



OSTEONECROSIS OF THE JAWS. ANALYSIS OF RISK FACTORS AND DENTAL MANAGEMENT STRATEGIES- PART I

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ABSTRACT

This comprehensive review examines medication-related osteonecrosis of the jaw (MRONJ), a complex and debilitating pathological condition primarily associated with the use of anti-resorptive agents such as bisphosphonates and denosumab, as well as anti-angiogenic drugs. The article discusses the recent shift from the term BRONJ to MRONJ to reflect the broader range of causative medications. It details the pathophysiological mechanisms—including alterations in bone remodeling, impaired osteoclastic activity, compromised vascularization, and immune dysfunction—that contribute to its development. The review analyzes various risk factors, encompassing pharmacological variables (drug type, dosage, route, and duration), systemic health conditions (such as diabetes, osteoporosis, and cancer metastases), and local factors like invasive dental procedures and chronic inflammatory diseases. Prevention strategies focus on meticulous risk assessment, oral health optimization, timing of treatments, and minimally invasive surgical protocols. The potential utility of biomarkers, particularly serum CTX levels, for early risk prediction is explored, although further validation is needed. The review underscores the importance of further prospective studies to improve understanding of the pathogenetic mechanisms, validate prognostic biomarkers, and evaluate innovative treatment options, ultimately aiming to enhance patient management, reduce incidence, and preserve quality of life in at-risk populations.

KEYWORDS: *MRONJ, anti-resorptive, risk factor, prevention, biomarker*

INTRODUCTION

The American Association of Oral and Maxillofacial Surgeons (AAOMS) has recently proposed replacing the term "bisphosphonate-related osteonecrosis of the jaw (BRONJ)" with "medication-related osteonecrosis of the jaw (MRONJ)." This modification takes into account the increase in cases of osteonecrosis due to drug intake. When we talk about osteonecrosis of the jawbones, we refer to a pathological condition in which the bone cells die for various reasons. Anti-angiogenic and anti-resorptive agents can cause drug-induced osteonecrosis, the latter being the result of the combination of drugs, microbiota, and trauma. When we talk about MRONJ, we are referring to a highly debilitating condition that presents a high mortality rate. This pathological condition is associated with problems in swallowing, feeding, and the appearance of oedematous and painful mucous membranes (1). To make a diagnosis, certain criteria are

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taken into consideration: Ongoing or previous therapy with anti-resorptives, exposed bone persisting for more than eight weeks, absence of radiotherapy in the jaw area (2). The risk of developing osteonecrosis is correlated with the type of drug taken, its dosage, the method of administration (parenteral/oral), and also the duration of the treatment. All those that fall under invasive therapies predispose the onset of such a condition, including: dental extractions, periodontal surgery, and implant surgery; as additional risk factors, poor oral hygiene, periodontitis, and other inflammatory conditions are included. This pathology predominantly affects the mandible, particularly the lingual portion, due to its thin mucosa and poor blood supply (1). The American Association of Oral and Maxillofacial Surgeons introduced a classification in 2007 that includes three stages for cases of medication-related osteonecrosis of the jaw. In the First stage, we have exposure of necrotic bone, without painful symptoms and without any signs of infection. In the Second stage, it manifests with exposed necrotic bone accompanied by clinical signs of infection. In the Third stage, we have the presence of exposed necrotic bone, painful symptoms, infection, extraoral fistulas, oroantral and orosinus communications, pathological fractures of the mandible, and extension of necrosis involving: zygoma, maxillary sinus, mandibular ramus, or the lower border of the alveolar bone (3). This article focusses on the phenomenon of medication-induced osteonecrosis of the jaws, analyzing the possible causes, risk factors (pharmacological, systemic, local, genetic, and demographic), the anatomical and pathophysiological characteristics involved, and the prevention strategies and diagnosis. The role of anti-resorptive drugs (such as bisphosphonates and denosumab) and anti-angiogenic agents in the genesis of MRONJ is examined, highlighting the importance of alterations in bone remodeling, osteoclastic activity, vascularization, and immune response. Specific risk factors related to dental procedures and in relation to the anatomical and biomechanical changes of the maxillary bone are also discussed.

MATERIALS AND METHODS

This review article was conducted through a search and critical analysis of the existing scientific literature on medication-related osteonecrosis of the jaw (MRONJ). Electronic databases such as PubMed, Scopus, and Google Scholar were consulted to identify relevant published articles, using specific keywords such as drug-induced osteonecrosis of the jaws, MRONJ, bisphosphonates, denosumab, etc. Clinical studies, reviews, and case reports relevant to the etiopathogenesis, risk factors, diagnosis, prevention, and treatment of MRONJ were included, excluding irrelevant articles. The extracted information was organized into thematic categories (definition, mechanisms, drugs, risk factors, clinical aspects, prevention, biomarkers), synthesized, and critically analysed for a comprehensive overview, with attention to gaps and controversies and an assessment of methodological quality.

DISCUSSION

Among the possible hypotheses that could induce MRONJ are: bone remodeling with alteration of osteoclastic/osteoblastic activity and inhibition of angiogenesis with compromised vascularization due to the drugs, immune dysfunction with possible infections, inflammation, and reduced salivation with the presence of constant microtraumas (4,5). Anti-resorptive drugs inhibit the differentiation of osteoclastic cells, which causes apoptosis and leads to a reduction in bone resorption and remodeling. In particular, bisphosphonates, in addition to osteoclasts, also influence the activity of osteoblasts, fibroblasts, and keratinocytes. When the death of fibroblasts affects the oral epithelial cells, there is bone exposure and delayed healing, which plays a key role in the onset and development of osteonecrosis (2). Although the differentiation and function of osteoclasts play an important role in the process of healing and bone remodeling in all skeletal regions, MRONJ mainly occurs only in the alveolar bone of the maxilla and mandible. The high rate of bone resorption in the maxilla explains the different predisposition to the development of MRONJ compared to other portions of the axial and vertical skeleton (6). It has been demonstrated that human jaws have a higher collagen content compared to long bones, and these anatomical characteristics make the mandible more prone to osteonecrosis. 55 Bisphosphonates act on both cytokines responsible for osteoclastogenesis, such as IL-6, IL-17, IL-23, and IFN- γ , suppressing their action, while increasing the activity of anti-osteoclastogenic cytokines such as IL-4, IL-10, and TGF- β . The first to demonstrate that TGF- β signalling is involved in the pathogenesis of MRONJ were Wehrhan et al.; this signalling pathway is crucial for bone remodeling through increased matrix production and osteoblast differentiation (7). Maxillary osteonecrosis occurs more frequently in the mandible (70%) compared to the maxilla (30%). The occurrence of MRONJ is increasing due to the introduction of more and more new drugs, unlike osteoradionecrosis which is in regression as radiotherapy techniques are continuously improving (1,8).

Risk factors

For conditions like MRONJ, it is essential to classify patients according to the risk level of developing the condition, identifying the risk factors; based on this, the patient may have a high, low, or unidentifiable risk.

One class of risk factors are those related to drugs, where the two main classes of drugs are distinguished preventively: anti-resorptive drugs (e.g., denosumab and bisphosphonates) and drugs with anti-angiogenic activity, among these anti-angiogenic drugs, bevacizumab has been associated with the development of osteonecrosis of the jaw in several cases (9). The type of molecule is a variable, as it varies whether they are bisphosphonates, denosumab, or drugs with predominantly anti-angiogenic activity. Bisphosphonates (BP), especially amino-bisphosphonates like zoledronic acid and risedronic acid, possess a high affinity for bone due to the presence of an amino group and a nitrogen-containing heterocyclic ring in the R2 radical. Ibandronate, with nitrogen fractions in the R2 radical, is more potent than alendronate and pamidronate. Denosumab, on the other hand, inhibits the RANK-L complex, reducing osteoclastic activity, but its effects diminish within six months of discontinuation. This drug also alters the cellular inflammatory response, influencing monocytes. Several studies have highlighted the fundamental role of cells (10) and cytokines (11) in the pathogenesis of oral and intestinal inflammation (12) and in cancer development in diagnosis (13,14). It is also important to consider the route of administration, as orally administered drugs undergo initial metabolism at the intestinal and hepatic levels, which reduces their availability in active form in the bloodstream. The drug administered intravenously is introduced into circulation, bypassing any stations that partially inactivate it, so that it is found in greater quantities in its active form in the blood. For this reason, this second category would be more prone to the onset of ONJ. Another factor is the amount of cumulative dose, this parameter is closely related to the drug's retention in the body and the duration of the treatment; bisphosphonates remain in the skeletal system for a long period of time, with a duration of about 10 years, whereas denosumab has a shorter half-life of about 32 days, and its effects on bone resorption gradually diminish within six months after the end of administration (15,16). As a final factor, we have the duration of treatment, which is a significant factor in the onset of bisphosphonate-associated osteonecrosis of the jaw (ONJ), with manifestation times generally within 2 years for intravenous use and tendentially longer for oral use (usually after 3 years). Regarding denosumab, there are conflicting opinions; some studies suggest that the total dose and duration of treatment do not influence the risk of ONJ, with cases reported even after a single administration, while others indicate that prolonged use may increase the risk (17,18). For anti-angiogenic drugs, simultaneous or subsequent administration with bisphosphonates seems to reduce the onset time of ONJ compared to those who take only bisphosphonates. This period becomes even shorter when only anti-angiogenic drugs are used, both via injection (about 6-7 months) and orally (about 16-17 months).

Another class of risk factors are the systemic ones, which we can distinguish into two groups: In the first group, there are those diseases strongly associated with MRONJ for which the patient is forced to take the drugs considered risk factors, including diseases such as multiple myeloma, prostate cancer, and breast cancer from which bone metastases can arise. In the second group, all those conditions that can generate situations of osteopenia/osteoporosis, altering bone metabolism, are included; among such comorbidities are diabetes, chronic renal failure, and rheumatoid arthritis (15). It has been proven that high blood sugar levels can promote an increase in osteoclast differentiation and cause programmed cell death of osteoblasts. Additionally, the increase in osmolarity caused by hyperglycemia suppresses the expression of osteocalcin, MMP-13, and vascular endothelial growth factor (VEGF), which are essential for osteoblast maturation. Additionally, it has been found that AGEs inhibit the adhesion of osteoblasts to the bone matrix, worsening osteopenia (19). Patients with rheumatoid arthritis receive therapies that include anti-inflammatory drugs, immunosuppressants, and anti-resorptive drugs; it is hypothesized that the increased risk of drug-related ONJ is due not only to the disease itself, which involves a predisposing chronic inflammation, but also especially to the combined effects of anti-resorptive/anti-angiogenic agents on bone metabolism and the immunosuppressive effects of polypharmacological therapy (20). Regarding chronic renal insufficiency, it is associated with reduced calcium reabsorption at the renal level, which can cause secondary osteoporosis (15).

Another class, besides those considered the most important risk factors in the onset of ONJ, are the local factors. Regarding dento-alveolar surgery interventions, there is considerable interest in researching a link between practices such as tooth extraction and the onset of maxillary osteonecrosis. In the 2014 summary document by the American Association of Oral and Maxillofacial Surgeons (AAOMS) on medication-related osteonecrosis of the jaw, oral surgical procedures such as tooth extraction are mentioned as a potential risk factor for the onset of MRONJ (1). Many studies consider tooth extraction to be a risk factor, including a longitudinal cohort study conducted by Vahtsevanos et al., which found that out of a total of 1621 patients with breast cancer, prostate cancer, or multiple myeloma treated with bisphosphonates, 4.9% (60 patients) developed osteonecrosis of the jaws. Moreover, tooth extraction has been associated with a 33-fold increase in the risk of developing MRONJ (21). Numerous studies have shown that among patients with osteonecrosis, tooth extraction is a frequent predisposing factor, occurring in 52%-61% of cases (22). Inflammatory periodontal and peri-

implant diseases also fall under chronic inflammatory conditions, creating local irritation that increases the risk of osteonecrosis in patients taking anti-resorptive medications. Therefore, the effective decontamination of implant surfaces, through the use of ultrasonic ablation, electrolytic cleaning and air-abrasive powders, can help reduce the risk of peri-implant inflammation (23,24). In particular, in the bone, chronic inflammation can predispose to tissue necrosis, which occurs both due to the release of chemical mediators such as cytokines, prostaglandins, and growth factors, which contribute to damaging bone cells, and due to the ischaemic action caused by oedema. A large number of bacteria that we encounter in these inflammatory situations present membrane lipopolysaccharides that have a demolitive effect on bone by activating numerous prostaglandins; Among the most relevant bacterial elements is *Porphyromonas gingivalis*, which has a direct action on RANK-L and osteoprotegerin (15). In confirmation of this, clinical evidence has shown that periodontitis is frequently found in patients with drug-induced osteonecrosis of the jaws and that the extent and severity of periodontitis may be indicative of the risk of developing osteonecrosis (25). Implant therapy is also considered a risk for the onset of osteonecrosis. Not only the surgical procedure of placing dental implants in patients who have received or are receiving antiresorptive therapy, but also the permanence of the bone implants can be linked to the development of osteonecrosis of the jaws. For this reason, two different categories are discussed: the first concerns osteonecrosis following the surgical act of implant insertion (ISTO), and the second is osteonecrosis due to the presence of an already previously osteointegrated implant (IPTO) (26). Certainly, at the present state, it is noteworthy that the majority of peri-implant osteonecrosis is not related to the surgical procedure but rather develops on implants that were previously osteointegrated. Moreover, analyses of some reviews highlight that osteonecrosis is more prevalent in those implants that are under functional load (22). IPTO should be considered closely associated with the appearance of inflammatory phenomena such as peri-implantitis, or the presence of microfractures caused by masticatory occlusal load. In fact, unlike natural teeth, there are no ligaments to absorb the impact of occlusal function, and the forces are transmitted to the peri-implant bone, resulting in the formation of microfractures (15). It is important to emphasise that osseointegration can be influenced by various characteristics of the implants. Studies have highlighted how the macro and nanostructure of the surface (27) and the use or non-use of bone grafts (28) play a crucial role in the biological response and bone integration. A new laser microtopography of dental implants has been shown to positively influence human osteoblast proliferation and bone deposition, potentially improving the outcomes of osseointegration (29). Given that MRONJ can have significant consequences and that implant surgery is a highly selective procedure, it is essential to provide adequate counselling and obtain comprehensive informed consent from the patient (30). Furthermore, the use of innovative grafting biomaterials in regenerated sites has shown promising implant survival rates, improving the predictability of these procedures (31). Despite this, new technologies such as fully digital workflows in implant therapy are improving the precision and predictability of procedures, with potential benefits for osseointegration and trauma reduction (32-34). Therefore, we can say that implant osseointegration is a process that requires proper bone metabolism, namely the resorption of old bone and the formation of new bone by osteoclasts and osteoblasts, respectively. Additionally, for these processes, blood supply and consequently proper angiogenesis will be essential. Both of these elements can be blocked by anti-resorptive drugs, which would therefore inhibit them, leading to the early loss of implants (35).

Finally, it is essential to consider the age of the patient. It has been observed that patients under the age of 24 treated with anti-resorptives for non-malignant bone conditions do not present a risk of developing MRONJ, even with prolonged therapies (1). A systematic review from 2017, considering a group of 4,106 cases of MRONJ, highlighted that 61.5% involved female patients, 31.5% male patients, while in the remaining 7%, the patient's sex had not been clarified. The average age of patients at the time of MRONJ diagnosis was recorded as 65 years. The specific location of MRONJ was reported in only 2,973 cases, with involvement of the mandible in 65% of patients, the maxilla in 28%, while in a minority of cases (7%) both jaws were involved (36). The genetic background can also be a risk factor in the case of MRONJ; a mutation of the CBFA1/RUNX2 gene can be a risk factor (37).

Preventive approaches towards MRONJ

Currently, preventive strategies constitute the most effective method to protect the dental health of patients who need to take, are taking, or have taken medications related to maxillary osteonecrosis. Preventive measures for mandibular osteonecrosis are conducted on patients who are about to start or are already taking drugs related to ONJ, but have not yet shown any oral cavity problems. This type of prevention focusses on controlling the risk factors known to date. Furthermore, treatments for the common side effects of anticancer therapies, such as oral mucositis, can be important. A promising approach for the treatment of oral mucositis is the use of platelet-rich fibrin (PRF), which has shown potential benefits in oncological patients" (38). The main objective is to maintain or restore the health of the patient's periodontium and teeth, both in oncological and osteometabolic contexts. Such an approach aims to reduce the likelihood of developing inflammatory or infectious events that could require invasive procedures. The data in the literature show that there is a

higher risk of osteonecrosis in oncological patients compared to patients undergoing treatment for osteometabolic disorders. For this reason, some authors believe that patients not undergoing oncological therapy need a less rigid preventive protocol, and that these types of patients should start dental treatments 6 months before the start of therapy and undergo regular check-ups every 6 months, similar to a subject without pathology. In oncological patients, however, the state of oral health should be arbitrarily checked 6 months before the start of therapy, and check-ups should be strictly performed every 4 months; if there is a need to perform extractions, they should be carried out 6 months before the start of the therapy, and the latter could be postponed until the complete healing of the site (39). Patients are divided into two categories: those who are scheduled to take drugs related to osteonecrosis but have not yet started the therapy, and those who have already started the therapy or have already completed the therapy. It is necessary to consider the dose of the drug that the patient is taking, and especially for how long. Based on this information, we can distinguish between two categories of patients: high risk and low risk. The patient who receives low doses of medication (bisphosphonates taken orally/denosumab 60 mg every 6 months) for a period of less than 4 years is considered, provided there are no additional risk factors, to be at low risk. Regarding patients who take high doses (intravenous bisphosphonates / denosumab 120 mg every 4 weeks), they are considered at high risk of developing osteonecrosis. Low-risk patients in pre-therapy are those who have yet to start treatment with drugs associated with osteonecrosis of the mandible and should undergo a preventive dental visit before starting the treatments, eliminating inflammations or infections, adjusting any prostheses, and maintaining oral hygiene, waiting for the surgical sites to heal completely before starting the therapy. For those already undergoing therapy, it is important to maintain an optimal state of oral health with regular check-ups and conservative interventions such as root canals and periodontal treatments, avoiding unnecessary invasive procedures, although simple extractions can be performed if the treatment has been initiated for less than three years, considering the low risk. Implant therapy can also be considered for these patients but always informing them about the risks and carefully evaluating each case. Essentially, the goal is to adopt preventive measures and constant monitoring to reduce the risk of complications and osteonecrosis. Instead, in patients identified as high risk, the approaches change. For patients in pre-therapy, that is, those who have yet to start treatment with drugs at risk of ONJ, it is essential to conduct a preventive dental evaluation before starting the therapy. This includes a complete mouth examination, X-rays, and conservative interventions such as root canals and prosthetic systems, prioritizing healthy teeth and removing those that are compromised and could become risk factors. All necessary surgical interventions must be completed before the start of therapy, and the tissues must be completely healed, generally after 2 weeks to a month, accompanied by excellent oral hygiene and good adaptability of the prostheses. For patients already undergoing therapy, the risk of osteonecrosis is higher. In these cases, it is important to promptly identify and treat any infections or periapical issues, generally with conservative care and non-surgical endodontic treatments, avoiding invasive procedures if possible. The preservation of teeth through conservative treatments and stabilization is preferable; in some cases, extractions may be necessary, but they should be done with caution and following precise protocols to reduce the risk of developing ONJ. Many researchers have observed the development of several inflammatory processes around teeth, novel dental implant, regenerated maxillary sites with biomaterials. (41,42) Recent sentences have determined the crucial role of the biofilm adhesion and bacterial colonization to promote hard and soft tissues pathogenesis (43,44) with bone loss, gingivitis, periodontitis, carcinogenesis, mucositis and peri-implantitis consequences related to the immune-cells genetic (45, 46) and cytokines cascade activation. (47)

In this context, innovative alveolar preservation techniques have been developed that demonstrate promising results in improving clinical outcomes and potentially facilitating subsequent implant placement (40). Furthermore, preventive measures can be adopted such as the use of biomarkers (e.g., sCTX) to assess bone risk, adhering to strict surgical protocols, and, if indicated, temporarily suspending high-risk medications before surgical interventions, under medical supervision, to improve prognosis and reduce incidents of osteonecrosis (48).

Biomarkers

It is widely recognized that the development of MRONJ is closely linked to the decrease in bone turnover. This condition can be monitored through various biomarkers that reflect the levels of bone resorption and formation. Numerous studies have identified various potentially useful biomarkers for predicting the onset of MRONJ, such as bone-specific alkaline phosphatase (BAP), parathyroid hormone (PTH), osteocalcin (OC), type 1 collagen amino-terminal propeptide (PINP), and others; among these, the C-terminal telopeptide of type I collagen (CTX) has been the most studied. The evaluation of serum levels of the C-terminal telopeptide, which is the degradation product of the carboxy-terminal portion of the non-helical regions of type I collagen, by the action of osteoclastic cathepsin K, is a predictor of the risk of developing osteonecrosis of the jaws; in fact, its study provides a value that indicates osteoblastic and osteoclastic activity. The value that many researchers consider as the threshold is 150 pg/ml; in fact, above this value the doctor can perform surgical therapy, as the risk is minimal; instead, in situations where the values are equal to or below 100 pg/ml, the higher

risk of developing osteonecrosis must be taken into consideration; for values between 100 and 150 pg/ml, the risk is moderate. Some authors recommend discontinuing the drug for values below 150 pg/ml. Bone turnover and angiogenesis biomarkers are considered ideal for this assessment, as they could contribute to more effective preventive strategies. Several cross-sectional studies have attempted to explore the predictive value of these markers, but so far there is insufficient scientific evidence to support the use of such biomarkers to assess the risk of MRONJ (49). The use of predictive biomarkers would represent a significant advancement for patients taking drugs associated with osteonecrosis; however, in the literature, there are no data that significantly support a certain correlation between these markers and the risk of developing osteonecrosis of the jaws (50).

CONCLUSIONS

In conclusion, MRONJ represents a complex and debilitating multifactorial pathology associated with the use of anti-resorptive and anti-angiogenic drugs. The etiopathogenesis involves alterations in bone remodeling, osteoclastic activity, vascularization, and immune response. Pharmacological risk factors (type of drug, route of administration, dose, duration), systemic factors (comorbidities, immune status), and local factors (invasive dental procedures, chronic inflammations) play a crucial role. Prevention, through a meticulous risk assessment, optimization of oral health, and the adoption of minimally invasive surgical protocols, represents the most effective strategy. The use of biomarkers for risk stratification is promising but requires further validation. Further prospective and controlled studies are necessary to clarify the pathogenetic mechanisms, identify reliable predictive biomarkers, and evaluate the effectiveness of innovative therapeutic strategies, in order to improve the management of this complex pathology and preserve the quality of life of at-risk patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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