Medication-related osteonecrosis of the jaw (MRONJ): New insights on ethically responsible risk preventive strategies.
Part 1: Current knowledge and controversial issues

Johan Hartshorne[1] and Hugo Johan Kotzé[2]

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[1] Johan Hartshorne
B.Sc., B.Ch.D., M.Ch.D., M.P.A., Ph.D. (Stell), FFPH.RCP (UK)
General Dental Practitioner
Intercare Medical and Dental Centre, Tyger Valley, Bellville, South Africa, 7530
Email: johan.laptop@intercare.co.za

[2] Hugo Johan Kotzé
BDS (UWC)
General Dental Practitioner
Intercare Medical and Dental Centre, Tygervalley, Bellville, South Africa, 7530
Email: hugokotze17@gmail.com

Executive summary

Clinical significance

- Medication-related osteonecrosis of the jaw (MRONJ) is a rare but serious adverse effect that occurs primarily in patients taking anti-resorptive (AR) and/or antiangiogenic agents (AA) for the treatment of metastatic cancer or osteoporosis.
- Dentists play a significant role in identifying at-risk patients, implementing preventive measures, and ensuring early detection of MRONJ.
- The purpose of this three-part narrative review is to: (i) summarize current knowledge and controversies related to MRONJ; (ii) inform dental practitioners on the risk factors, triggers, and modifiers associated with MRONJ and to provide an ethical framework for clinical decision-making; and (iii) provide guidance on ethically responsible preventive strategies.

Key points

- Anti-resorptive (AR) and anti-angiogenic (AA) medications are the most common pharmacological classes that are associated with the development of MRONJ.
- AR and AA therapy are typically prescribed in the management of osteoporosis and cancer metastases.
- MRONJ may occur spontaneously or because of invasive dental procedures.
- Tooth extraction is identified as a principal precipitating factor for MRONJ.
- The estimated global incidence of MRONJ is 4,34%.
- MRONJ is more prevalent among elderly women and predominantly affects the mandible.
- A comprehensive patient medical history and clinical oral and dental assessment remain the most sensitive diagnostic tools for early detection and prevention of MRONJ.
- Computed Tomography (CT) imaging has become the gold standard for detecting

the most common characteristics of MRONJ, which include osteolysis and osteosclerosis

Practice implications

- Dental practitioners play a critical role in early detection of patients at risk, preventive dental care, and comprehensive management, and increasing patient awareness to reduce MRONJ risk.
- Comprehensive medical and dental history, clinical assessment, and orthopantomography are crucial and should serve as the initial investigative method for prevention and management of MRONJ
- Prevention and management of MRONJ necessitate a multidisciplinary framework that emphasises inter-professional collaboration and liaison.
- For medically complex patients whom you would normally seek advice, including higher-risk patients who are being treated with AR or AA medications for the management of cancer, it is ethically responsible to consult an oral maxillofacial specialist (OMFS) concerning clinical assessment and treatment planning.

Background

- ***The problem***

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but serious (adverse condition) complication in patients receiving anti-resorptive (AA) and/or antiangiogenic (AA) therapy for bone metastatic cancers or osteoporosis, causing progressive bone destruction in the maxillo-facial region.[1-5] MRONJ may occur spontaneously or following invasive dental procedures such as tooth extraction, periodontal treatment, implant placement, or the use of ill-fitting dentures. Among these, tooth extraction remains the most common precipitating event. [2,4,6]

Clinical manifestations include delayed healing following a dental extraction or other dentoalveolar intervention, pain, soft tissue infection and swelling, numbness, paraesthesia, or exposed bone.[7] Some patients, however, may be asymptomatic at presentation, with MRONJ detected incidentally during examination.[7] A history of AR or AA medication use in these patients should alert dental practitioners to the possibility of MRONJ.[7]

MRONJ has emerged as a significant comorbidity in cancer patients treated with AA or high doses of AR medications such as bisphosphonates (BPs) or denosumab.8 In patients diagnosed with osteoporosis, AR medications such as BP and denosumab are commonly used as part of treatment. While in patients with osteolytic bone diseases such as bone metastasis from solid tumours (e.g., breast, prostate, and lung cancer), treatment protocols typically include a combination of AR and AA medications. These medications are essential for managing disease progression as well as the skeletal consequences from osteoporosis or bone metastases, which can lead to increased pain, mortality rates, and reduced quality of life.[10,11]

Although these therapies are effective in controlling skeletal-related events, they may carry the risk of MRONJ. However, the benefits of these medications on managing the primary disease (i.e., bone metastatic cancers, osteoporosis, and bone diseases) far outweigh the risk; therefore, the prevention of MRONJ is of critical importance.

The alveolar bone of the jaw exhibits a unique physiological function and anatomical structure, including its high intramembranous ossification activity, elevated calcium and collagen levels, and a diverse oral microbial environment, which makes it more susceptible to MRONJ.1[2,13] In general, MRONJ is more prevalent among older women and predominantly affects the mandible.[14] Patients can present with multiple oral complaints that significantly impair the quality of life.[15]

- ***The Challenge***

Dentists play a critical role in identifying patients at risk and ensuring early detection of MRONJ.[16] Dental practitioners are frequently challenged with the clinical dilemma of whether tooth extractions are safe in patients receiving AR or AA medications for osteoporosis and bone-metastatic cancers.[17]

The global prevalence and burden of osteoporosis[18] and cancers such as prostate, breast, and lung cancer, and multiple myeloma continue to rise every year[8,19], resulting in an associated rise in the use of AR and AA medications. With the increasing use of these medications, there is an associated increase in the incidence of MRONJ cases, making MRONJ risk prevention and dental treatment very challenging.[8,17,20]

Assessing risk, preventing, and managing MRONJ are challenging clinical processes with significant implications for patients and clinicians.[1,5,9,21] Therefore, preventive interventions should be implemented before, during, and after AR or AA therapy to minimise MRONJ risks.[20,22-27]

- ***Purpose and Scope***

This three-part narrative review series is primarily directed at dentists who manage patients receiving AR or AA medications prescribed for the prevention and treatment of various medical conditions. The objective of this series is as follows:

Part 1: Current knowledge and controversial issues - to summarize current evidence-, consensus-, and expert opinion-based knowledge together with emerging insights related to MRONJ.

Part 2: Risk factors, triggers, and modifiers and ethical considerations - to inform dental practitioners on the risk factors associated with MRONJ and guide classification of a patient's risk level, and define the ethical principles of clinical decision-making for prevention of MRONJ.

Part 3: Preventive strategies for minimising risk of MRONJ - to provide clinical guidance on ethically responsible preventive strategies aimed at (i) minimising the risk of MRONJ in patients before treatment; (ii) managing those currently receiving AR or AA treatment for osteoporosis or metastatic bone cancers; and (iii) applying preventive strategies when tooth extraction is indicated.

The specialist management and treatment of patients with MRONJ is beyond the scope of this series and is discussed in detail elsewhere.[4,5,8,9,12,28,29,30]

Current Knowledge and Insights Related to MRONJ

• *Case definition of MRONJ*

According to the American Association of Oral and Maxillofacial Surgeons (AAOMS), a patient must meet all the following criteria to establish a correct MRONJ diagnosis:[4]

(i) Previous or current use of AA or AR medications alone, or AR in combination with AA medications or immune modulators;

(ii) Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks; and

(iii) No history of radiation therapy or metastatic disease to the jaws.

• *Incidence of MRONJ*

MRONJ is generally considered to be a rare condition, with prevalence and incidence rates largely derived from estimated data. Without true incidence data, clinicians cannot confidently and ethically provide patients with evidence relating to risk when prescribing antiresorptive and antiangiogenic medications or when undertaking procedures (e.g., extractions) that may precipitate MRONJ.[21]

In a recent review of the global incidence of MRONJ, the overall mean incidence of MRONJ across all studies was 4.34% (median 2.42%, range 0% to 31.8%) (Range: 0 – 3180 cases of MRONJ per 10,000) The mean incidence reported per patient group was cancer patients (6.22%) (Range: 0 – 3180 cases MRONJ per 10000 (number of participants 32954), osteoporosis (0.58%) (Range: 0 – 389 cases of MRONJ per 10000) (number of participants 498443), and cancer and osteoporosis (7.21%) (Range: 0 – 2760 cases of MRONJ per 10000) (number of participants 547651).[21]

• *Pathogenesis of MRONJ*

A thorough knowledge and understanding of the theories and potential mechanisms of MRONJ etiopathogenesis is essential for identifying at-risk populations and enabling appropriate preventive and treatment interventions.[8,9,31,32] According to the scientific literature, the pathophysiology of MRONJ is considered multifactorial, but remains incompletely understood.[32,33] Although the mechanisms by which these medications cause MRONJ have not been clearly elucidated,[32] several theories have been suggested, including: over-suppression of bone turnover and remodelling, soft tissue bisphosphonate toxicity, chronic microtrauma, inhibition of angiogenesis, suppression of innate or acquired immunity, vitamin D deficiency, alterations in bone remodelling, and infection and inflammation.[4,12,34,35,36,37,38]

According to the American Cancer Society,[39] disruption in bone remodelling in metastatic disease may be caused by systemic or locally acting factors such as parathyroid hormone, prostaglandins, or interleukins, and usually results in a mix of disordered osteoblastic and osteoclastic activity. All the bone-modifying agents (ARs) share the ability to suppress osteoclast activity, reducing bone turnover that can affect bone-healing capacity.[40] ARs suppress osteoclast function and remodelling, which is beneficial for fracture prevention but may impair socket healing and predispose to MRONJ in the presence of oral inflammation or surgical trauma.[40]

Osteonecrosis is broadly defined as necrosis of the bone due to obstruction of the blood supply.[41] Because osteonecrosis is classically considered an interruption in vascular supply, inhibition of angiogenesis by the AA medications is considered a likely risk factor.[1,4,12,42]

• *Diagnostic criteria and clinical stages of MRONJ*

The classification of MRONJ clinical stages was originally developed by Ruggiero in 2006 and was introduced and adopted by the AAOMS in 2009, updated in the 2014

MRONJ Position Paper[43], and kept the current classification without changes in the AAOMS 2022 MRONJ Position Paper.[4]

A comprehensive medical and dental history, clinical assessment, and orthopantomography are crucial and should be the initial investigative method for the prevention and management of MRONJ.[8] For a more thorough assessment, digital imaging techniques such as cone-beam computed tomography (CBCT) are recommended.[44,45] CBCT enhances differential diagnosis by distinguishing MRONJ from other conditions with similar features while also providing more detailed information on disease extent in patients with overt disease."[46]

Radiographic characteristics such as sclerotic bone or a combination of radiopaque and radiolucent lesions, along with the presence of a non-healing extraction socket, are commonly present in the early stages of MRONJ.[8]

The radiographic signs in MRONJ include a persisting alveolar socket, osteosclerosis, osteolysis, thickening of the lamina dura, narrowing of the mandibular canal, widening of the periodontal ligament space, and sequestrum formation.[40] The radiographic presentation in advanced stages of MRONJ may include sequestrum formation, lamina dura thickening, and pathological fractures.[45]

Computed tomography has become the gold standard method for detecting the most common characteristics of and staging of MRONJ.[47,48]

Insights into controversial issues

The 2022 AAOMS position paper remains the most widely cited surgical guidance. It emphasises pre-therapy dental optimization, avoidance of dento-alveolar surgery when feasible, preference for root-retentive strategies, and cautioning that "drug holidays" (medication interruption) remain controversial due to limited evidence.[4]

Similarly, the American Dental Association (ADA) reports insufficient evidence to recommend routine drug holidays or the use of serum bone turnover markers (e.g., CTX) to predict risk. The Scottish Dental Clinical Effectiveness Program (SDCEP)[8] provides practical, primary-care-oriented guidance for managing patients at risk of MRONJ.[7]

• *8-Week diagnostic window period – Wait or referral*

The diagnostic eight-week MRONJ case definition is intended as a gatekeeper to improve the specificity of the diagnostic criteria for MRONJ (See case definition) by excluding other conditions expected to resolve within that timeframe. This arbitrary window may lead to delays in referral and treatment, potentially leading to risk of harm to the patient.[40]

• *Use of CBCT – diagnostic accuracy or overtreatment*

Advanced digital imaging techniques such as computed tomography (CT) and conebeam CT (CBCT) can contribute to a more thorough radiographic assessment, producing high-quality tomographic images that reveal the presence of MRONJ lesions.[49,50] It is suggested that these advanced imaging techniques (CT and CBCT) should be incorporated into the MRONJ diagnosis and staging guidelines to improve early detection and determine disease extent.[40,49,50] Radiographic 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.[49]

Subsequently, CT imaging has become the standard method for detecting the most common characteristics of MRONJ, which include osteolysis and osteosclerosis.[47,48]

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).[47] Unlike panoramic radiographs, CT is also effective in detecting MRONJ signs, such as changes in trabecular bone density and bone sequestrum/sequestra.[47,48]

In clinical trials, CT showed a higher sensitivity in detecting MRONJ at 96%, compared to 54% for panoramic radiographs and 92% for MRI.[47,50,51] Thus, for clinical staging purposes, CT imaging is highly recommended.[47,48]

Advanced digital imaging is sometimes necessary for suspected cases of MRONJ to provide further comprehensive diagnostic imaging to confirm suspected MRONJ diagnoses. The main concern is that with CBCT and CT, the Stage 0 terminology may lead to MRONJ overdiagnosis and thus overtreatment that may not serve the patients' best interest.

• *Drug Holidays (Medication interruption) – risk vs benefit*

Current evidence remains insufficient to endorse routine drug holidays for osteoporosis-dose AR to prevent MRONJ in dental surgery. Clinicians should avoid over-promising benefits and instead emphasize good surgical technique and infection control. For patients receiving denosumab, prolonged delay is potentially harmful due to rebound fracture risk; any short postponement should be deliberate, brief, and coordinated with the prescribing physician.

Key extrinsic risk enhancers include active periodontal/endodontic infection, traumatic extractions, poor oral hygiene, and ill-fitting dentures. Denosumab—via RANKL inhibition—has a pharmacokinetic profile (rapid onset/

offset) with concern for rebound vertebral fractures if doses are delayed excessively; this complicates the ethics of drug holidays.

Further research is required to identify subgroups that may benefit from temporarily interrupting AR/AA therapy before an intervention, considering the potential risk of rebound remodelling after stopping AR therapy.[40]

In a recent study conducted by Park and co-workers (2025), it was found that in patients treated with BPs, the risk for MRONJ was substantially lower when AR treatment was paused for 90 days, and lowest risk when treatment was paused for 1 year. The risk reduction was more consistent with ibandronate users, whereas with zolendronate, only treatment pauses longer than one year showed a meaningful risk reduction.[52] The level of evidence supporting the "drug holiday" concept is limited, and therefore, the AAOMS panel has not reached a consensus on its recommendation.[4,53]

• Biomarkers (e.g., CTX) – Optimal timing for dento-alveolar surgery

Currently, no bone turnover marker has been validated for determining the optimal timing for dentoalveolar surgery in patients using AR medications. 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.[4]

Major professional organisations do not recommend serum CTX or other turnover markers to predict MRONJ risk in this setting. Consequently, it is suggested to rely on clinical risk assessment and sound surgical technique.

• Adjunctive Preventive Measures

Systematic reviews comparing adjuncts (e.g., platelet-rich fibrin (PRF), socket grafting, laser bio stimulation) have not demonstrated clear superiority across studies; clinicians may consider them selectively, but patient counselling should reflect the uncertain incremental benefit. In a recent study, no superiority was demonstrated between preventive strategies (PRF, oxygen-ozone therapy, and different surgical closure techniques) in reducing the risk of MRONJ in patients undergoing tooth extraction.[17,54]

Conclusion

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but serious adverse condition, triggered mainly by invasive dental procedures such as tooth extraction in patients receiving AR and/or AA therapy for bone metastatic cancers or osteoporosis.

Although overall MRONJ incidence remains relatively low, its clinical implications warrant increased awareness among dental practitioners, particularly those involved in the dental management of cancer and osteoporotic patients receiving AR and/or AA therapy.

With the increasing number of patients undergoing AR or AA medication and the significant morbidity associated with MRONJ, dental practitioners will increasingly face the challenge of early identification of patients at elevated risk of MRONJ.

In treatment decisions where complications are readily corrected, decisions are implemented and a straightforward fashion. However, where complications are significant, deciding to treat becomes more challenging. It is of utmost importance that dental practitioners base their patient treatment decisions on currently available scientific evidence. Dentists play a crucial role in primary prevention by early detection of patients at risk of MRONJ, regular oral examinations, and prioritising oral health by encouraging patients to maintain good oral hygiene and scheduling regular check-ups, prompt diagnosis, and comprehensive treatment of local dental and periodontal infections. Clinicians should anchor their clinical decisions in transparent consent, individualized risk assessment, and interprofessional collaboration and liaison.

While dentists may be first in line to diagnose and treat patients, they have to collaborate closely with oncologists and physicians in a coordinated manner to be able to diagnose and treat patients with a greater chance of success.

Although no single technique or measure can eliminate MRONJ risk, recognising risk factors and using tailored preventive measures for individual patients remains the most effective approach.

Many existing recommendations about MRONJ are based on limited high-level evidence, thus requiring higher-quality investigations for evidence-based treatments.

Furthermore, several controversies with ethical implications were identified where consensus is lacking. Ongoing research is required to elucidate the fundamental factors and modifiers of MRONJ patient-and treatment-specific risk factors, severity, progression, and healing to inform clinical decision-making and to determine what treatment is in the patients' best interest.

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