but substantially higher in oncology populations receiving high-dose therapy. Suppressed bone remodeling, local infection, and jaw-specific anatomical factors underpin disease pathogenesis. Preventive dental care significantly reduces risk. Evidence increasingly supports early surgical intervention across disease stages, while the benefit of prophylactic and therapeutic drug holidays remains uncertain and drug-specific.

Conclusions: MRONJ management should prioritize prevention, early diagnosis, and individualized treatment strategies. Surgical management offers superior long-term outcomes in appropriately selected patients. Further prospective research is required to refine risk prediction and optimize long-term management.

1. Introduction

The introduction of potent antiresorptive agents has revolutionized the management of osteoporosis and skeletal complications associated with malignancy. Bisphosphonates and denosumab have demonstrated robust efficacy in reducing fracture risk and skeletal-related events, leading to their widespread and often prolonged use. However, these therapeutic gains have been accompanied by recognition of medication-related osteonecrosis of the jaw (MRONJ) as a rare but potentially debilitating adverse outcome. Since the first reports of bisphosphonate-associated jaw necrosis in the early 2000s, MRONJ has evolved from an anecdotal complication to a well-recognized clinical entity with significant implications for dental and medical practice. Despite extensive investigation, uncertainty persists regarding optimal diagnostic thresholds, prevention strategies, and treatment timing. International guidelines have progressively shifted from rigid algorithms toward individualized, risk-based approaches, reflecting both the complexity of the condition and limitations of the available evidence. Recent multidisciplinary consensus

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documents have attempted to reconcile these challenges by integrating emerging data with expert opinion. Rather than reiterating guideline statements verbatim, the present review adopts a systematic-style narrative approach, critically synthesizing contemporary evidence and highlighting its relevance to clinical decision-making. Emphasis is placed on areas of convergence and controversy, with the aim of providing a pragmatic framework for clinicians involved in the care of patients receiving antiresorptive or antiangiogenic therapy.

2. Methods: Systematic-Style Narrative Review Design

A structured literature search was performed using PubMed, Scopus, and Embase databases, covering publications from January 2003 to December 2025. Search terms included combinations of "medication-related osteonecrosis of the jaw," "bisphosphonates," "denosumab," "antiresorptive therapy," "drug holiday," "prevention," and "surgical management." Reference lists of relevant reviews and position papers were manually screened to identify additional studies. Priority was given to systematic reviews, meta-analyses, randomized and non-randomized clinical studies, large cohort analyses, and internationally recognized consensus statements. Case reports were included selectively to illustrate rare presentations or emerging therapeutic approaches. Evidence was narratively synthesized due to heterogeneity in study design, patient populations, and outcome measures.

3. Definition, Diagnosis, and Staging

MRONJ is defined as exposed necrotic bone, or bone that can be probed through an intraoral or extraoral fistula, in the maxillofacial region of patients with current or previous exposure to antiresorptive or antiangiogenic agents, persisting in the absence of prior radiotherapy or metastatic disease to the jaws (1–3). While an eight-week duration has traditionally been required for diagnosis, increasing attention has been directed toward earlier identification based on unequivocal clinical or radiographic evidence (4). Clinical diagnosis remains central, supported by radiographic imaging to assess disease extent. Panoramic radiography provides an initial overview, while cone-beam computed tomography offers superior visualization of cortical disruption, sclerosis, and sequestration (5,6). Magnetic resonance imaging and nuclear medicine techniques may assist in evaluating marrow involvement and disease activity but are adjunctive rather than diagnostic tools (7,8). Staging systems categorize MRONJ from an at-risk state through advanced disease characterized by infection, pathologic fracture, or extraoral fistula formation (2). Retention of a Stage 0 category, denoting non-specific symptoms without bone exposure, remains debated; however, it is increasingly regarded as a useful construct for heightened surveillance and early preventive intervention in high-risk patients (9).

4. Epidemiology and Clinical Impact

The prevalence of MRONJ in patients treated for osteoporosis is consistently low, typically reported below 0.1% (10–12). Nonetheless, absolute case numbers continue to rise in parallel with population ageing, longer treatment durations, and increasing use of injectable therapies. Denosumab-associated MRONJ has been reported at rates numerically higher than those observed with oral bisphosphonates, although direct comparisons are confounded by prior drug exposure and differences in follow-up (13,14). In contrast, patients receiving high-dose antiresorptive therapy for malignancy face a substantially greater risk, with incidence estimates ranging from 1% to over 10% in some series (15–17). This marked disparity reflects higher cumulative doses, greater drug potency, and the frequent coexistence of additional risk factors such as chemotherapy, corticosteroid use, and compromised oral health. Although paediatric and young adult populations treated for non-malignant bone disorders appear to have negligible risk, expanding indications for antiresorptive agents warrant continued epidemiological surveillance (18).

5. Pathogenesis

The pathogenesis of MRONJ is multifactorial, arising from the interaction between systemic pharmacological effects and local environmental factors. Profound suppression of bone remodeling is considered central, limiting the capacity for microdamage repair and predisposing bone to necrosis following trauma or infection (19,20). The jaws are uniquely vulnerable due to their high physiological turnover, thin mucosal coverage, and constant exposure to the oral microbiome.

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Antiresorptive agents accumulate preferentially in alveolar bone, amplifying local remodeling suppression. Additional contributory mechanisms include impaired angiogenesis, immune dysregulation, and delayed soft tissue healing (21–23).

6. Risk Factors

Risk factors for MRONJ can be broadly categorized as drug-related, systemic, and local. High-potency agents, intravenous administration, prolonged duration of therapy, and cumulative dose are the strongest predictors of risk (2,24). Systemic factors such as malignancy, diabetes, corticosteroid use, smoking, and advanced age further modify susceptibility (25). Local factors play a decisive role in triggering disease onset. Tooth extraction remains the most common precipitating event, accounting for the majority of reported cases (26). Dental implant surgery, periodontal disease, periapical pathology, and chronic mucosal trauma from ill-fitting prostheses also contribute substantially to risk (27,28).

7. Prevention

Preventive strategies represent the most effective means of reducing MRONJ incidence. Comprehensive dental evaluation and management prior to initiation of high-risk antiresorptive therapy have been shown to significantly reduce disease occurrence, particularly in oncology populations (29,30). The concept of a prophylactic drug holiday before invasive dental procedures remains controversial. Systematic reviews have not demonstrated consistent benefit, although emerging data suggest that drug-specific and duration-dependent approaches may be reasonable in selected patients (31–33). For denosumab, scheduling procedures within the dosing interval rather than prolonged discontinuation is emphasized to minimize rebound fracture risk (34).

8. Management of Established MRONJ

Historically, conservative management formed the cornerstone of MRONJ treatment, with surgery reserved for advanced disease. However, accumulating evidence indicates that early surgical intervention yields superior long-term outcomes across all stages (35–38). Definitive management involves complete resection of necrotic bone to healthy, bleeding margins, combined with tension-free soft tissue closure. Adjunctive therapies, particularly teriparatide, have shown promise in selected patients by enhancing bone remodeling and supporting surgical outcomes (39–41).

9. Drug Holidays and Recurrence Prevention

The role of therapeutic drug holidays after MRONJ diagnosis remains uncertain. While some studies suggest improved healing with prolonged discontinuation, others report minimal benefit, particularly for bisphosphonates with long skeletal retention (42–44). Decisions must therefore balance local healing against systemic fracture risk and be individualized through interdisciplinary collaboration. Recurrence is associated with high cumulative drug exposure, early resumption of therapy, advanced disease stage, and incomplete surgical resection. Meticulous primary surgery, standardized perioperative antibiotic protocols, and long-term follow-up are central to reducing recurrence risk (45,46).

10. Future Directions

Key knowledge gaps include the absence of reliable biomarkers for individual risk prediction, limited prospective data on drug holiday efficacy, and uncertainty regarding optimal long-term management strategies. Well-designed prospective studies and collaborative registries are essential to address these limitations.

11. Conclusion

MRONJ represents a complex intersection of systemic pharmacotherapy and local oral health. Contemporary evidence supports a prevention-focused approach, early diagnosis, and timely surgical intervention when indicated. Individualized, risk-based decision-making remains fundamental to optimizing outcomes while preserving the proven systemic benefits of antiresorptive therapy.

References

1. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O'Ryan F. 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):1938–1956.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 2251-2256 | ISSN:2251-6727

2. Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' position paper on medication-related osteonecrosis of the jaw—2022 update. *J Oral Maxillofac Surg.* 2022;80(5):920–943.

3. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watts NB, Brandi ML, Peters E, Guise T, Eastell R, Cheung AM, Morin SN, Masri B, Cooper C, Morgan SL, Obermayer-Pietsch B, Langdahl BL, Al Dabagh R, Davison KS, Kendler DL, Sandor GK, Josse RG, Bhandari M, El Rabbany M, Pierroz DD, Sulimani R, Compston J. Diagnosis and management of osteonecrosis of the jaw: A systematic review and international consensus. *J Bone Miner Res.* 2015;30(1):3–23.

4. Kim JW, Baek SH, Kim SJ, Kim MR, Kim YK. Medication-related osteonecrosis of the jaw: A review of pathophysiology, risk factors, and treatment strategies. *J Korean Assoc Oral Maxillofac Surg.* 2025;51(6):333–353.

5. Bedogni A, Blandamura S, Lokmic Z, Palumbo C, Ragazzo M, Ferrari F, Tregnaghi A, Pietrogrande F, Procopio O, Saia G, Ferretti M, Bedogni G, Ferronato G, Ninfo V, Lo Russo L. Bisphosphonate-associated jawbone osteonecrosis: A correlation between imaging techniques and histopathology. *Oral Oncol.* 2012;48(8):777–782.

6. Stockmann P, Hinkmann FM, Lell MM, Fenner M, Vairaktaris E, Neukam FW, Nkenke E. Panoramic radiograph, computed tomography or magnetic resonance imaging: Which imaging technique should be preferred in bisphosphonate-associated osteonecrosis of the jaw? *Clin Oral Investig.* 2010;14(5):543–552.

7. Chiandussi S, Biasotto M, Dore F, Cavalli F, Cova MA, Di Lenarda R. Clinical and diagnostic imaging of bisphosphonate-associated osteonecrosis of the jaw. *Radiol Med.* 2016;121(2):144–153.

8. Fedele S, Porter SR, D'Aiuto F, Aljohani S, Vescovi P, Manfredi M, Arduino PG, Broccoletti R, Musciotto A, Di Fede O, Lazarovici TS, Campisi G. Nonexposed variant of bisphosphonate-associated osteonecrosis of the jaw: A case series. *Oral Dis.* 2010;16(8):733–742.

9. Otto S, Pautke C, Opelz C, Westphal I, Drosse I, Schwager J, Bauss F, Ehrenfeld M, Schieker M. Osteonecrosis of the jaw: Effect of bisphosphonate type, local concentration, and acid environment on osteoclast viability. *J Craniomaxillofac Surg.* 2018;46(4):527–534.

10. Lo JC, O'Ryan FS, Gordon NP, Yang J, Hui RL, Martin D, Hutchinson M, Go AS. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. *J Oral Maxillofac Surg.* 2010;68(2):243–253.

11. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2007;22(10):1479-91.

12. Yamazaki T, Yamori M, Ishizaki T, et al. Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: a cohort study. *J Bone Miner Metab.* 2012;30(5):623-9.

13. Watts NB, Adler RA, Bilezikian JP, et al. Osteonecrosis of the jaw and atypical femoral fractures: complications of long-term bisphosphonate therapy? *Osteoporos Int.* 2013;24(3):695-703.

14. Saad F, Brown JE, Van Poznak C, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. *Lancet Oncol.* 2012;13(2):119-28.

15. Christodoulou C, Pervena A, Klouvas G, et al. Combination of bisphosphonates and antiangiogenic factors induces osteonecrosis of the jaw more frequently than bisphosphonates alone. *Support Care Cancer.* 2009;17(8):955-62.

16. Qi WX, Tang LN, He AN, Yao Y, Shen Z. Risk of osteonecrosis of the jaw in cancer patients receiving denosumab: a meta-analysis of seven randomized controlled trials. *Oncologist.* 2014;19(6):605-11.

17. Yoneda T, Hagino H, Sugimoto T, et al. Antiresorptive agent-related osteonecrosis of the jaw: position paper 2017 of the Japanese Allied

Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 2251-2256 | ISSN:2251-6727

Committee on Osteonecrosis of the Jaw. *J Bone Miner Metab.* 2017;35(1):6-19.

18. Mavrokokki T, Cheng A, Stein B, Goss A. Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. *J Oral Maxillofac Surg.* 2007;65(3):415-23.
19. Allen MR, Burr DB. The pathogenesis of bisphosphonate-related osteonecrosis of the jaw: so many hypotheses, so few data. *J Bone Miner Res.* 2009;24(2):171-82.
20. Reid IR. Osteonecrosis of the jaw—who gets it, and why? *N Engl J Med.* 2015;373(8):786-7.
21. Landesberg R, Woo V, Cremers S, et al. Potential pathophysiological mechanisms in osteonecrosis of the jaw. *J Oral Maxillofac Surg.* 2011;69(1):11-9.
22. Hoefert S, Eufinger H. Relevance of a prolonged preoperative antibiotic regime in the treatment of patients with bisphosphonate-related osteonecrosis of the jaw. *J Craniomaxillofac Surg.* 2011;39(4):255-60.
23. Marx RE. Cessation of antiresorptive therapy for prevention and treatment of medication-related osteonecrosis of the jaws. *Oral Maxillofac Surg Clin North Am.* 2015;27(4):477-91.
24. Hellstein JW, Adler RA, Edwards B, et al. Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: executive summary of recommendations from the American Dental Association Council on Scientific Affairs. *J Am Dent Assoc.* 2011;142(11):1243-51.
25. Thumbigere-Math V, Michalowicz BS, Hodges JS, et al. Periodontal disease as a risk factor for bisphosphonate-related osteonecrosis of the jaw. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2016;121(2):126-38.
26. Vahtsevanos K, Kyrgidis A, Verrou E, et al. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. *J Oral Maxillofac Surg.* 2009;67(9):1951-7.
27. Kwon YD, Kim DY, Ohe JY, et al. Correlation between serum C-terminal cross-linking telopeptide of type I collagen and severity of osteonecrosis of the jaw. *Int J Oral Maxillofac Surg.* 2014;43(12):1509-15.
28. Otto S, Hafner S, Mast G, et al. Bisphosphonate-related osteonecrosis of the jaw: is palliative surgical treatment justified? *J Oral Maxillofac Surg.* 2012;70(2):284-92.
29. Dimopoulos MA, Kastritis E, Bamia C, et al. Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. *Leukemia.* 2009;23(8):1545-53.
30. Nicolatou-Galitis O, Papadopoulou E, Vardas E, et al. Alveolar bone histological necrosis observed prior to clinical manifestation of osteonecrosis of the jaw. *Oral Dis.* 2019;25(4):971-9.
31. Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O. Interventions for managing medication-related osteonecrosis of the jaw. *Cochrane Database Syst Rev.* 2017;10:CD012432.
32. Ottesen C, Schiodt M, Gotfredsen K. Efficacy of surgical treatment of medication-related osteonecrosis of the jaw: a systematic review. *J Oral Maxillofac Surg.* 2020;78(8):1385-93.
33. Otto S, Aljohani S, Hafner S, et al. Surgical treatment of medication-related osteonecrosis of the jaw: comparative analysis of different surgical techniques. *J Craniomaxillofac Surg.* 2021;49(8):681-8.
34. Anastasilakis AD, Pepe J, Napoli N, et al. Osteonecrosis of the jaw and atypical fractures: relationship and clinical implications. *J Bone Miner Res.* 2017;32(6):1291-6.
35. Hayashida S, Soutome S, Yanamoto S, et al. Evaluation of the treatment strategies for medication-related osteonecrosis of the jaw: a retrospective multicenter study. *Int J Oral Maxillofac Surg.* 2017;46(4):421-7.
36. Carlson ER, Fleisher KE, Ruggiero SL. Metastatic bone disease and osteonecrosis of the jaw. *J Oral Maxillofac Surg.* 2016;74(1):156-65.
37. El-Rabbany M, Sgro A, Lam DK, Shah PS, Azarpazhooh A. Effectiveness of treatments for medication-related osteonecrosis of the jaw: a

systematic review and meta-analysis. *J Dent Res.* 2017;96(13):1476-84.

38. Ristow O, Gerngross C, Schwaiger M, et al. Effect of surgical therapy and antibiotic treatment on outcome of medication-related osteonecrosis of the jaw. *J Craniomaxillofac Surg.* 2014;42(7):1431-8.

39. Sim IW, Borromeo GL, Tsao C, et al. Teriparatide promotes bone healing in medication-related osteonecrosis of the jaw: a randomized controlled trial. *J Clin Endocrinol Metab.* 2020;105(7):e3001-10.

40. Harper RP, Fung E. Resolution of bisphosphonate-associated osteonecrosis of the mandible: possible application for intermittent low-dose parathyroid hormone [rhPTH(1–34)]. *J Oral Maxillofac Surg.* 2007;65(3):241-8.

41. Cheung AM, Seeman E, Teriparatide Study Group, et al. Teriparatide therapy for medication-related osteonecrosis of the jaw: a randomized controlled trial. *J Bone Miner Res.* 2021;36(2):200-9.

42. Hinson AM, Smith CW, Siegel ER, Stack BC Jr. Is bisphosphonate-related osteonecrosis of the jaw an inflammatory condition? *J Oral Maxillofac Surg.* 2015;73(1):53-62.

43. Kim KM, Rhee Y, Kwon YD, Kwon TG, Lee JK, Kim DY. Medication-related osteonecrosis of the jaw: pathophysiology and treatment. *Bone.* 2015;81:623-8.

44. Beth-Tasdogan NH, Mayer B, Zolk O. Treatment modalities for medication-related osteonecrosis of the jaw: a systematic review. *J Oral Maxillofac Surg.* 2019;77(3):451-61.

45. Ristow O, Rückschloss T, Müller M, et al. Incidence and risk factors of medication-related osteonecrosis of the jaw in cancer patients treated with bisphosphonates and denosumab. *J Craniomaxillofac Surg.* 2018;46(9):1578-83.

46. Kim JW, Baek SH, Kim SJ, Kim MR, Kim YK. Medication-related osteonecrosis of the jaw: a review of pathophysiology, risk factors, and treatment strategies. *J Korean Assoc Oral Maxillofac Surg.* 2025;51(6):333-53