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REVIEW ARTICLE

Management and maintenance of oral health: Personalized primary prevention strategies and protocols in patients at risk of developing medication-related osteonecrosis of the jaw

Giovanna Mosaico[1]* and Cinzia Casu[2]

[1]Independent Researcher, Carovigno, Brindisi, Italy

[2]Department of Surgical Science, Oral Biotechology Laboratory, University of Cagliari, Italy

Abstract

Skeletal complications arising from osteoporosis or bone metastases are associated with considerable pain, increased mortality, and diminished quality of life. Agents that prevent bone resorption, such as bisphosphonates, denosumab, and antiangiogenic agents, prove effective in reducing fracture risk and find extensive use in patients with osteoporosis or bone cancer metastases. Medication-related osteonecrosis of the jaw (MRONJ) is a potentially serious adverse event associated with high cumulative doses of antiresorptive drugs. Other risk factors for osteonecrosis of the jaw include glucocorticoid use, maxillary or mandibular bone surgery, poor oral hygiene, chronic inflammation, diabetes mellitus, inappropriate dentures, and other MRONJ-related medications. Preventive strategies encompass completing necessary oral surgery before initiating antiresorptive drug therapy, administering antibiotics before and/or after the procedure, rinsing the mouth with chlorhexidine, ensuring adequate wound healing post-tooth extraction, and maintaining good oral hygiene. The primary goal of treatment is to improve the patient's quality of life by managing pain and infection, preventing the development of new lesions, and decelerating disease progression. Dentists and dental hygienists, operating within a multi-professional team, play a key role in the primary prevention of MRONJ. However, a standardized multidisciplinary approach, fostering sustained dialog between specialists involved in the management of patients at risk for MRONJ, remains essential. This review describes the preventive and individualized oral hygiene management in patients at risk for this condition.

Keywords: Preventive protocols; Patients at risk of MRONJ; Antiresorptive drugs; Oral hygiene; Healthy lifestyles

***Corresponding author:**
Giovanna Mosaico
(gimosaico@tiscali.it)

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1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is an adverse event associated with antiresorptive drug therapy, often administered in combination with anti-angiogenics. It is a potentially serious and debilitating complication defined by the American Association of Oral and Maxillofacial Surgeons as the presence of an area of exposed bone in the maxillofacial region persisting for more than 8 weeks in the absence of prior radiotherapy treatment[1,2]. The diagnosis of MRONJ relies on the patient's history and clinical and

radiological features demonstrating progressive bone destruction (both exposed and unexposed)[3-5]. Common signs and symptoms of MRONJ include exposed necrotic bone, sinus tract or fistula, recurring abscesses, gingival swelling, bad breath, loosening of teeth, jaw fracture, sinus pain, and numbness or dysesthesia of the lower lip. Diagnosis of MRONJ is considered when exposed bone in the maxillofacial region does not heal within 8 weeks in a patient treated with an antiresorptive agent[1-7]. While MRONJ is reported as a rare adverse event in patients with osteoporosis, its incidence is higher in cancer patients with bone metastases or malignant hypercalcemia (up to 1 – 10% of patients)[8,9]. However, even in patients with osteoporosis, there is an increased risk of MRONJ following oral surgical therapies. For this reason, an evaluation of the route of administration of antiresorptive drugs, the duration of treatment, and the drug withdrawal period are essential to prevent post-operative MRONJ in this patient category[10]. The pathophysiology of MRONJ remains incompletely understood, with oral microbiota and dental infections considered central to its development[11-14]. Since the initial reporting of MRONJ more than 20 years ago, attention has been directed toward the association between tooth extraction and adverse events in patients already receiving ONJ-related medications[15,16]. Recently, dentoperiodontal and peri-implant infections have been highlighted as key local risk factors for MRONJ, often serving as the primary rationale for surgical procedures involving tooth extraction or implant removal[17-22]. The link between periodontal disease and the development of MRONJ has been extensively demonstrated, with the spread of bacteria through periodontal pockets identified as a primary mechanism for infection propagation through the alveolar bone. Notably, the promotion of MRONJ development is likely influenced not only by the presence of *Porphyromonas gingivalis* and other periodontogenic bacteria in the periodontal pockets but also by IgG products[3,18,23-26].

1.1. Monitoring and evaluation of the patient candidate for therapy with antiresorptive drugs

Primary prevention aims to eliminate oral and dental risk factors by focusing on restoring and/or maintaining good oral health, thereby reducing the risk of pathological conditions or other adverse events[26-30].

The preventive protocols and recommendations include several key practices, including completing necessary oral surgery before initiating antiresorptive drug therapy, administering antibiotics 2 – 4 days before and 7 – 10 days after the surgery procedures, using antimicrobial mouthwash, ensuring adequate wound closure after tooth extraction, and maintaining good oral hygiene[31,32]. Therefore, the International Task Force on Osteonecrosis of the Jaw recommends that during invasive oral surgery, patients should have their anti-resorptive therapy withheld until soft-tissue healing occurs[33]. Another equally important recommendation includes initiating MRONJ prevention before, during, and after the end of antiresorptive therapy[6,10,26,27,33-36] (Table 1). For low-risk patients, the same recommendations apply to preventive dental visits, maintaining optimal oral health aligned with general population standards. However, for cancer patients, the dental checks will be more stringent.

2. Systematic review methods

We conducted a literature review to compile practical guidelines for health-care professionals regarding the management and maintenance of oral health in patients at risk of MRONJ. The search for scientific articles was conducted on medical databases such as PubMed, Cochrane, and Google Scholar on October 23, 2023. The keywords used were "Prevention and MRONJ," "Oral hygiene and MRONJ," and "Microbiota and MRONJ". In addition, a manual search was conducted to improve the article pool. The search strategy is summarized in Table 2.

After preliminary screening and removal of duplicates, the abstracts and titles of articles were assessed to determine eligibility for further evaluation. The selected

Table 1. Prevention of osteonecrosis of the jaw related to antiresorptive drugs

Prevention before, during, and after treatment	• First visit with complete radiographic examinations • Complete oral-dental examination, evaluation of the mucous membranes and tongue • Careful examination of the condition of the back of the tongue • Dental formula • Compilation/updating of the periodontal record • Evaluation of the quantity and consistency of saliva • Mapping of oral lesions • Photographic documentation • Oral checks (4 – 6 months) • Instruct the patients to maintain optimal oral health and to recognize possible signs and symptoms of MRONJ

Table 2. Article search strategy

Search strategy	Parameters
Keywords	• Prevention and MRONJ • Microbiota and MRONJ • Oral hygiene and MRONJ
Publication years	• 2003 – 2023
Electronic database	• PubMed • Cochrane • Google Scholar

Abbreviation: MRONJ: Medication-related osteonecrosis of the jaw.

articles were ultimately included for qualitative analysis. The inclusion criteria encompassed articles in any language reporting clinical trials, expert reviews, literature reviews, meta-analyses, and systematic reviews. The exclusion criteria were scientific articles not reporting on primary prevention and oral hygiene in patients with MRONJ, as well as case reports.

3. Results

A total of 1,735 articles were retrieved from manual and electronic databases. Out of these, 1,323 articles were reviewed, and eight were considered to meet the inclusion criteria for qualitative review (Figure 1).

3.1. Synthesis of results

In efforts to prevent MRONJ, there is a significant focus on optimizing oral health, given its demonstrated effectiveness in reducing the associated risk. The included articles concur that primary prevention plays a fundamental role in maintaining healthy oral microbiota and mitigating the risk of MRONJ (Table 3).

4. Discussion

The included studies affirm and emphasize the need for multidisciplinary dialog among specialists involved in both primary and secondary prevention of MRONJ. While systemic risk factors, such as oncological disease and comorbidities associated with hyperthyroidism, diabetes, hypovitaminosis D, rheumatoid arthritis, hypocalcemia, osteomyelitis, chronic renal failure, and anemia, pose challenges in terms of modification, they remain open to improvement. In contrast, local risk factors are modifiable and offer a wide field of intervention through primary prevention and secondary. The control of local inflammatory factors, especially those associated with dento-periodontal and peri-implant conditions, is considered one of the main risk factors contributing to the development of ONJ. The ONJ International Task Force highlights the importance of managing periodontal disease before the commencement of antiresorptive therapy[6,9,26,27,32,37-52]. Preventive protocols and comprehensive oral and extraoral clinical examination must be conducted indiscriminately in patients with dentition, as well as in edentulous patients, especially for those utilizing removable dentures. This is crucial since removable dentures are identified as risk factors linked to ONJ and have the potential to induce microtrauma to the oral mucosa, creating an environment conducive to predominantly fungal bacteriology. Mechanical cleansing of the mucous membranes is beneficial not only for disorganizing the bacterial biofilm but also for stimulating blood circulation and improving resistance to trauma[53]. Therefore, even in these patients, the initial pre-treatment visit should include a complete clinical and radiographic examination, along with precise mapping of the oral mucosa through accurate photographic documentation. For individuals utilizing prosthetic devices, meticulous

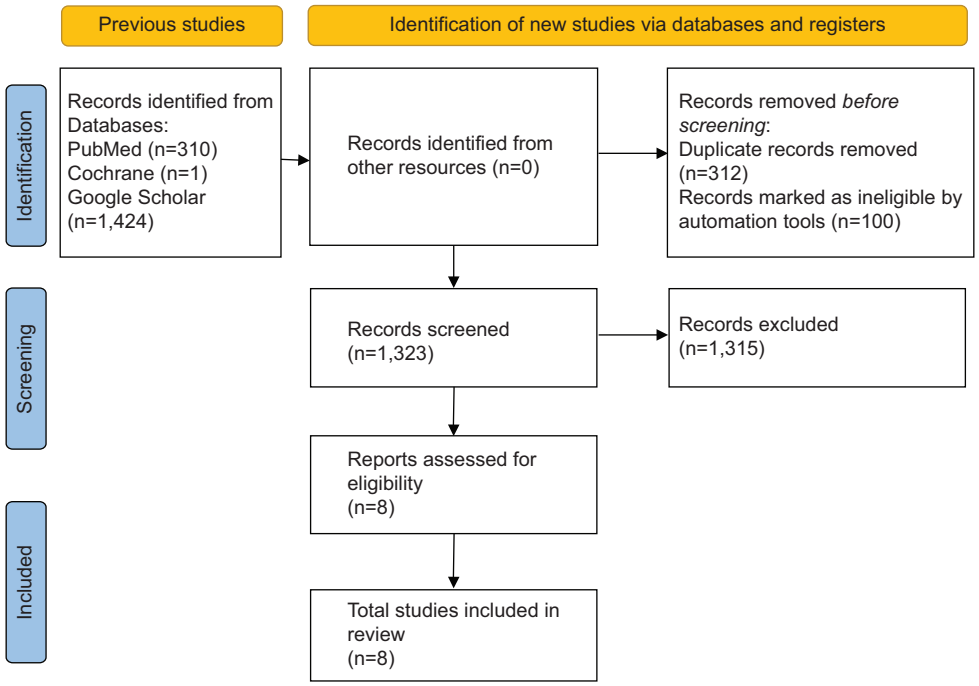


Figure 1. PRISMA flowchart assessment of the included studies.

Table 3. Information of articles included in this review

Studies	Key outcomes/findings
AlRowis *et al.*[41]	Careful dental preparation and instructions on oral hygiene significantly reduce the risk of ONJ.
Nicolatou-Galitis *et al.*[27]	Oral clinicians play a critical role in the prevention of MRONJ as part of a multidisciplinary team.
Drudge-Coates *et al.*[38]	Health-care professionals can play a key role alongside prescribers and oral clinicians in assessing the risk of MRONJ, thereby contributing to the prevention and management of the care pathway for these patients.
Fassio *et al.*[9]	The majority of patients with MRONJ can be managed conservatively through optimal oral hygiene, regular professional dental care, and elimination of active dental and periodontal disease.
Khan *et al.*[32]	The development of ONJ can be mitigated by optimizing oral hygiene, and periodontal disease must be managed before starting doses of antiresorptive drugs.
Migliario *et al.*[42]	Primary prevention, carried out by dental hygienists, and secondary prevention, through professional oral hygiene and periodic monitoring of the oral health status of patients at risk, are of fundamental importance to prevent the onset of lesions.
Campisi *et al.*[6]	The diagnosis and prevention of MRONJ play a significant role not only in the quality of life of patients but also in the decision-making process of the majority of doctors involved in the prevention of ONJ (primary and secondary).
Di Fede *et al.*[26]	The application of primary and secondary prevention protocols by doctors and oral hygienists, in synergy with prescribers and adequate patient awareness, is key to implementing strategies aimed at a common objective – the reduction of MRONJ outbreaks.

Abbreviations: MRONJ: Medication-related osteonecrosis of the jaw; ONJ: Osteonecrosis of the jaw.



Figure 2. A brochure outlining oral hygiene clinical protocols for patients undergoing antiresorptive drug treatment. The content of the brochure is modified from references Giovanna Mosaico *et al.*[30], Drudge-Coates *et al.*[38], Migliario *et al.*[42], and National Cancer Institute[44].

finishing and polishing, especially in the lower jaw, are imperative, as the edges of these prosthetic artifacts must be rounded and beveled[54,55].

At each follow-up visit, it is essential to reinforce the motivation for maintaining oral health and controlling diabetes and MRONJ-related risk factors (Table 3)[56]. To encourage patient compliance and raise patients' awareness of the importance of home oral hygiene, an oral hygiene manual may be provided during the first visit with oral health professionals. Furthermore, this same informational brochure could be disseminated in advance by the rheumatologist, orthopedist, and oncologist, aiming to promptly activate the MRONJ preventive

protocols. This approach is consistently directed toward the patients' health and underscores the importance of a multidisciplinary manner (Figure 2). Maintaining healthy lifestyles in MRONJ patients includes several key elements:

- Blood sugar control;
- Elimination of risk factors such as smoking and alcohol consumption;
- Adherence to proper nutrition rich in vitamins and avoiding excessively sour, spicy, crunchy and hot food;
- Vigilance toward possible injuries or pains in the oral cavity;
- Control of bacterial biofilm through oral hygiene practice, including brushing of teeth, gums, and tongue, conducted twice a day.

4.1. Professional oral hygiene in cancer patients at risk of MRONJ

Professional oral hygiene is increasingly indicated in the recent literature for cancer patients at risk of MRONJ. However, a clear and unequivocal operating protocol for oral professionals caring for these patients is currently lacking[43].

Minimally invasive non-surgical periodontal therapy must be carefully planned to ensure regular removal of plaque and tartar, together with periodic clinical screening of the oral and periodontal health status of patients undergoing treatment. For the management of acute gum disease, chlorhexidine rinses at concentrations between 0.12% and 0.2% are recommended, administered 2 to 4 times a day, depending on the severity. Nonsurgical periodontal therapy can be performed when there are no significant oral lesions that limit mouth opening and when the neutrophil count is >2,000/ml and the platelet count is >40,000/ml. The professional oral hygiene program includes the compilation and updating of the periodontal record, including recording the probing depth, clinical level of attachment, recessions, mobility, and furcation involvement. Furthermore, the evaluation of periodontal health includes the evaluation of the quality of oral hygiene, including plaque and bleeding indices. Professional oral hygiene procedures encompass deplaquing and tartar removal utilizing low-frequency mechanical instruments. Moreover, the program emphasizes the strengthening and education of home oral hygiene practices, covering both the oral cavity and dentures, to mitigate the risk of periodontal infections[42,44]. Therefore, it is essential to plan a follow-up period of 3 – 4 months for cancer patients undergoing treatment and 6 months for patients at low risk of MRONJ. This planning should not overlook the significant role of the patient in maintaining effective oral hygiene at home, including self-screening[45,46].

If MRONJ is suspected, it is imperative to refer the patient promptly to an oral and maxillofacial surgeon or a specialized cancer center. In the meantime, the dentist may consider prescribing a mouthwash containing 0.12% chlorhexidine and/or a course of amoxicillin with clavulanic acid to treat any related infections[47-50].

4.2. Limitations

MRONJ remains a condition marked by uncertain and controversial aspects among the most recently studied oral diseases. Numerous questions persist, particularly concerning the diagnosis, the optimal frequency of checks, and the formulation of effective professional and home oral hygiene protocols. The objective of this review is to shed light on the management of primary prevention and provide guidance to oral health professionals for patients at risk. The limited number of studies available for analysis is a notable constraint, indicative of the scarcity of studies conducted on this specific topic. Future studies will be essential to validate the preliminary findings and establish a more comprehensive understanding of MRONJ.

5. Conclusion

The number of patients, both with cancer and without, undergoing treatment with MRONJ-related drugs and, therefore, the potential occurrence of adverse events appears to be steadily increasing. Recent confirmation highlights that effective prevention of MRONJ necessitates the application of appropriate protocols for primary prevention in both pre-treatment and treatment phases for patients receiving antiresorptive drugs. The Consensus Conference emphasizes the importance of adherence to these principles by key figures such as physicians, drug prescribers, dentists, and oral hygienists. To improve the efficacy of therapeutic strategies and enhance the quality of life for patients, a standardized multidisciplinary approach is recommended. Central to the prevention strategy is periodontal therapy, personalized oral hygiene education, and motivation for adopting healthy lifestyles. Periodontal screening remains indispensable for clinicians, facilitating the establishment of a correct multidisciplinary approach to managing MRONJ. The examination of the posterior aspect of the tongue emerges as a valid indicator of the patient's microbiota status, offering the possibility of conducting minimally invasive bacteriological tests to monitor bacterial load.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Giovanna Mosaico
Formal analysis: Giovanna Mosaico
Investigation: Giovanna Mosaico
Methodology: Cinzia Casu
Writing – original draft: Giovanna Mosaico
Writing – review & editing: Cinzia Casu

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

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Further disclosure

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