

## REVIEWS

# MEDICATION-RELATED OSTEONECROSIS OF THE JAW—ETIOLOGY, PATHOPHYSIOLOGY, CLINICAL AND RADIOLOGICAL CHARACTERISTICS, AND STAGING: A REVIEW

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## ABSTRACT

**INTRODUCTION:** Medication-related osteonecrosis of the jaw (MRONJ) is a rare but serious condition, caused by several classes of pharmaceutical agents, the most common of which are antiresorptive and antiangiogenic drugs. It is characterized by exposed necrotic bone, most commonly associated with antiangiogenic or antiresorptive therapy, and without a history of radiation exposure to the head and neck.

**AIM:** This review aims to compare, and summarize the current knowledge on the etiology, pathophysiology, clinical and radiological characteristics, and staging of MRONJ, to identify the research gaps in the scientific literature, and to give recommendations for further research.

**MATERIALS AND METHODS:** An advanced electronic search was performed in PubMed, Scopus, and Web of Science, using selected keywords. Results were extracted to an MS Excel spreadsheet and assessed for eligibility after duplicate removal. After analysis of the obtained data, 35 articles were included in this study.

**RESULTS AND DISCUSSION:** The most common medications that cause MRONJ are antiresorptive and antiangiogenic drugs. Other possible agents are immunomodulators, monoclonal antibodies, corticoids, cytostatic drugs, etc. Numerous hypotheses for the pathophysiology of MRONJ have been suggested, including bone remodeling inhibition, impaired angiogenesis, specific infections, etc. Further research is necessary to confirm the role of different drugs in the pathogenesis of MRONJ.

**CONCLUSION:** Despite the strong association between MRONJ and antiresorptive and antiangiogenic drugs, the exact pathophysiology of the disease is not fully understood. Future studies should investigate their mechanisms of action and correlation to MRONJ. Understanding its etiopathogenesis is essential for all medical practitioners in order to reduce MRONJ incidence and avoid its misdiagnosis.

**Keywords:** medication-related osteonecrosis, jaw, MRONJ

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## INTRODUCTION

Historically, osteonecrosis of the jaw (ONJ) was first described at the end of the 19<sup>th</sup> century by the term *phossy jaw* in association with phosphorous intoxication (1). In 2003, ONJ was associated with bisphosphonate therapy, leading to the term *bisphosphonate-related osteonecrosis of the jaw* (BRONJ) (2). In 2010, the monoclonal antibody denosumab was reported as a cause of ONJ (3), which subsequently



led to the replacement of the term BRONJ with *medication-related osteonecrosis of the jaw* (MRONJ). It is a rare but serious condition, caused by several classes of pharmaceutical agents, the most common of which are antiresorptive and antiangiogenic drugs. They can affect both jaws, but predominantly the mandible.

Recently, some new medications (bevacizumab, sunitinib, mTOR inhibitors) have been reported as potential etiological agents for MRONJ, and reports have suggested an increasing number of these pharmaceutical agents (4,5). Medication-related osteonecrosis of the jaw is characterized by exposed necrotic bone, associated with antiangiogenic or antiresorptive therapy, and without a history of radiation exposure to the head and neck (6,7). The most frequently used diagnostic criteria are those of the American Association of Oral and Maxillofacial Surgeons (AAOMS).

The pathogenesis of MRONJ is still disputable and not confirmed. The most popular hypotheses include suppressed bone remodeling, deficient angiogenesis, microtrauma, local infection, and chronic inflammation (4,8). Various classifications and staging systems have been adopted in order to clarify the diagnosis, differentiate MRONJ from ONJ with other etiology, such as osteoradionecrosis, and navigate the treatment protocol.

## AIM

This review aims to compare and summarize the current knowledge on the etiology, pathogenesis, clinical and radiological characteristics, and staging of MRONJ, and to give recommendations for further research.

## MATERIALS AND METHODS

An advanced electronic search was performed in PubMed, Scopus, and Web of Science databases on 4 September 2024, using the following search strategies:

1. For the Web of Science database: ALL=((medication-related osteonecrosis) OR (MRONJ)) AND ((staging) OR (stages)) AND (etiology) AND (pathophysiology))
2. In PubMed a combination of keyword and MeSH terms were used: (“medication-related”[All Fields]

AND (“osteonecrosis”[MeSH Terms] OR “osteonecrosis”[All Fields] OR “osteonecroses”[All Fields]) AND (“jaw”[MeSH Terms] OR “jaw”[All Fields])) OR “MRONJ”[All Fields]) AND (“stage”[All Fields] OR “staged”[All Fields] OR “stages”[All Fields] OR “staging”[All Fields] OR “stagings”[All Fields]) AND (“aetiologie”[All Fields] OR “aetiologies”[All Fields] OR “aetiology”[All Fields] OR “etiologies”[All Fields] OR “etiology”[MeSH Subheading] OR “etiology”[All Fields] OR “causality”[MeSH Terms] OR “causality”[All Fields]) AND (“pathophysiologies”[All Fields] OR “physiopathology”[MeSH Subheading] OR “physiopathology”[All Fields] OR “pathophysiology”[All Fields])

3. The keywords that were used in the Scopus database were: ( ( ( medication-related ) AND ( osteonecrosis ) AND ( jaw ) ) OR ( MRONJ ) ) AND ( ( staging ) OR ( stages ) ) AND ( etiology ) AND ( pathophysiology ) AND ( LIMIT-TO ( LANGUAGE , “English” ) )

The inclusion criteria were as follows: 1. studies that evaluated MRONJ etiology and/or pathophysiology and/or staging; 2. original articles, review articles, or case reports (case series); 3. articles written in English.

The exclusion criteria were as follows: 1. books, book chapters, and abstracts; 2. studies irrelevant to the topic; 3. articles in languages other than English.

The research titles, abstracts, and author names were exported to an MS Excel Spreadsheet. Following duplicate removal, the titles and abstracts were assessed for eligibility by three independent reviewers (R.Y. and T.G)Then the articles were subjected to the selected inclusion and exclusion criteria. Discrepancies among the three reviewers were resolved through discussion and consensus.

After analysis of the obtained data, 35 articles were included in this study.

## RESULTS AND DISCUSSION

Medication-related osteonecrosis of the jaw is an adverse drug reaction leading to bone necrosis and progressive destruction of the jaw in patients with a history of medication therapy, which is the cause of such complications (9).

**Etiology**

The most common medications that are known to cause the condition are antiresorptive drugs (bisphosphonates (BPs), denosumab) and antiangiogenic

(axitinib, bevacizumab, dasatinib, erlotinib). However, the possible causative agents include immunomodulators, cytostatic drugs, vascular endothelial growth factor (VEGF) inhibitors (antiangiogenics), tyrosine kinase (TK) inhibitors (antiangiogenic

*Table 1. Drugs related to osteonecrosis of the jaw and their therapeutic application (8,10).*

Drug Class	Representatives	Use
<b>Bisphosphonates</b>	Alendronate	Osteoporosis Osseous metastatic disease Multiple myeloma Hypercalcemia Skeletal dysplasia
	Clodronate	
	Etidronate	
	Ibandronate	
	Pamidronate	
	Risedronate	
	Tiludronate	
Zoledronate		
<b>RANKL antibody</b>	Denosumab	Osteoporosis Osseous metastatic disease Pathological fractures Hypercalcemia
<b>Immunomodulators and immunosuppressants</b>	Corticosteroids	Malignancy Auto-immune diseases (rheumatoid arthritis, psoriasis, pemphigus vulgaris, etc.)
	Methotrexate	
	Thalidomide	
<b>Anti-TNF alpha</b>	Adalimumab	Autoimmune diseases
	Infliximab	
<b>Anti-VEGF</b>	Aflibercept	Malignancy Diabetic retinopathy
	Bevacizumab	
	Cabozantinib	
	Pazopanib	
<b>TKInhibitors</b>	Axitinib	Malignancy Pulmonary fibrosis
	Dasatinib	
	Erlotinib	
	Imatinib	
	Sorafenib	
<b>Anti-CD20</b>	Sutinib	Malignancy
	Rituximab	
<b>mTOR inhibitors</b>	Everolimus	Malignancy Transplant rejection
	Temsirolimus	
<b>BRAF inhibitor</b>	Dabrafenib	Malignancy
	Trametinib	
<b>Chemotherapeutic agents</b>	5-azacitidin	Malignancy
	Cyclophosphamide	
	Cytarabine	
	Daunorubicin	
	Doxorubicin	
	Gemcitabine	
	Idarubicin	
	Metotrexate	
Vinorelbine		

genics), tumor necrosis factor alpha (TNF $\alpha$ ) inhibitors, etc. (Table 1) (8,10).

**Bisphosphonates** are pyrophosphate analogs, which inhibit bone metabolism and remodeling by binding to the bone matrix and inducing osteoclast apoptosis (11,12). Since the osteoblast function remains unchanged, the bone mass increases (13). They are indicated for patients with bone metastases, multiple myeloma, osteoporosis, osteopenia, osteogenesis imperfecta, Paget's disease, and kidney transplantation (5,12,14,15). Bisphosphonates are generally divided into nitrogen-containing (alendronate, ibandronate, pamidronate, risedronate, and zoledronic acid) and non-nitrogen-containing (clodronate, etidronate, tiludronate) (5,16).

Bisphosphonates can be administered intravenously or orally. The first route is usually used in patients with bone metastases, while oral administration is more common for osteoporosis treatment (5). Bisphosphonates bind to the bone matrix for a prolonged time and the effect can last more than 10 years after therapy discontinuation (17,18). The risk of MRONJ in patients on BP therapy depends on their dose, period of treatment, and administration route. In addition, simultaneous corticoid therapy, comorbidity, and smoking can increase the risk (5).

Non-nitrogenated BPs pose a lower risk of MRONJ. Nitrogenated BPs are 10–1000 times more potent and demonstrate a 0.1–6.7% prevalence of MRONJ (5,17,19). The risk is the highest with pamidronate and zoledronate, which are administered intravenously, usually in cases of malignancy. The zoledronate therapy increases the risk of MRONJ by up to 400 times compared to patients, who are not on antiresorptive treatment (20,21).

**Denosumab** is a human monoclonal antibody, an antiresorptive drug, which targets the receptor activator of nuclear factor kappa-B (RANKL) and, thus, inhibits osteoclasts (22). Denosumab inhibits bone resorption and increases bone density. It is administered subcutaneously and is usually used to treat osteoporosis and bone metastases, to prevent hypercalcemia and bone fractures. Since it does not accumulate, its effect is reversible—between 6 and 24 months (5,9,17). However, the risk of MRONJ in patients treated with denosumab is as high as in patients treated with zoledronate (0.7–1.9%) (11,19–21).

The risk in patients treated for osteoporosis is about 0.04% (5).

**Antiangiogenic drugs**, such as anti-VEGF and TK inhibitors, inhibit neoangiogenesis and, therefore, are used to inhibit tumor growth (23). They have been associated with MRONJ, the possible mechanism for which is reduced bone regeneration potential, delayed healing and remodeling, and increased susceptibility to infection (24,25). Moreover, these agents can affect cellular differentiation and chemotaxis, altering the immune response (5).

**Immunomodulators and immunosuppressants**, such as corticoids and methotrexate, can increase the risk of MRONJ. Long-term systemic corticoids have been associated with avascular bone necrosis (26,27). Methotrexate has been recently reported to cause MRONJ when used for a long time (28). The exact pathogenic mechanism is still unknown, but it is probably related to changes in the immune response and osteoclast inhibition (5).

There are other drug classes, associated with MRONJ, but further research is necessary to confirm this relation and their exact mechanism of action.

### **Pathogenesis**

The pathogenesis of MRONJ is supposed to be multifactorial but the exact mechanisms are not fully understood (29). Numerous hypotheses have been suggested, including bone remodeling inhibition, impaired angiogenesis, specific infections (actinomycosis), immune dysfunction, etc. (15,29).

### **Inhibited Bone Remodeling**

This theory is explained by the direct effect of antiresorptive drugs on osteoclast differentiation and functionality. Human and animal studies have demonstrated osteoclast inhibition and bone necrosis, caused by BP and denosumab therapies (30,31). An intriguing phenomenon is that osteonecrosis develops primarily in the alveolar bone and not in other skeletal bones. This could be due to the higher remodeling rate of the jaw (10). Indirect evidence for this theory is the improved post-extraction healing and successful MRONJ prevention when parathyroid hormone was administered in rodents (32,33).

### **Inhibited Angiogenesis**

This theory relates to the effect of antiangiogenic agents and is explained by decreased blood supply and avascular necrosis. It should be noted that the in-

cidence of MRONJ caused by antiresorptive drugs is much higher than the incidence caused by antiangiogenic drugs (15).

### Infection and Inflammation

A commonly reported reason for MRONJ is periapical or periodontal inflammation. A complex microbial biofilm has been found in histological specimens from necrotic bone (34,35). Inflammatory cytokines at the site of jaw necrosis confirm the role of inflammation, while the presence of bacteria at the site contributes to the severity of MRONJ.

### Immune Suppression

The rationale for that hypothesis is the higher incidence and severity of MRONJ when immuno-

modulators and chemotherapeutic drugs are used simultaneously with BP or antiangiogenics (10).

### Diagnosis

The **diagnostic criteria** for MRONJ, developed by AAOMS, include the following components: 1. ongoing or previous treatment with antiresorptive drugs alone or combined with antiangiogenic drugs or immunomodulators; 2. persisting (>8 weeks) exposed bone or bone that can be probed through a fistula (intraoral or extraoral); 3. no history of radiation to the maxillofacial area or metastatic disease, affecting the jaws.

Other clinical symptoms include local pain, altered neurosensory function, exudations, ulcers, fistulas, oroantral communications, swelling, teeth

*Table 2. MRONJ Staging, suggested by the American Association of Oral and Maxillofacial Surgeons.*

Stage	Symptoms	Clinical and Radiographic Characteristics
Stage 0 (potential precursor to MRONJ)	Odontalgia without an obvious odontogenic cause, dull jaw pain, sinus pain, altered neurosensory response	Tooth mobility without periodontal cause Swelling— intraoral or extraoral Alveolar bone resorption without periodontal cause Changed trabecular pattern Not healing post-extraction sockets Osteosclerotic areas in the alveolar and/or basilar bone Thickening of the periodontal ligament and sclerosis of lamina dura Exposed necrotic bone or bone that can be probed through a fistula No evidence of infection or inflammation
Stage 1	Asymptomatic	Alveolar bone resorption without periodontal cause Changed trabecular pattern Not healing post-extraction sockets Osteosclerotic areas in the alveolar and/or basilar bone Thickening of the periodontal ligament and sclerosis of lamina dura Exposed necrotic bone or bone that can be probed through a fistula Evidence of infection or inflammation
Stage 2	Symptomatic	Alveolar bone resorption without periodontal cause Changed trabecular pattern Not healing post-extraction sockets Osteosclerotic areas in the alveolar and/or basilar bone Thickening of the periodontal ligament and sclerosis of lamina dura Exposed necrotic bone or bone that can be probed through a fistula Evidence of infection
Stage 3	Symptomatic	At least one of the following criteria: the exposed necrotic bone extends beyond the alveolar ridge pathologic fracture extraoral fistula oroantral/oronasal communication osteolysis reaching the inferior border of the mandible or the maxillary sinus

mobility, maxillary sinusitis, halitosis, and pathological jaw fractures (1,29).

Medication-related osteonecrosis of the jaw must be differentiated from radiation osteonecrosis, primary or recurrent tumors, metastases, osteomyelitis, sinusitis, odontogenic pathology, alveolar osteitis, etc.

Imaging methods provide diagnosis, monitoring, and assessment of disease progression (10). Orthopantomography is necessary for the radiological evaluation of MRONJ. Radiographic findings include regions of osteosclerosis and bone resorption, subperiosteal bone deposition, changes in trabecular pattern, delayed bone remodeling in post-extraction sockets, thickened lamina dura, and in advanced stages—bone sequestra and pathological fractures (29). Digital imaging, such as computed tomography (CT), cone-beam CT (CBCT), and magnetic resonance imaging (MRI) can provide more detailed and accurate diagnosis. Magnetic resonance imaging is not commonly used. It can be beneficial for evaluating the extent of the lesions to the soft tissues (18).

Histological examination is not mandatory and can be performed after surgical treatment. The results evidence necrotic bone, bone marrow fibrosis, hypocellularity, thrombosis of the blood vessel, and soft tissue fibrosis (29).

### Staging

There are numerous staging systems of MRONJ (8), the most widely adopted of which is introduced by AAOMS in 2009, and modified in 2014. It facilitates the correct diagnosis, prognosis, and treatment of the disease. The authors also define the term *patient at risk* which refers to asymptomatic patients without clinical presentation of bone necrosis but who have been treated with antiresorptive drugs (15). Table 2 presents the staging system of MRONJ, suggested by AAOMS.

### Future Directions

Most of the scientific data about the etiopathogenesis of MRONJ is based on case reports and small case series. Further research is necessary to confirm and extend the current knowledge, especially prospective preclinical and clinical studies, and randomized controlled trials.

## CONCLUSION

Despite the strong association between MRONJ and antiresorptive and antiangiogenic drugs, the exact pathogenesis of the disease is not fully understood. Future studies should investigate their mechanisms of action and correlation to MRONJ. Different hypotheses exist for its development, including inhibited bone remodeling, impaired angiogenesis, infections, immune dysfunction, microtrauma, and direct toxicity. Understanding its etiopathogenesis is essential for all medical practitioners in order to reduce MRONJ incidence and avoid its misdiagnosis.

## REFERENCES

1. Otto S, Pautke C, Van den Wyngaert T, Niepel D, Schjødt M. Medication-related osteonecrosis of the jaw: Prevention, diagnosis and management in patients with cancer and bone metastases. *Cancer Treat Rev.* 2018;69:177-87. doi: 10.1016/j.ctrv.2018.06.007.
2. 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.
3. Aghaloo TL, Felsenfeld AL, Tetradis S. Osteonecrosis of the jaw in a patient on Denosumab. *J Oral Maxillofac Surg.* 2010;68(5):959-63. doi: 10.1016/j.joms.2009.10.010.
4. Otto S, Aljohani S, Fliefel R, Ecke S, Ristow O, Burian E, et al. Infection as an important factor in medication-related osteonecrosis of the jaw (MRONJ). *Medicina(Kaunas).* 2021;57(5):463. doi: 10.3390/medicina57050463.
5. 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.
6. 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.
7. 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;22:369-78. doi: 10.1007/s10006-018-0732-8.
8. Kuehn S, Scariot R, Elsalanty M. Medication-Related Osteonecrosis: Why the Jawbone? Dent J. 2023 Apr 23;11(5):109. doi: 10.3390/dj11050109.
  9. Campisi G, Mauceri R, Bertoldo F, Bettini G, Bisotto M, Colella G, et al. Medication-related osteonecrosis of jaws (MRONJ) prevention and diagnosis: Italian consensus update 2020. Int J Environ Res Public Health. 020 Aug 18;17(16):5998. doi: 10.3390/ijerph17165998.
  10. 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.
  11. Tai TW, Su FC, Chen CY, Jou IM, Lin CF. Activation of p38 MAPK-regulated Bcl-xL signaling increases survival against zoledronic acid-induced apoptosis in osteoclast precursors. Bone. 2014;67:166-74. doi: 10.1016/j.bone.2014.07.003.
  12. Lončar Brzak B, Horvat Aleksijević L, Vindiš E, Kordić I, Granić M, Vidović Juras D, et al. Osteonecrosis of the Jaw. Dent J. 2023;11(1):23. doi: 10.3390/dj11010023.
  13. Yamashita J, McCauley LK. Antiresorptives and osteonecrosis of the jaw. J Evid Based Dent Pract. 2012;12(3):233-47. doi: 10.1016/S1532-3382(12)70046-5.
  14. Pabst AM, Krüger M, Blatt S, Ziebart T, Rahimi-Nedjat R, Goetze E, Walter C. Angiogenesis in the development of medication-related osteonecrosis of the jaws: an overview. Dent J. 2016;5(1):2. doi: 10.3390/dj5010002.
  15. 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.
  16. Shibahara T. Antiresorptive agent-related osteonecrosis of the jaw (ARONJ): a twist of fate in the bone. Tohoku J Exp Med. 2019;247(2):75-86. doi: 10.1620/tjem.247.75.
  17. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. 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):1938-56. doi: 10.1016/j.joms.2014.04.031.
  18. AlDhalaan NA, BaQais A, Al-Omar A. Medication-related osteonecrosis of the jaw: a review. Cureus. 2020;12(2). doi: 10.7759/cureus.6944.
  19. Lo JC, O’Ryan FS, Gordon NP, Yang J, Hui RL, Martin D, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. J Oral Maxillofac Surg. 2010;68(2):243-53. doi: 10.1016/j.joms.2009.03.050.
  20. 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. Int J Clin Oncol. 2014;19:403-10. doi: 10.1007/s10147-013-0561-6.
  21. Mauri D, Valachis A, Polyzos IP, Polyzos NP, Kampouras K, Pesce LL. Osteonecrosis of the jaw and use of bisphosphonates in adjuvant breast cancer treatment: a metanalysis. Breast Cancer Res Treat. 2009;116:433-9. doi: 10.1007/s10549-009-0432-z.
  22. Nicolatou-Galitis O, Schiødt M, Mendes RA, Ripamonti C, Hope S, Drudge-Coates L, et al. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019;127(2):117-35. doi: 10.1016/j.oooo.2018.09.008.
  23. Mander KA, Finnie JW. Tumour angiogenesis, anti-angiogenic therapy and chemotherapeutic resistance. Aust Vet J. 2018;96(10):371-8. doi: 10.1111/avj.12747.
  24. Pimolbutr K, Porter S, Fedele S. Osteonecrosis of the jaw associated with antiangiogenics in antiresorptive-naïve patient: A comprehensive review of the literature. BioMed Res Int. 2018;2018(1):8071579. doi: 10.1155/2018/8071579.
  25. Chang J, Hakam AE, McCauley LK. Current Understanding of the Pathophysiology of Osteonecrosis of the Jaw. Curr Osteoporos Rep. 2018;16:584-95. doi: 10.1007/s11914-018-0474-4.
  26. Weinstein RS. Glucocorticoid-induced osteonecrosis. Endocrine. 2012;41:183-90. doi: 10.1007/s12020-011-9580-0.
  27. Powell C, Chang C, Gershwin ME. Current concepts on the pathogenesis and natural history of steroid-induced osteonecrosis. Clin Rev Allergy Immunol. 2011;41:102-13. doi: 10.1007/s12016-010-8217-z.

28. Henien M, Carey B, Hullah E, Sproat C, Patel V. Methotrexate-associated osteonecrosis of the jaw: A report of two cases. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2017;124(6):e283-7. doi: 10.1016/j.oooo.2017.09.005.
29. 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.
30. Soundia A, Hadaya D, Esfandi N, de Molon RS, Bezouglaia O, Dry SM, et al. Osteonecrosis of the jaws (ONJ) in mice after extraction of teeth with periradicular disease. *Bone.* 2016;90:133-41. doi: 10.1016/j.bone.2016.06.011.
31. Wehrhan F, Gross C, Creutzburg K, Amann K, Ries J, Kesting M, et al. Osteoclastic expression of higher-level regulators NFATc1 and BCL6 in medication-related osteonecrosis of the jaw secondary to bisphosphonate therapy: a comparison with osteoradionecrosis and osteomyelitis. *J Transl Med.* 2019;17(1):69. doi: 10.1186/s12967-019-1819-1.
32. de Molon RS, Shimamoto H, Bezouglaia O, Pirih FQ, Dry SM, Kostenuik P, et al. OPG-Fc but Not Zoledronic Acid Discontinuation Reverses Osteonecrosis of the Jaws (ONJ) in Mice. *J Bone Miner Res.* 2015;30(9):1627-40. doi: 10.1002/jbmr.2490.
33. Hadaya D, Soundia A, Gkouveris I, Bezouglaia O, Dry SM, Pirih FQ, et al. Antiresorptive-Type and Discontinuation-Timing Affect ONJ Burden. *J Dent Res.* 2021;100(7):746-53. doi: 10.1177/0022034520986804.
34. Sedghizadeh PP, Kumar SK, Gorur A, Schaudinn C, Shuler CF, Costerton JW. Identification of microbial biofilms in osteonecrosis of the jaws secondary to bisphosphonate therapy. *J Oral Maxillofac Surg.* 2008;66(4):767-75. doi: 10.1016/j.joms.2007.11.035.
35. Boff RC, Salum FG, Figueiredo MA, Cherubini K. Important aspects regarding the role of microorganisms in bisphosphonate-related osteonecrosis of the jaws. *Arch Oral Biol.* 2014;59(8):790-9. doi: 10.1016/j.archoralbio.2014.05.002.