ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 06 | June - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAWS (BRONJ): A REVIEW

Oral Medicine

Dr. Preeti Patil* Senior Lecturer, Dept of Oral Medicine and Radiology, Dayananda Sagar College of Dental Sciences, Bangalore. *Corresponding Author

Dr Chaya M David Professor and Head, Dept of Oral Medicine and Radiology, Dayananda Sagar College of Dental Sciences, Bangalore.

Dr Farzana Postgraduate student, Dept of Oral Medicine and Radiology, Dayananda Sagar College of Dental Sciences, Bangalore.

ABSTRACT

Bisphosphonates are potent antiresorptive medications that suppress the osteoclastic activity and have been known to reduce bone pain, improve life quality and prevent skeletal complications. Osteonecrosis of the jaw in patients treated with bisphosphonates is a relatively rare but a well-known complication. Bisphosphonates related osteonecrosis of the jaw (BRONJ), which was thought to be due to IV Bisphosphonates, has now been increasingly reported in patients taking oral Bisphosphonates. In this paper we review the pathogenesis, clinical features, radiographic features, management and dental considerations in BRONJ.

KEYWORDS

Bisphosphonates, BRONJ, osteonecrosis, Jaws, dental considerations

INTRODUCTION:

Bisphosphonates (BPs) are a group of synthetic drugs used in calcium metabolism disorders, which inhibit osteoclastic and resorptive process. They have been used since two decades to treat patients with osteoporosis and to control malignancies that compromise bone integrity. They act by decreasing bone turnover via the inhibition of osteoclastic processes.[1] They are known to improve bone morphology, prevent destruction of and pathologic fractures, and decrease pain associated with the metastatic bone disease all of which significantly improve the quality of patient's life.

BPs accumulate for long periods within the bone matrix, depending on the treatment duration and type of BPs prescribed and may remain in the body for several years. Classically, BPs have been classified into: non-nitrogen containing BPs (NNBP) and nitrogen containing BPs (NBP) depending on the presence or absence of nitrogen in their R2 group. Clinically, both the NNBPs and NBPs are used as antiresorptive agents but the NNBP are known to be less potent and thus are mainly used in management of osteoporosis whereas the heterocyclic NBPs are the most potent BPs used in severe bone resorption cases like in malignancies.

Although there are many adverse effects of Bisphosphonate, osteonecrosis of the jaws is one among the most serious adverse condition. The incidence of Bisphosphonate-related osteonecrosis of the jaw (BRONJ) depends strongly on the route of administration, duration of therapy, and type of bisphosphonate. The first case of bisphosphonate related osteonecrosis of jaws (BRONJ) was reported by Marx in 2003.[3] He observed painful exposed bone in mandible, maxilla or both jaws in 36 patients who were treated with intravenous bisphosphonates.

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is characterized as bone in the maxillofacial area with necrosis recurring for more than 8 weeks in bisphosphonate treated patients without history of radiation therapy. This working definition was adapted by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2007.[4] The jaw bone is more susceptible to BRONJ as there is very rapid turnover rate of jaw bones and the supporting structures like teeth and gums are may act as portal for bacterial infections.[5]

BRONJ was initially thought to be due to administration of high doses of intravenous BPs, but recent literature have indicated that BRONJ also occurs in patients receiving low doses of oral BPs for the treatment of osteoporosis.[6]

Pathogenesis of BRONJ:

Bisphosphonates get deposited and accumulated within the alveolar bone which have a higher turnover rate. They impair the ability of the osteoclasts to form the ruffled border, their ability to adhere to the bony surface and to produce the protons necessary for continued bone resorption.[7]

During physiological remodeling of the bone, osteocytes get exposed to the buried BPs and are damaged, causing micronecrosis of the bones.[8] The amounts of the necrosed bone gradually increase as the osteoclasts cannot degrade the necrosed bone. Thus, it appears that reduced resorptive activity is a key factor behind the impaired healing capacity of these lesions.

It has been suggested that high concentrations of bisphosphonate in the oral cavity disrupt the oral mucosa[9]. Failure of healing of the soft tissue may lead to secondary infection of the underlying bone usually because of reduced blood supply. BPs cause osteonecrosis through effects on blood vessels in bone, possibly by inhibition of vascular endothelial growth.[10] This prevents angiogenesis and delays the migration of neutrophils, macrophages, and osteoclast progenitors to the site needed for wound healing and bone remodeling.

In the jaws, structures like teeth and gums are may act as portal of entry for bacteria. Bacterial contamination with *Actinomyces* and *Staphylococcus* may play a role in maintaining osteomyelitis. Since there is reduced resorptive activity, there is impaired healing capacity of these lesions. Due to altered wound healing, there is delayed epithelial closure of a mucosal opening that leads to chronic infection and the necrosis of bone.

Clinical Characteristics:

The incidence of BRONJ in these studies ranges from 4 to 10%[11] and the mean time of onset varies from 1 to 3 years.[12] General risk factors include malignancies, chemotherapy, glucocorticoid treatment, and high dose or long-term bisphosphonate treatment. Local risk factors include anatomical features where protruding cortical bone with thin mucosal coverage like tori and exostoses implies greater risk for necrosis as well as periodontal disease, any surgical intervention which breaks the mucosal lining, especially tooth extractions.[13]

BRONJ is more commonly seen in the mandible than in the maxilla with the ratio of 2:1, in areas of thin mucosa overlying bony prominences, such as tori and mylohyoid ridge.[14] The condition may be asymptomatic for long time. Clinical presentations and levels of pain can vary to a great extent. The first signs and symptoms reported are deep pain in the bone and tooth mobility.[15] In 60% of the cases pain in the exposed bone is reported when the lesion becomes symptomatic due to the surrounding tissue inflammation or infection. The amount of exposed bone varies and may measure from a few millimeters to larger areas. There can be associated soft-tissue swelling and infection, loosening of teeth and draining fistula. Patients may have other symptoms such as trismus, halitosis and recurrent abscesses, sinusitis with or without oro-antral fistula.[4] Pathological fractures of the mandible and impairment of inferior alveolar nerve function can also be seen in BRONJ.

Radiographic Features:

The radiologic findings of BRONJ are not specific and may be similar to conditions such as osteomyelitis, osteoradionecrosis, cancer metastasis and Paget's disease.[16] Dental panoramic radiograph and computed tomography can be considered as the most widely available imaging techniques for BRONJ evaluation. In early disease Focal sclerosis is present with the presence of a disorganized, trabecular pattern and poor corticomedullary differentiation. Periapical radiograph and orthopantogram findings include thickening of the lamina dura, osteolysis, diffuse sclerosis, narrowing of the mandibular canal and poor healing or non-healing of extraction sites. In the later stages, sequestrum formation, fractures, and periosteal reactions are seen. [17]

Computed Tomography scans will help to identify findings difficult to appreciate on plain films and also provide three-dimensional information and better delineation of the extent of the lesions. It is superior to panoramic radiographs in depicting initial changes, soft tissue swelling, new bone, and sequestrum.[18] The CT findings for BRONJ also include cervical lymphadenopathy, which is related to the presence of infection in the exposed bone. The maxillary sinus adjoining to the area may show evidence of mucoperiosteal thickening, air-fluid levels, and fistula formation. Magnetic Resonance Imaging in BRONJ can be used for the assessment of the involvement of the bone marrow, adjacent soft tissues, neurovascular bundles, and lymphadenopathy. A study conducted by Guggenberger et.al revealed PET/CT and MRI revealed more extensive involvement of BRONJ compared with CBCT and clinical examinations and although scintigraphy is a very sensitive investigation it can give false positive results. [19]

Management:

The American Association of Oral and Maxillofacial Surgeons (AAOMS) has proposed a staging system to choose the best treatment strategy for a given patient. There are four stages of BRONJ, which are as follows,

Stage 0	signs and symptoms short of exposed necrotic bone in patients that might indicate a histological necrosis or a prenecrotic state
Stage 1	exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage 2	exposed/ necrotic bone in patients with pain and clinical evidence of infection
Stage 3	exposed/necrotic bone in patients with pain, infection and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border.

Patients with stage 1 and 2 BRONJ should be treated using a conservative approach to prevent progression of lesions and limit complications associated with chronic infection.[20] This approach includes conservative debridement of bone sequestra, local irrigation with povidone-iodine and oral rinse with 0.12% chlorhexidine mouthwash, antibiotic therapy and pain control. Surgical debridement has been variably effective in eradicating the necrotic bone. Surgical modalities range from conservative (debridement, bone curettage, and sequestrectomy) to radical (marginal/segmental resection).[21] The goal of surgery should be to remove sequestrum, which acts as foreign material. The necrotic areas that act as constant source of soft tissue irritation should be removed without exposure of additional bone. The surgical resection of necrotic jawbone has traditionally been considered palliative rather than curative, as it has been offered primarily to patients with advanced disease who have not responded to nonsurgical.

Dental Considerations:

Uniqueness of the oral cavity and jawbone makes them prone to bisphosphonates effects. Management of oral hygiene, patient education, and providing proper dental treatment are critical for preventing BRONJ. There is a little evidence that suggest that temporary cessation of BPs treatment is effective for preventing BRONJ. Routine dental treatment can be provided to low risk patients while high-risk patients may be referred to an oral and maxillofacial surgeon. High risk patients include cancer patients on intravenous bisphosphonate, patients on bisphosphonate therapy with exposure to chemotherapeutic agents (i.e. cyclophosphamide, erythropoietin, thalidomide and steroids), patients on oral bisphosphonates for more than 3 months, smokers and patients with other systemic diseases like cancer, diabetes, obesity etc.

For patients planning to begin bisphosphonate therapy or have recently started therapy for osteoporosis, eliminate oral infection and minimize periodontal inflammation. Removal of tori and bony exotosis are indicated in patients who are wearing dentures, adjustment of ill fitting dentures. BP therapy should be delayed until the extraction site is epithelized or adequate osseous healing has completed. Oral hygiene in the form of brushing, flossing and rinsing with fluoride mouthwash is adviced.[22]

For Patients on oral bisphosphonates**,** elective dentoalveolar surgery and extractions are not contraindicated, provided the necessary precautions are taken. For patients on oral bisphosphonate therapy for more than 3 years with or without concomitant steroid therapy, discontinuation of BP 3 months prior to oral surgery should be considered in consultation with physician if the systemic condition permits and resumed after osseous healing has occurred. Patients who are taking oral BP less than 3 years without concomitant steroid medication and have no clinical risk factors, dentoalveolar surgery and extractions can proceed without any alteration. For patients on oral bisphosphonate therapy less than 3 years with concomitant steroid medication, a 3-month drug holiday should be considered, in consultation with the prescribing physician**.** Patients on intravenous bisphosphonates, maintenance and conservative dental care are performed as far as possible to reduce the risk of BRONJ development.[22]

CONCLUSION:

BRONJ is a rare but serious and debilitating complication of bisphosphonates. The development of BRONJ is associated with many local and systemic factors including poor oral hygiene, dental infections, ill-fitting dentures etc. Prevention is the keystone to reduce the incidence of BRONJ, as it is difficult to treat. Before starting BP therapy, oral health professionals have to thoroughly evaluate patient's oral condition and provide necessary treatment to prevent development of BRONJ.

REFERENCES:

1. Fleisch H, Russell RG, Francis MD. Diphosphonates inhibit hydroxyapatite dissolution in vitro and bone resorption in tissue culture and in vivo. Science. 1969 Sep 19;165(3899):1262-4.
2. Morag Y, Morag-Hezroni M, Jamadar DA, Ward BB, Jacobson JA, Zwetchkenbaum SR, et al. Bisphosphonate-related osteonecrosis of the jaw: A pictorial review. Radiographics 2009;29:1971-84
3. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic. J Oral Maxillofac Surg 2003;61:1115-7
4. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws—2009 update. *Journal of Oral and Maxillofacial Surgery.* 2009;67(5):2–12
5. Yoneda T, Hagino H, Sugimoto T, et al. Bisphosphonate-related osteonecrosis of the jaw: position paper from the Allied Task Force Committee of Japanese Society for Bone and Mineral Research, Japan Osteoporosis Society, Japanese Society of Periodontology Japanese Society for Oral and Maxillofacial Radiology, and Japanese Society of Oral and Maxillofacial Surgeons. J Bone Miner Metab 2010;28:365–83
6. Solomon DH, Mercer E, Woo SB, Avorn J, Schneeweiss S, Treister N. Defining the epidemiology of bisphosphonate-associated osteonecrosis of the jaw: prior work and current challenges. *Osteoporos Int.* 2013;24:237–244.
7. Drake, M.T.; Clarke, B.L.; Khosla, S. Bisphosphonates: Mechanism of Action and Role in Clinical Practice. *Mayo Clin. Proc.* 2008, *83*, 1032–1045
8. J. Yamashita, L.K. McCauley, C. Van Poznak. Updates on osteonecrosis of the jaw. Curr Opin Support Palliat Care. 2010:200-206
9. I. R. Reid, M. J. Bolland, and A. B. Grey, "Is bisphosphonate-associated osteonecrosis of the jaw caused by soft tissue toxicity?" *Bone*, 2007;41(3):318–320.
10. Fournier P, Boissier S, Filleur S, Guglielmi J, Cabon F, Colombel M, et al. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. *Cancer Res.* 2002;62:6538–6544.
11. P. Vescovi, G. Campisi, V. Fusco et al., "Surgery-triggered and non surgery-triggered Bisphosphonate-related Osteonecrosis of the Jaws (BRONJ): a retrospective analysis of 567 cases in an Italian multicenter study," *Oral Oncology*2011;47(3): 191–194
12. J. P. Bilezikian, "Osteonecrosis of the jaw—do bisphosphonates pose a risk?" *The New England Journal of Medicine*, 2006;355:2278–2281
13. R. E. Marx, Y. Sawatari, M. Fortin, and V. Broumand, "Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment," *Journal of Oral and Maxillofacial Surgery* 2005;63;11: 1567–1575.
14. Ruggiero SL, Mehrotra B, Rosenberg TJ, et al. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg.* 2004;62:527–34.
15. Sawatari Y, Marx RE. Bisphosphonates and bisphosphonate induced osteonecrosis. Oral Maxillofac Surg Clin North Am 2007; 19(4):487–98.
16. Fatterpekar GM, Emmrich JV, Eloy JA, Aggarwal A. Bone-within-bone appearance: a red flag for biphosphonate-associated osteonecrosis of the jaw. *Journal of Computer Assisted Tomography.* 2011;35(5):553–556.
17. Haworth AE, Webb J. Skeletal complications of bisphosphonate use: what the radiologist should know. *British Journal of Radiology.* 2012;85(1018):1333–1342.
18. Bianchi SD, Scoletta M, Cassione FB, Migliaretti G, Mozzati M. Computerized tomographic findings in bisphosphonate-associated osteonecrosis of the jaw in patients with cancer. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.* 2007;104(2):249–258.
19. Guggenberger R, Fischer DR, Metzler P, et al. Bisphosphonate-induced osteonecrosis of the jaw: comparison of disease extent on contrast-enhanced MR imaging, [18F] fluoride PET/CT, and conebeam CT imaging. *American Journal of Neuroradiology.*

2013;34(6):1242–1247.
20. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B. Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaw - 2009 update. *Aust Endod J*. 2009;35:119–30
21. Kishimoto H, Noguchi K, Takaoka K. Novel insight into the management of bisphosphonate-related osteonecrosis of the jaw (BRONJ). The Japanese Dental Science Review. 2019;55:95-102
22. Juen Bin Lai, Choy Yoke Poon. A Rational Approach to Dental Management of Patients on Bisphosphonates. Singapore Dental Journal. 2011;2(1):1-13.