Primljen / Received on: 13. 4. 2025.
Revidiran / Revised on: 29. 4. 2025.
Prihvaćen / Accepted on: 15. 5. 2025.

ORIGINALNI RAD
ORIGINAL ARTICLE
doi: 10.5937/asn2591033J

KORELACIJA IZMEĐU RADIOLOŠKOG STADIJUMA I INTENZITETA BOLA KOD OSTEONEKROZE VILICE POVEZANE SA LEKOVIMA

CORELATION BETWEEN RADIOLOGICAL STAGE AND PAIN INTENSITY IN MEDICATION RELATED OSTEONECROSIS OF THE JAW

Maja Jocić

UNIVERZITETSKI KLINIČKI CENTAR NIŠ, CENTAR ZA RADIOLOGIJU, NIŠ, SRBIJA

UNIVERSITY CLINICAL CENTER NIŠ, CENTER FOR RADIOLOGY, NIŠ, SERBIA

Sažetak

Uvod: *Osteonekroza vilice se definiše kao avaskularna nekroza alveolarne spongiozne i kortikalne kosti maksile ili mandibule, najčešće kao rezultat terapijskih intervencija - bilo radioterapije ili farmakološkog tretmana. Osteonekroza vilice povezana sa lekovima (MRONJ) definiše se određenim kriterijumima i može se klasifikovati u četiri stepena. MRONJ se razvija kao posledica sistemskih efekata određenih lekova, prvenstveno bisfosfonata, koji inhibiraju remodeliranje kostiju suzbijanjem aktivnosti ćelija koje resorbuju kost - osteoklasta.*
Cilj studije *bio je da se uporede MSCT radiološke promene kod MRONJ-a izazvanog bisfosfonatima sa kliničkim znacima i simptomima kao što su prisustvo bola, infekcije i fistule kod pacijenata sa dijagnostikovanom MRONJ.*
Materijali i metode: *Podaci o pacijentima su prikupljeni iz medicinske dokumentacije i obuhvatali su trajanje terapije bisfosfonatima, stadijum MRONJ, nalaze MSCT radiografije i upitnik o prisustvu i intenzitetu bola, mereno pomoću numeričke skale za procenu bola.*
Rezultati: *Svi pacijenti su primali oralnu antiresorptivnu terapiju bisfosfonatima u periodu od 1 do 15 godina; 63,63% pacijenata je bilo na terapiji bisfosfonatima duže od tri godine, 27,27% manje od tri godine, 9,09% duže od 15 godina. Kod pacijenata sa razvijenim stadijumom II, prosečan intenzitet bola bio je 5,1±1,1; stadijum III je prijavio nivo bola 8, MRONJ u stadijumu I je imao blagi bol 2. Nije bilo prekida terapije ni kod jednog pacijenta uključenog u studiju.*
Zaključak: *Radiolozi igraju važnu ulogu u ranoj dijagnozi svih stadijuma MRONJ-a. Bol se može smatrati ranim znakom ovog patološkog stanja kosti i povezan je sa stadijumom MRONJ kod lezija izazvanih korišćenjem bisfosfonata.*

Ključne reči: *MSCT radiografija, MRONJ, bol*

Abstract

Introduction: *Osteonecrosis of the jaw is defined as avascular necrosis of the alveolar cancellous and cortical bone of the maxilla or mandible, most commonly as the result of a therapeutic intervention—either radiotherapy or pharmacological treatment. Certain criteria define medication-related osteonecrosis of the jaw (MRONJ) and can be staged in four degrees. MRONJ develops as a consequence of the systemic effects of certain medications, primarily bisphosphonates, that inhibit bone remodeling by suppressing the activity of bone-resorbing cells—osteoclasts.*
Aim. *The study aimed to compare the multislice computed tomography (MSCT) radiological changes in MRONJ caused by bisphosphonates stage to clinical signs and symptoms, such as the presence of pain, infection and fistula in patients with diagnosed MORNJ.*
Materials and Methods: *Patient data were collected from medical records and included duration of bisphosphonate therapy, stage of MRONJ, MSCT radiograph findings, and questionnaire about the presence and intensity of pain, measured using a numerical pain rating scale.*
Results: *All patients had been receiving oral antiresorptive bisphosphonate therapy for periods ranging from 1 to 15 years; 63.63% had been on bisphosphonate therapy for more than three years, 27.27% for less than three years, and 9.09% for more than 15 years. In patients who developed Stage II, the mean pain intensity was 5.1 ± 1.1; Stage III reported pain level 8, Stage II MRONJ experienced mild pain 2. There was no drug holiday in any patient involved in the study.*
Conclusion: *Radiologists play an important role in the early diagnosis of all stages of MRONJ. Pain could be considered as an early sign of this pathological condition of the bone, and it correlates with the stage of MRONJ in lesions caused by bisphosphonate intake.*

Key words: : *MSCT radiography MRONJ, pain*

Corresponding author:
Maja Jocić, Radiologist, PhD Student
University clinical center niš, Center for radiology
48 Dr Zorana Djindjic Blvd., Niš, Serbia
E-mail: majajocic722@gmail.com

Introduction

Osteonecrosis represents the necrosis of bone tissue, resulting from impaired vascular perfusion and the loss of viability of bone marrow cells, with certain radiographic manifestations through structural and morphological alterations within the bone. The radiological presentation of osteonecrosis typically reveals a localized area of nonviable bone tissue characterized by necrosis, reparative processes, and resorption phenomena (osteolysis, osteosclerosis, or mixed patterns). In some cases, sequestra may be present, with a distinct line demarcating necrotic from viable bone. In advanced stages, cortical discontinuity and secondary infections may also be observed.

Radiological findings for MRONJ on Computed tomography (CT) include bone changes such as osteolysis/osteonecrosis—presents as an ill-defined zone of hypodensity with visible destruction of the edge of the cortex, osteosclerosis—presents as an increased density zone of the part of the bone where it occurs, periosteal reaction—abnormal bone formation on the surface of the bone itself, i.e. it presents as a thickening of the bone cortex, sequestrum—a fragment of dead bone that has separated from the surrounding bones, soft tissue inflammation—like swelling of the surrounding tissue around the bone.

Osteonecrosis of the jaw is defined as avascular necrosis of the alveolar cancellous and cortical bone of the maxilla or mandible, most commonly as the result of a therapeutic intervention—either radiotherapy or pharmacological treatment. Radiation-induced osteonecrosis of the jaw (RONJ) is the consequence of the therapeutic localized ionizing radiation, typically administered in the head and neck region, and occasionally in the treatment of breast malignancies[1,2]. RONJ represents ischemic necrosis caused primarily by vascular injury (endarteritis obliterans), causing the death of the osteocyte. Radiotherapy induces pronounced hypoxia within the jawbone, accompanied by ischemia and osseous fibrosis. The mandible is most frequently affected[2]. Medication-related osteonecrosis of the jaw (MRONJ) develops as a consequence of the systemic effects of certain medications, that primarily inhibit bone remodeling by suppressing the activity of bone-resorbing cells—osteoclasts. This inhibition disrupts normal bone turnover, leading to impaired remodeling, while vascularization is reduced but relatively preserved[3]. Necrosis develops due to the continuous exposure of the jawbones to daily microtrauma and the consequent remodeling inability, often accompanied by secondary infection[4]. Radiographically, MRONJ typically appears as diffuse osteosclerosis or a combination of osteosclerotic and osteolytic changes, sometimes followed by sequestrum formation[5]. Fibrosis is generally quite pronounced. The mandible is more commonly affected than the maxilla, with an approximate ratio of 2:1. MRONJ most frequently involves the alveolar ridge and, in advanced stages, extends to adjacent structures. A pronounced periosteal reaction is often observed. Soft-tissue changes range from mild to severe, including intraoral mucosal and extraoral cutaneous fistulas. Pain intensity may vary from mild to moderate, and less frequently, severe. It is emphasized that the intensity of pain does not necessarily follow the progression of the disease. MRONJ is the most common caused by antiresorptive drugs, such as bisphosphonates and denosumab[3–6].

This pathological condition may also be developed as a result of the action of antiangiogenic agents. These agents inhibit vascular endothelial growth factor (VEGF), preventing tissue neovascularization in oncological patients. In the jaw, this leads to a reduction in bone marrow microcirculation, resulting in ischemia and hypoxia of the bone, followed by avascular necrosis with secondary infection. In this case, radiography shows a combination of osteolytic and osteosclerotic changes, often accompanied by partial sequestration, cortical layer disruption, and soft tissue thickening. Compared with bisphosphonate-related osteonecrosis, these changes typically show less extension beyond the alveolar ridge and are generally less pronounced[4,5]. Other medications, such as antimetabolites and immunosuppressive agents (e.g., methotrexate or corticosteroids), may also induce osteonecrosis, although this occurs less frequently in the jawbones. Their isolated contribution to the development of jaw osteonecrosis is extremely rare and usually observed when administered concomitantly with drugs exerting similar effects. Osteonecrosis caused by these agents leads to immunosuppression, disturbances in bone remodeling and vascularization, but with less severe consequences for the jawbone. Radiographically, osteolysis predominates with significantly less pronounced osteosclerosis and minimal sequestration.

Medication-related osteonecrosis of the jaw is defined by certain criteria: a current or previous history of antiresorptive or antiangiogenic drug use, exposed bone that can be probed through an intraoral or extraoral fistula in the orofacial region, persistence of the condition for at least 8 weeks, and no prior history of radiotherapy to the jaw, or metastases in jawbones[7].

The aim

The study aimed to compare the multislice computed tomography (MSCT) radiological changes in MRONJ caused by bisphosphonates stage due to clinical signs and the symptoms such as the presence of pain, infection and fistula in patients with diagnosed MRONJ.

Materials and Methods

The study was conducted at the Center for Radiology, University Clinical Center Niš, from January 2024 to December 2024. The research involved 11 patients who had been receiving antiresorptive medication. MRONJ diagnosis was based on clinical and radiographic findings and the criteria recommended in the American Association of Oral and Maxillofacial Surgeons position paper[7].

At-Risk Stage: Patients receive antiresorptive or antiangiogenic therapy but exhibit no clinical signs of necrotic bone or related symptoms. Stage 0: No clinical evidence of necrotic bone is present; however, patients may experience nonspecific symptoms or display subtle clinical and radiographic changes. Stage I: Exposed and necrotic bone, or a fistula through which bone can be probed, is present in asymptomatic patients with no signs of infection. Stage II: Along with exposed and necrotic bone or a probing fistula, there is clinical evidence of infection, and patients typically report pain or other symptoms. Stage III: Characterized by exposed and necrotic bone or a probing fistula, clinical signs of infection, and at least one of the following: necrotic bone extending beyond the alveolar region (e.g., into the maxillary sinus or mandibular border), extraoral fistula, pathologic fracture, oroantral or oronasal communication, or osteolysis reaching the sinus floor or mandibular border.

Patient data were collected from medical records and included information such as age, sex, lesion site, disease stage at admission, duration of bisphosphonate therapy, presence or absence of a drug holiday. All participants provided written informed consent before enrollment. They also completed a questionnaire assessing the presence and intensity of jaw pain, measured using a numerical pain rating scale. Clinical evaluations recorded the presence of intraoral or extraoral fistula, bone sequestra, infection, and soft tissue suppuration.

The patients received antibiotic therapy according to the protocol for MRONJ[6] and local hygienic treatment. The patients were further referred to radiological institutes for a more detailed MSCT analysis of changes in bone tissue. The patients were referred for exams in a GE Revolution EVO 128-Slice MSCT device located in the Center for Radiology, University Clinical Centre of Niš.

A correlation was established between the stage of MRONJ according to the clinical and radiological features of the disease and pain intensity.

Results

A total of 11 patients participated in the study; all of them were female, while there were no male participants. The mean age of the patients was 66.8 ± 5.1 years. All patients had been receiving oral antiresorptive bisphosphonate therapy for periods ranging from 1 to 15 years. Seven patients (63.63%) had been on bisphosphonate therapy for more than three years, three patients (27.27%) for less than three years, and one patient (9.09%) for more than 15 years (Figure 1).

The primary indication for bisphosphonate use was diagnosed osteoporosis in nine patients (81.8%), while two patients (18.2%) were oncology patients who received bisphosphonates for the prevention of metastatic bone fractures (Figure 2).

Stage I was diagnosed in one patient (9.09%), stage II in eight patients (72.7%), and stage III in two patients (18.1%). The reason for MRONJ development was a previous tooth extraction (Figure 3).

Pain intensity was defined as moderate (NRS 4–6) in six patients (54.5%), as mild pain (NRS = 2) in four patients (36.4%), and severe pain (NRS = 9) by one patient (9.09%) (Figure 4).

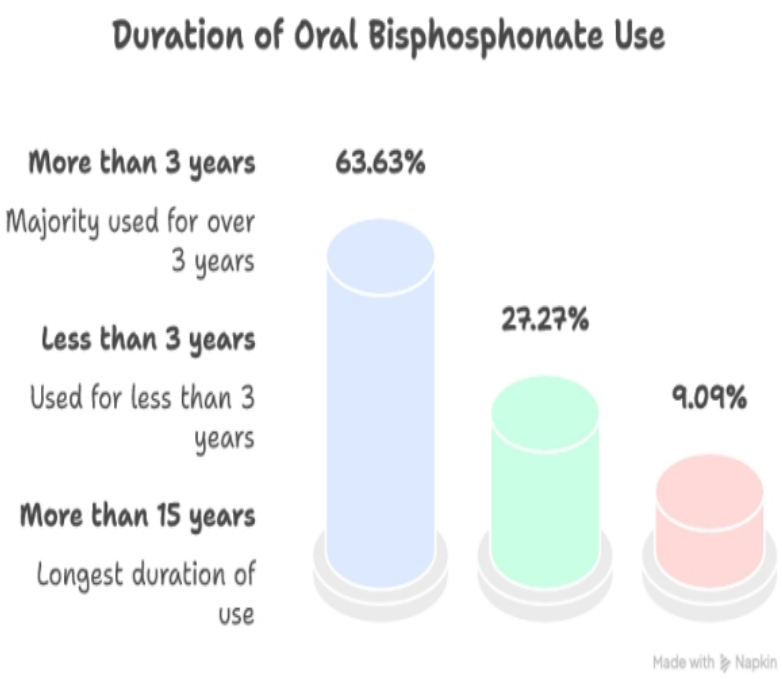


Figure 1. Duration of bisphosphonate intake

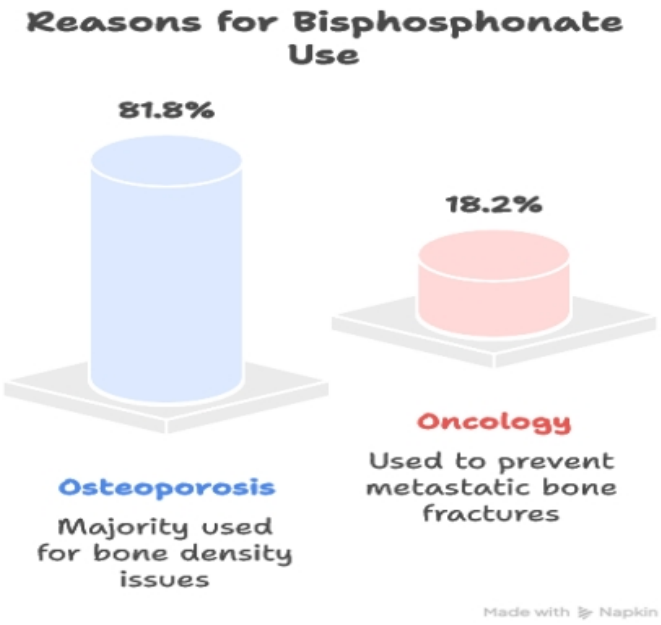


Figure 2. Bisphosphonate intake depends on disease

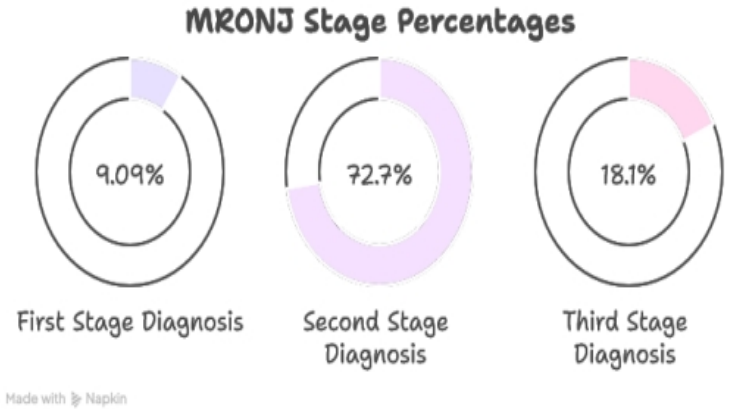


Figure 3. Patient representation by MRONJ stage

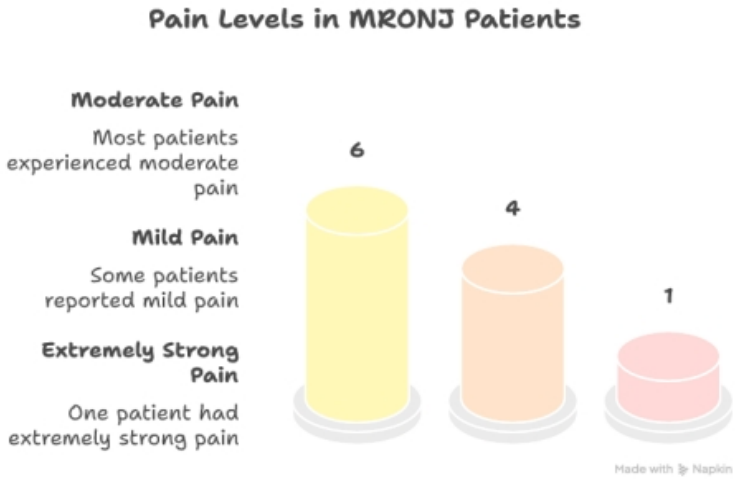
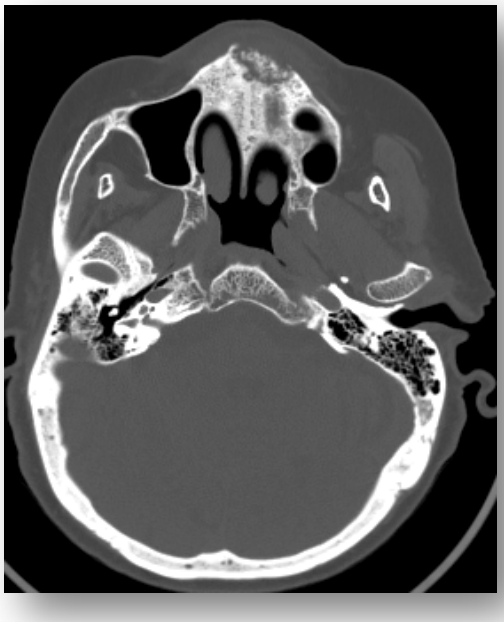


Figure 4. Intensity of pain in patients with different stages of MRONJ

Among patients in the largest subgroup with stage II—the mean pain intensity was 5.1 ± 1.1. Of the two patients with stage III, one reported extreme pain (NRS = 9)., While the other one reported pain on the border between moderate to severe pain (NRS = 7). In this group average pain was 8 (severe). In contrast, the patient diagnosed with stage I MRONJ experienced mild pain (NRS = 2).

The patient experiencing the most severe pain also presented with the most advanced stage of MRONJ, characterized by an intraoral fistula at the site of the previously extracted upper second molar. The lesion extended beyond the alveolar ridge and partially involved the maxillary sinus (Figures 5 and 6). The patient exhibited a poor response to analgesic therapy.

The other patient with stage III MRONJ. experianced moderate to severe pain, but destruction of bone was quite large, with bony sequestra inside (Figure 7,8,9,10). The patient also exhibited a poor response to analgesic therapy.



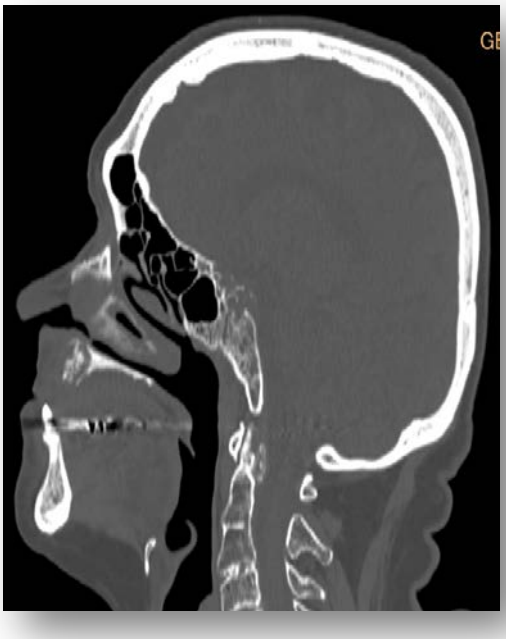


Figure 5. and 6. In this case MSCT findings for this patient revealed an ovoid, irregular hypodense area in the right half of the maxilla, accompanied by destruction of the outer contour of the mandibular cortex. Within this area, changes were observed along the root of the affected tooth, with a surrounding zone of osteosclerosis. The remaining portions of the maxilla demonstrated signs of osteoporosis

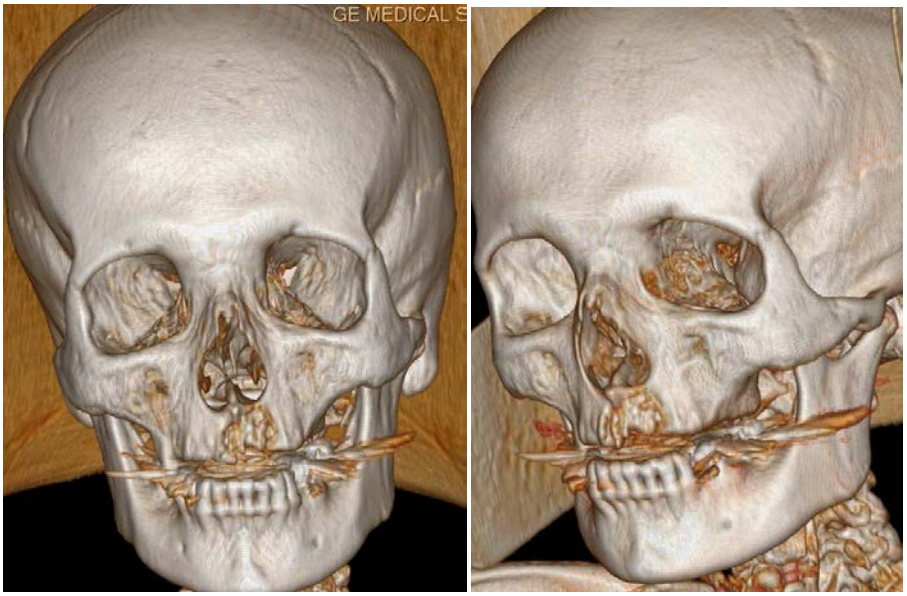


Figure 7. and ***Figure 8.***

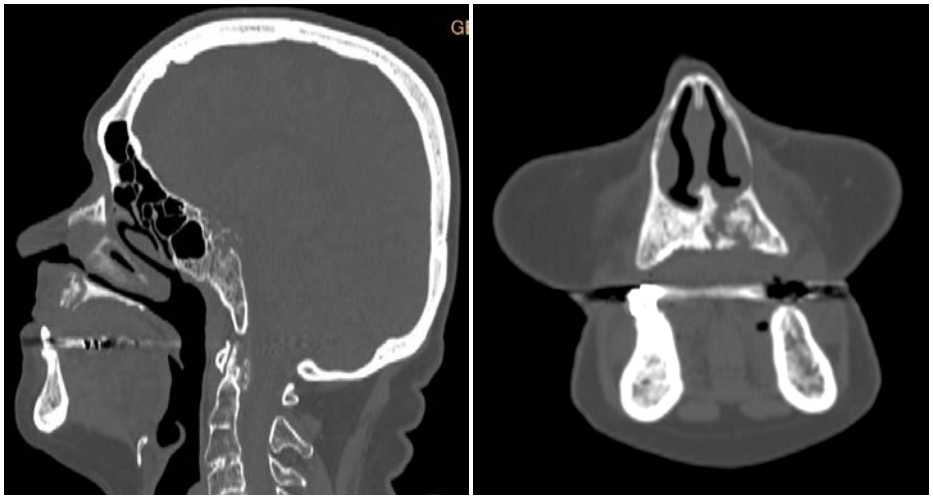


Figure 9. and ***Figure 10.***

Figures 7, 8, 9, 10. Stage III of MRONJ. Osteolytic irregular lesion with sequestrations on the left side of the maxilla

Discussion

Patients experiencing osteoporosis, osteopenia, and multiple forms of cancer are often prescribed agents that inhibit osteoclast resorption of the bone. A calendar year study demonstrated that 5.1 million patients aged over 55 years received prescriptions for IV bisphosphonates alone[7]. The development of MRONJ has been extensively investigated and is believed to be associated with impaired bone remodeling due to osteoclast inhibition, which may lead to bone sclerosis and reduced blood supply (ischemia). Research indicates that patients receiving these medications intravenously are at a significantly higher risk of developing this condition compared to those taking them orally. Genetic or individual predisposition plays an important role in the pathogenesis of MRONJ, as the condition does not occur uniformly among patients exposed to identical risk factors. The key factor in the pathogenesis of this condition is the oral biofilm and infection from the teeth[4,7].

The diagnosis of MRONJ is primarily based on clinical and radiographic criteria established by the American Association of Oral and Maxillofacial Surgeons (AAOMS)[7].

According to the AAOMS position paper, MRONJ can be diagnosed when the following criteria are met: 1) current or previous treatment with antiresorptive or antiangiogenic agents; 2) exposed bone, or bone that can be probed through an intraoral or extraoral fistula, persisting for more than eight weeks; and 3) no history of radiation therapy to the jaws or evident metastatic disease involving the jawbones. Based on the severity of clinical and radiological findings, MRONJ is classified into several stages, ranging from Stage 0—characterized by nonspecific symptoms and radiographic changes without bone exposure—to Stage 3, which involves extensive bone necrosis, pathologic fractures, extraoral fistulae, or involvement of the maxillary sinus or the inferior border of the mandible.

Radiologists play a crucial role throughout all stages of patient management—from the initial evaluation of lesions and monitoring of disease progression to the detection of potential complications, such as extension into adjacent structures[7]. Muttanahally et al.[5] suggest that there are no specific or distinctive radiographic patterns observed in any of the cases of MRONJ, regardless of the type of medication used. In this study, the pain as the predominant symptom of the stage of MRONJ depends on bone destruction and the presence of infection. The radiologists should possess a comprehensive understanding of the full range of imaging manifestations, recognizing that no single radiologic feature is pathognomonic for MRONJ in order to prevent the worsening of MRONJ, and to relieve the patient of pain. Imaging findings must always be interpreted in conjunction with the patient's clinical presentation and therapeutic history. In line with current radiologic standards, the diagnosis of MRONJ is primarily supported by advanced imaging modalities, including orthopantomography (OPT), cone-beam computed tomography (CBCT), and multislice computed tomography (MSCT). These techniques can demonstrate characteristic radiologic features such as areas of osteolysis, osteosclerosis, osteonecrosis, thickening of the lamina dura, widening of the periodontal ligament space, presence of bony sequestra, and pathological fractures. Radiologic imaging remains the cornerstone for confirming diagnosis, evaluating the extent of skeletal involvement, determining disease stage, and guiding the selection of appropriate therapeutic strategies. In cases where necrotic bone is not clinically exposed or when clinical findings are inconclusive, advanced imaging modalities—such as multislice computed tomography (MSCT), positron emission tomography (PET), and magnetic resonance imaging (MRI)—can greatly improve early detection and delineation of the affected bone structures[8,9].

Patients in Stage 0 should be regarded as potential precursors of MRONJ, where MSCT can assist in confirming the diagnosis, evaluating the extent of osseous involvement, and identifying possible complications. MSCT may also be valuable in detecting subtle bone alterations before MRONJ becomes clinically apparent[9,10]. Yanaguizawa et al.[11] in their MSCT study concluded that, in patients with Stage 0 (before the clinical manifestation of bone exposure), the computed tomography values of cancellous bone in affected areas were significantly higher than those in unaffected regions. Furthermore, compared with healthy controls, patients receiving bisphosphonate therapy—including those in Stage 0—demonstrated elevated CT values in cancellous bone, suggesting increased bone density relative to individuals not exposed to bisphosphonates. Additionally, thickening of the lamina dura and localized areas of sclerosis are considered potential early indicators that may be detectable before the disease becomes clinically evident. Even in the absence of distinct radiologic or clinical lesions, patients in Stage 0 may present with pain of varying intensity[12–14]. Pain often persists even after standard therapy (antibiotic treatment combined with local antiseptic measures) and demonstrates a certain degree of persistence, suggesting the presence of a neuralgiform component—that is, pain not solely attributable to inflammatory or infectious processes, but potentially possessing neuropathic characteristics. In this study, the patient, classified as Stage 1—where no distinct fistula is present—exhibited an intense, persistent, neuralgiform pain but mild intensity.

In patients receiving antiresorptive, antiangiogenic, or other medications associated with the development of MRONJ, the condition may occur spontaneously; however, the most common predisposing factor is tooth extraction or other invasive surgical procedures involving the jawbones. In this study, all patients developed MRONJ following tooth extraction.

Diagnostic and therapeutic strategies for MRONJ remain subjects of ongoing debate, as no universally accepted standard has yet been established. Currently, diagnosis relies on a combination of clinical, radiographic, and histopathological assessments. The most

common clinical manifestations include delayed healing of extraction sites, exposed necrotic bone, paresthesia, and pain. However, as noted by Kawahara et al., a substantial proportion of patients may remain asymptomatic, with the condition often identified incidentally during routine clinical or radiologic examinations[14]. In this study, the intensity of pain corresponded with the development of clinical signs and symptoms of the disease, equal to the MRONJ stage.

According to the literature, the staging of MRONJ is primarily determined by clinical symptoms and the duration of pain rather than by radiologic characteristics[15–18]. Notably, the early manifestations of different MRONJ stages may exhibit similar radiographic appearances. Duration of bisphosphonate intake affects the appearance of MRONJ. According to the Scottish Effectiveness Programe[4], bisphosphonate intake for longer than 5 years increases the possibility of MRONJ more times. In the present study, a clear correlation was observed between disease stage, clinical presentation, duration of medication intake and pain intensity. In the study by Haviv et al.[19], the stage of MRONJ, the type of pharmacotherapy, lesion size, and location were not correlated with the level of pain. Among patients diagnosed with MRONJ, a total of 67.5% experienced some pain, while 36.5% reported moderate to severe pain[19]. In contrast, the study by Polyakov et al. demonstrated a direct association between pain intensity and the stage of disease progression, with pain being analyzed both before and after treatment[20]. Patients who experienced a high level of pain had better responses to the surgical and conservative treatment and realizing of pain compared to those with moderate pain.

Conclusion

Radiologists play an important role in early diagnosis of all stages of MRONJ. Pain could be considered as early sign of this pathological condition of the bone, and it correlates with the stage of MRONJ in lesions caused by bisphosphonate intake.

CT characteristics of MRONJ can help in more accurate diagnosis and treatment planning, especially in differentiating active necrosis from other pathological conditions of the jaw. CT imaging plays an important role in the detection, classification and follow-up of MRONJ, as it provides detailed information on the degree of involvement of the bone and surrounding structures, which are not always clearly visible by clinical examination or classic X-ray. Future studies should include analyses of larger patient samples encompassing various medications as well as combination therapies.

Acknowledgement: Nil

Conflict of Interest: Nil

LITERATURA/REFERENCES

1. AlDhalaan NA, BaQais A, Al-Omar A: Medication-related osteonecrosis of the jaw: a review . Cureus. 2020,12:e6944.
2. Mallya SM, Tetradis S: Imaging of radiation- and medication-related osteonecrosis . Radiol Clin North Am. 2018, 56:77-89
3. Campisi G, Mauceri R, Bertoldo F, Bettini G, Biasotto M, Colella G, et al. Medication-Related osteonecrosis of jaws (MRONJ) prevention and diagnosis: Italian consensus update 2020. *Int J Environ Res Public Health.* 2020; 17(16):5998.
4. Scotish Dental Medical Effectiveness programe. Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw. Reviewed and extant March 2024; https://www.sdcep.org.uk/published-guidance/medication-related-osteonecrosis-of-the-jaw
5. Muttanahally KS, Tadinada A. Radiographic Evaluation of Medication-Related Osteonecrosis of the Jaw (MRONJ) With Different Primary Cancers and Medication Therapies. Cureus. 2023; Aug 1;15(8):e42830.
6. Lo, J.C.; O'Ryan, F.S.; Gordon, N.P.; Yang, J.; Hui, R.L.; Martin, D.; Hutchinson, M.; Lathon, P.V.; Sanchez, G.; Silver, P.; et al.Prevalence of Osteonecrosis of the Jaw in Patients With Oral Bisphosphonate Exposure. J. Oral Maxillofac. Surg. 2010; 68, 243–253.
7. Ruggiero, S.L. Reply: AAOMS Position Paper on Medication-Related Osteonecrosis of the Jaws—2022 Update. Diagnostic Milestones, Doubts, and Perspectives on MRONJ. J. Oral Maxillofac. Surg. 2022; 80, 1724.
8. Stockmann P, Hinkmann FM, Lell MM, Fenner M, Vairaktaris E, Neukam FW, Nkenke E: Panoramic radiograph, computed tomography or magnetic resonance imaging. Which imaging technique should be preferred in bisphosphonate-associated osteonecrosis of the jaw? A prospective clinical study. Clin Oral Investig. 2010; 14:311-7.
9. Hutchinson M, O'Ryan F, Chavez V, et al.: Radiographic findings in bisphosphonate-treated patients with stage 0 disease in the absence of bone exposure. J Oral Maxillofac Surg. 2010; 68:2232-40
10. Rabie CM, García-Larraín S, Medina DCD, Cabello-Salazar I, Fontenele RC, Wyngaert TV, Jacobs R. How does the clinical and tomographic appearance of MRONJ inuences its treatment prognosis? Dentomaxillofac Radiol. 2023;52(8):20230304.
11. Yanaguizawa WH, Barros FB, Kobayashi-Velasco S, Salineiro FC, Alves FA, Cavalcanti MG.Computed tomography bone density variations in oncological patients undergoing antiresorptive medication. Med Oral Patol Oral Cir Bucal. 2022;27(6):e489–96.
12. Hamada H, Matsuo A, Koizumi T, Satomi T, Chikazu D. A simple evaluation method for early detection of bisphosphonate-related osteonecrosis of the mandible using computed tomography. J Cranio- Maxillofacial Surg. 2014;42:924–9
13. Taniguchi T, Ariji Y, Nozawa M, Naitoh M, Kuroiwa Y, Kurita K, et al. Computed tomographic assessment of early changes of the mandible in bisphosphonate-treated patients. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122:362–72
14. Kawahara, M.; Kuroshima, S.; Sawase, T. Clinical Considerations for Medication-Related Osteonecrosis of the Jaw: A Comprehensive Literature Review. Int. J. Implant. Dent. 2021; 7, 47.
15. Millares RA, Armentia ES, Estepar SDC, Ferro MN. Medication-related osteonecrosis of the jaw: the radiologist's role. Radiologia (Engl Ed). 2023; Sep-Oct;65(5):473–80).
16. Feng X, McDonald JM: Disorders of bone remodeling . Annu Rev Pathol. 2011; 6:121-45.
17. 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.
18. Otto S, Pautke C, Van den Wyngaert T, Niepel D, Schiødt M. Medication-related osteonecrosis of the jaw: prevention, diagnosis and management in patients with cancer and bone metastasis. *Cancer Treat Rev.* 2018; 69:177–87.
19. Haviv Y, Geller Z, Mazor S, Sharav Y, Keshet N, Zadik Y. Pain characteristics in medication-related osteonecrosis of the jaws. Support Care Cancer. 2021 Feb;29(2):1073-1080.
20. Polyakov KA, Popova SV, Shamanaeva LS, Ivanov SY, Petruk PS, Ivanyushko TP. Assessment of Quality of Life in Patients with Medication-Related Osteonecrosis of the Jaw Following Reconstructive and Restorative Surgery. *Applied Sciences.* 2021; 11(24):11950