Scripta Scientifica Medica, 2024;56(3):18-22
DOI: 10.14748/ssm.v55i2.9905

ISSN 0582-3250 (Print)
ISSN 1314-6408 (Online)

REVIEWS

RISK FACTORS, PREVENTION, AND TREATMENT OF THE MEDICATION-RELATED OSTEONECROSIS OF THE JAW: A REVIEW

Ralitsa Yotsova[1], Tsvetalina Gerova-Vatsova[2]

[1]Department of Oral Surgery, Faculty of Dental Medicine, Medical University of Varna, Bulgaria
[2]Department of Periodontology and Dental Implantology, Faculty of Dental Medicine, Medical University of Varna, Bulgaria

ABSTRACT

Medication-related osteonecrosis of the jaw (MRONJ) is a serious complication associated with the administration of antiresorptive and antiangiogenic drugs. It can affect both jaws, but the lower one is more frequently involved. Its clinical features include bone exposure and necrosis in patients who have undergone antiangiogenic or antiresorptive therapy and without a history of radiation in the maxillofacial area.

This review aims to summarize and analyze the current knowledge on the risk factors, prevention, and treatment of MRONJ, to identify the research gaps, and to give recommendations for future research.

An electronic search in PubMed, Scopus, and Web of Science was conducted in August 2024. After analysis of the obtained data, 23 articles were included in this study.

Risk factors for developing MRONJ include the type of medication, treatment duration, dosage, and route of administration, poor oral hygiene, local infection and inflammation, smoking, corticosteroid therapy, and comorbidity. Triggering factors are invasive dental procedures, dentoalveolar surgery, and other traumatic agents, such as dentures that do not fit well.

Prevention strategies include full dental consultation, radiological evaluation, treatment, and professional oral hygiene before initiating antiresorptive or antiangiogenic therapy, perioperative antimicrobial prophylaxis, and primary wound closure. One of the most common prevention methods in case of dental problems requiring invasive treatment has been the so-called drug holiday, which is a pause from drug administration before bone surgery.

The treatment of MRONJ depends on its stage, severity, and individual characteristics. It includes conservative therapy, surgical interventions, adjuvant therapy, and a combination of them.

Keywords: *medication-related osteonecrosis of the jaw, MRONJ, risk factors, prevention, treatment*

Address for correspondence:
Ralitsa Yotsova
Faculty of Dental Medicine
Medical University of Varna
84 Tzar Osvboditel Blvd
9002 Varna, Bulgaria
e-mail: r.yotsova@abv.bg

Received: August 2, 2024
Accepted: September 8, 2024

© The Author(s) 2024. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a serious complication of varying severity associated with the intake or administration of specific drugs, such as antiresorptive and antiangiogenic agents, immunomodulators, immunosuppressants, monoclonal antibodies, etc. The condition was long related to bisphosphonate (BP) therapy and was known as bisphosphonate-related osteonecrosis of the jaw (BRONJ) (1). It was later found that other drug classes cause similar symptoms and the term MRONJ became more popular.

Medication-related osteonecrosis of the jaw can affect the upper and lower jaw, but the latter is more frequently involved. Its clinical features include bone exposure and necrosis in patients who have undergone antiangiogenic or antiresorptive therapy and without a history of radiation in the maxillofacial area (2,3).

Most recent studies aim to create evidence-based guidelines for medical behavior, risk assessment, treatment modalities, and prevention strategies for patients at risk of MRONJ.

AIM

This review aims to summarize and analyze the current knowledge on the risk factors, prevention, and treatment of MRONJ, to identify the research gaps, and to give recommendations for future research.

MATERIALS AND METHODS

An electronic search in PubMed, Scopus, and Web of Science was conducted in August 2024. The search strategy comprised an advanced search in the databases, using the selected keywords: ((((medication-related) AND (osteonecrosis) AND (jaw)) OR (MRONJ)) AND (treatment) AND (risk factors) AND (prevention)). After analysis of the obtained data, 23 articles were included in this study.

RESULTS AND DISCUSSION

The differential diagnosis of MRONJ includes but is not limited to osteoradionecrosis, alveolar osteitis, periodontal or periapical lesions, osteomyelitis, neoplasms, and sinusitis. The condition has a multifactorial nature and has been related to infection, trauma, autoimmune conditions, diabetes, and immunosuppression (4).

Risk Factors for MRONJ

The main risk factor for developing MRONJ is the administration of antiresorptive and antiangiogenic drugs, immunomodulators, monoclonal antibodies, cytostatics, and other suspected **medications.** Common **conditions** associated with a high incidence of MRONJ are bone metastatic disease, osteoporosis, and non-malignant bone lesions. In the first group, the estimated risk is up to 1%. In patients on zoledronate therapy, the risk can reach up to 18%, while in those on denosumab (DMB), the reported risk is up to 7%. In the osteoporotic group, the risk of developing MRONJ has been reported to be up to 0.05% for patients on BP therapy and up to 0.3% for those on DMB. The reported risk for patients with non-malignant bone lesions is up to 5% and up to 7% in children (4).

Treatment duration, dosage, and route of administration are other important risk factors for MRONJ. It has been reported to be 0.5% for the first year, 1% for the second year, and 1.3% for the third year in patients with malignancies treated with zoledronate. The risk in patients treated with DMB was 0.8% for the first year and 1.8% for the second and third years (5). Other researchers reported a risk of 1.6–4% after two years of treatment with zoledronate and 3.8–18% when the treatment continued for more than two years. Similarly, the risk of developing MRONJ in patients on DMB was reported to be between 2% for the first 2 years and 7% after the second year of treatment (6). In osteoporotic patients, the risk can increase from 0 to 0.2% over time, indicating a low overall risk. Parenteral administration poses a greater risk than oral intake. Regarding the BPs group, non-nitrogenated ones pose a lower risk than nitrogen-containing BPs (7).

Various **local factors** can contribute to or exacerbate the condition, the most common of which are **invasive dental procedures and dentoalveolar surgery**. Tooth extractions have been reported as a predisposing factor for 60–80% of the MRONJ cases (4). However, this does not answer the question of the risk of developing MRONJ after tooth extraction. Its spontaneous development can reach up to 35% (8). The reported risk after tooth extraction in patients

with osteoporosis undergoing BP therapy is up to 0.2%, while in those on DMB therapy, the risk is 1% (9, 10). For patients with malignancies, the risk associated with BP therapy is between 2% and 15% (4,11). Dental implant placement can be another triggering factor for the development of MRONJ (12). The reported risk is 0.5% in patients treated with DMB (10). It has been recently suggested that preexisting osseointegrated implants can also pose a risk of MRONJ (13,14).

A MRONJ development is more common in the lower than in the upper **jaw** and has been related to **denture wearing** (4). **Poor oral hygiene, infection, and inflammation**, such as chronic periodontitis, have also been reported as predisposing factors for MRONJ.

Gender distribution demonstrates a higher prevalence in female patients, which can be attributed to the nature of the diseases treated with the associated drugs. It has been suggested that younger patients are at a low risk of MRONJ. **Smoking, corticosteroid treatment, chemotherapy, and some comorbidities**, such as diabetes, anemia, and malignant diseases, have been suggested to contribute to the severity and extent of MRONJ but the data is heterogeneous. **Genetic predisposition** has also been suggested but further research is necessary to confirm its role (15).

Prevention Strategies

Before Initiation of the Drug Therapy

These strategies include full dental consultation, radiological evaluation, treatment, and professional oral hygiene before or shortly after the antiresorptive or antiangiogenic therapy initiation, perioperative antimicrobial prophylaxis, and primary wound closure. Collaboration between clinicians and patients and a multidisciplinary approach is required for treatment optimization and risk reduction (4,16). Dentures that do not fit well should be replaced (12). Patients should be provided with a thorough dental screening and a treatment plan in order to eliminate the active and potential sources of infection. Furthermore, they should be informed of all possible risks associated with the therapy and the triggering factors for MRONJ (4). Regular dental examinations and patient education for personal oral hygiene are key prerequisites for risk reduction (12).

During Drug Therapy

One of the most common prevention methods in case of dental problems requiring invasive treatment has been the so-called *drug holiday*, which is a temporary discontinuation of drug administration before bone surgery. There is a study heterogeneity regarding the benefits of drug holidays and the most appropriate periods. Bone turnover markers should be further investigated before validation as a tool for MRONJ risk assessment (4). For patients treated for metastatic bone disease, invasive dental treatment should be avoided if possible (12). If dentoalveolar surgery cannot be avoided, antibiotic prophylaxis and antibacterial mouth rinse are recommended. The intervention should be as minimally invasive as possible with primary wound closure and monitoring until complete healing. Vasoconstrictors should be avoided.

The risk assessment is individual for each patient and should be performed with great attention to all medication-related and patient-related factors (12).

Recent studies suggest adjunctive methods for the prevention of MRONJ, such as autologous platelet concentrates, ozone therapy, bone morphogenetic proteins, etc. (14).

Treatment Modalities

Numerous guidelines have been suggested through the years. However, the treatment modalities are based on an insufficient amount of evidence. The factors that influence the decision-making are the following: MRONJ stage, severity, age, gender, general health, and prognosis.

Conservative therapy is a treatment of choice when applicable. It is sufficient and does not require surgical interventions in most early-stage cases. Its success is greater for patients with osteoporosis than those with malignancy. The conservative approach includes professional and self-maintained oral hygiene, elimination of any possible dental and periodontal infections and inflammation, use of antiseptic mouth rinses, and, in some cases, antibiotic intake. The dosage and regimen of the latter depend on the MRONJ stage and the patient's comorbidities (15).

Physical and radiographic monitoring is required in patients at risk and patients must be in-

structed to identify early MRONJ symptoms. At stage 0, the condition is monitored and patients can be prescribed antiseptics and analgesics. At stage 1, surgical interventions and antibiotic prescriptions are still unnecessary, while at stage 2 oral antibiotics are prescribed along with antiseptic (chlorhexidine) mouth rinse (15). Teriparatide has been reported as a successful treatment approach in patients with osteonecrosis of the jaws (17,18). However, it is contraindicated in cases of active malignancy (15).

Surgical treatment is indicated at stage 2 and stage 3. It ranges from sequestrectomy to jaw resections with reconstructions when possible. A histopathological examination of the necrotic bone is necessary to confirm the diagnosis and exclude other diagnoses. Some authors suggest that surgical management is more effective than conservative therapy (16,19). Tension-free closure is required and some authors even recommend double closure with additional muscle or buccal fat tissue flaps (12,20,21). The surgical treatment is accompanied by appropriate antibiotic therapy (12). The latter includes the combination of amoxicillin and clavulanic acid, metronidazole, clindamycin, doxycycline, quinolones, and macrolides (12).

Adjuvant therapy includes hyperbaric oxygenation (contraindicated for patients with malignancy), laser and ozone therapies, the application of autologous platelet concentrates, bone morphogenic proteins, parathyroid hormone, pentoxifylline, and vitamin D supplementation (12,22,23).

Future Directions

This study is a literature review that presents some of the most common prevention strategies, and treatment modalities of MRONJ. However, long-term randomized controlled trials, systematic reviews, and meta-analyses are necessary to define and evaluate the possible risk factors, and the effectiveness of different prevention and treatment modalities.

CONCLUSION

Medication-related osteonecrosis of the jaw is a serious medical condition with a multifactorial etiology that requires the attention of clinicians and researchers in the field. The management of this complication is a challenging task for oral and maxillofacial surgeons. In addition, it requires a multidisciplinary approach, including other specialists, such as dentists, radiologists, and chemotherapists. This review focuses on the risk factors, prevention, and treatment methods, identifies some research gaps, and gives directions for further research.

REFERENCES

1. 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. doi: 10.1016/S0278-2391(03)00720-1.
2. Di Fede O, Panzarella V, Mauceri R, Fusco V, Bedogni A, Lo Muzio L, et al. The dental management of patients at risk of medication-related osteonecrosis of the jaw: new paradigm of primary prevention. BioMed Res Int. 2018; 2018(1):2684924. doi: 10.1155/2018/2684924.
3. Akashi M, Kusumoto J, Takeda D, Shigeta T, Hasegawa T, Komori T. A literature review of perioperative antibiotic administration in surgery for medication-related osteonecrosis of the jaw. Oral Maxillofac Surg. 2018;22(4):369-78. doi: 10.1007/s10006-018-0732-8.
4. 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 Jaws-2022 Update. J Oral Maxillofac Surg. 2022;80(5):920-43. doi: 10.1016/j.joms.2022.02.008.
5. Henry D, Vadhan-Raj S, Hirsh V, von Moos R, Hungria V, Costa L, et al. Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors. Support Care Cancer. 2014;22(3):679-87. doi: 10.1007/s00520-013-2022-1.
6. Ng TL, Tu MM, Ibrahim MFK, Basulaiman B, McGee SF, Srikanthan A, et al. Long-term impact of bone-modifying agents for the treatment of bone metastases: a systematic review. Support Care Cancer. 2021;29(2):925-943. doi: 10.1007/s00520-020-05556-0.
7. Eguia A, Bagan L, Cardona F. Review and update on drugs related to the development of osteonecrosis of the jaw. Med Oral Patol Oral Cir Bucal. 2020;25(1): e71. doi: 10.4317/medoral.23191.
8. Dalle Carbonare L, Mottes M, Valenti MT. Medication-related osteonecrosis of the jaw (MRONJ): Are antiresorptive drugs the main culprits or only accomplices? The Triggering role of vitamin D de-

ficiency. Nutrients. 2021;13(2):561. doi: 10.3390/nu13020561.

9. Shudo A, Kishimoto H, Takaoka K, Noguchi K. Long-term oral bisphosphonates delay healing after tooth extraction: a single institutional prospective study. Osteoporos Int. 2018;29(10):2315-21. doi: 10.1007/s00198-018-4621-7.

10. Watts NB, Grbic JT, Binkley N, Papapoulos S, Butler PW, Yin X, et al. Invasive oral procedures and events in postmenopausal women with osteoporosis treated with denosumab for up to 10 years. J Clin Endocrinol Metab. 2019;104(6):2443-52. doi: 10.1210/jc.2018-01965.

11. Yamazaki T, Yamori M, Ishizaki T, Asai K, Goto K, Takahashi K, et al. Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: a cohort study. Int J Oral Maxillofac Surg. 2012;41(11):1397-403. doi: 10.1016/j.ijom.2012.06.020.

12. Kün-Darbois JD, Fauvel F. Medication-related osteonecrosis and osteoradionecrosis of the jaws: Update and current management. Morphologie. 2021;105(349):170-87. doi: 10.1016/j.morpho.2020.11.008.

13. Giovannacci I, Meleti M, Manfredi M, Mortellaro C, Greco Lucchina A, Bonanini M, et al. Medication-related osteonecrosis of the jaw around dental implants: Implant surgery-triggered or implant presence-triggered osteonecrosis? J Craniofac Surg. 2016;27(3):697-701. doi: 10.1097/SCS.0000000000002564.

14. Kuehn S, Scariot R, Elsalanty M. Medication-related osteonecrosis: Why the jawbone? Dent J (Basel). 2023;11(5):109. doi: 10.3390/dj11050109.

15. Anastasilakis AD, Pepe J, Napoli N, Palermo A, Magopoulos C, Khan AA, et al. Osteonecrosis of the jaw and antiresorptive agents in benign and malignant diseases: A Critical review organized by the ECTS. J Clin Endocrinol Metab. 2022;107(5):1441-60. doi: 10.1210/clinem/dgab888.

16. Lončar Brzak B, Horvat Aleksijević L, Vindiš E, Kordić I, Granić M, Vidović Juras D, Andabak Rogulj A. Osteonecrosis of the Jaw. Dentistry J. 2023;11(1):23. doi: 10.3390/dj11010023.

17. Neuprez A, Rompen E, Crielaard JM, Reginster JY. Teriparatide therapy for denosumab-induced osteonecrosis of the jaw in a male osteoporotic patient. Calcif Tissue Int. 2014;95(1):94-6. doi: 10.1007/s00223-014-9858-3.

18. Kakehashi H, Ando T, Minamizato T, Nakatani Y, Kawasaki T, Ikeda H, et al. Administration of teriparatide improves the symptoms of advanced bisphosphonate-related osteonecrosis of the jaw: preliminary findings. Int J Oral Maxillofac Surg. 2015;44(12):1558-64. doi: 10.1016/j.ijom.2015.07.018.

19. Lesclous P, Grabar S, Abi Najm S, Carrel JP, Lombardi T, Saffar JL, et al. Relevance of surgical management of patients affected by bisphosphonate-associated osteonecrosis of the jaws. A prospective clinical and radiological study. Clin Oral Investig. 2014;18(2):391-9. doi: 10.1007/s00784-013-0979-2.

20. Lemound J, Eckardt A, Kokemüller H, von See C, Voss PJ, Tavassol F, et al. Bisphosphonate-associated osteonecrosis of the mandible: reliable soft tissue reconstruction using a local myofascial flap. Clin Oral Investig. 2012;16(4):1143-52. doi: 10.1007/s00784-011-0596-x.

21. Gallego L, Junquera L, Pelaz A, Hernando J, Megías J. The use of pedicled buccal fat pad combined with sequestrectomy in bisphosphonate-related osteonecrosis of the maxilla. Med Oral Patol Oral Cir Bucal. 2012;17(2):e236-41. doi: 10.4317/medoral.17422.

22. Curi MM, Cossolin GS, Koga DH, Zardetto C, Christianini S, Feher O, et al. Bisphosphonate-related osteonecrosis of the jaws--an initial case series report of treatment combining partial bone resection and autologous platelet-rich plasma. J Oral Maxillofac Surg. 2011;69(9):2465-72. doi: 10.1016/j.joms.2011.02.078.

23. Freiberger JJ. Utility of hyperbaric oxygen in treatment of bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg. 2009;67(5 Suppl):96-106. doi: 10.1016/j.joms.2008.12.003.