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REVIEW ARTICLE

BISPHOSPHONATE RELATED OSTEONECROSIS OF JAW: A REVIEW

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ABSTRACT:
The aim of this review is to highlight the occurrence of osteonecrosis of the jaws in patients treated with long term bisphosphonates therapy, also known as Bisphosphonates Related Osteonecrosis of Jaws (BRONJ) and reviews the guidelines for diagnosis, staging and management of the disease. BRONJ is mainly associated with infection, trauma to the jaw bones (such as dental extraction or simple dentoalveolar surgery) in patients with history of bisphosphonates therapy, which leads to failure of bone healing and ultimately bone necrosis, but it can also occur on its own. Bisphosphonates affect calcification by physicochemical mechanism. it also affects bone resorption at three levels mainly cellular, tissue and molecular level. Treatment of BRONJ depends on the stage of the disease, dose and type (IV or oral) of bisphosphonates intake. However, conservative approach is best method for treating BRONJ.
Keywords: Osteonecrosis, Jaws, Bisphosphonate (BPs).

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INTRODUCTION:

Bisphosphonate (BP)-associated ONJ (osteonecrosis of jaw) is defined by the American Society for Bone and Mineral Research (ASBMR) as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to BPs and who has not received radiation therapy to the craniofacial region. **1** The American Association of Oral and Maxillofacial Surgeons (AAOMS) has recently (2014) updated their definition of medication-related ONJ to (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(e) in the maxillofacial region that has persisted for more than 8 weeks; and (3) no history of radiation therapy to the jaws or obvious metastatic disease to the jaws.**2** The first report of BRONJ (bisphosphonate related osteonecrosis of jaw) came in 2003**3** and since then it has become a topic of debate in dentistry pertaining to a dilemmatic situation of the use of BPs or not.

CHEMISTRY AND CLASSIFICATION:

Chemically, bisphosphonates represent nonmetabolised analogues of pyrophosphates. It has a basic P-C-P structure with two variable groups R1 and R2 (Figure 1). Usually hydroxyl group occupies R1 position which enhances the molecule's affinity to bone (calcium crystals) and R2 position has a variable group which decides its anti-resorptive action, specifically its potency and efficacy.**4** Bisphosphonates can be classified mainly into- Nitrogen containing bisphosphonates (NBPs) and Non nitrogen containing bisphosphonates (NNBPs), on the basis of absence or presence of Nitrogen in R2 group. However, Russell et al. **5** further divided NBPs into Alkyl-amino and Heterocyclic NBPs based on the mode of action [Table1]. NBPs are more potent as compared to NNBPs, although both are anti resorptive agents. The widely used drug in generation first is Clodronate which is available under the brand name of Bonefos, in generation second is Pamidronate which is available under the brand name Aredia and in generation third is Zoledronate which is available under the brand name Reclast or Zometa.

BPs are used for the treatment of hyperemia of malignancy, breast cancer, prostate cancer, lung cancer, Paget's disease, multiple myeloma etc. Also, BPs are useful in treating osteoporosis and osteopenia and improving the quality of life of cancer patients.

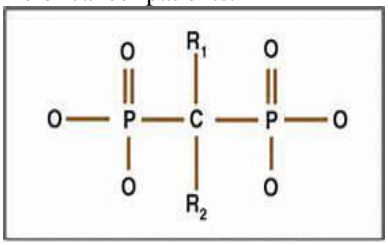

Figure 1: Basic P-C-P structure with two variable groups R1 and R2

TABLE 1: BISPHOSPHONATE- TYPES AND MODE OF ACTION

GENERATION	TYPE	EXAMPLES	MODE OF ACTION
First	NNBPs	Clodronate	Formation of an ATP derivative that impairs osteoclast function and induces osteoclastic apoptosis
Second	Alkyl-amino NBPs	Pamidronate	Inhibits sterol synthesis via the mevalonate pathway specifically inhibiting its Farnesyl pyrophosphate synthase (FPPS) enzyme
Third	Heterocyclic NBPs	Zoledronate	Inhibits FPPS enzyme and stabilize conformational changes

MECHANISMS OF ACTION

Bisphosphonates have the following mechanism of action6

- CALCIFICATION
- BONE RESORPTION
- OTHER EFFECTS

CALCIFICATION:

There is a close relationship between the ability of an individual bisphosphonate to inhibit calcium phosphate *in vitro* and its effectiveness on calcification *in vivo;* 7, 8,9 therefore, the mechanism is likely to be a physicochemical one. Continuous presence of bisphosphonates is important for this effect. They inhibit the formation and aggregation of calcium phosphate crystals from clear solutions, even at very low concentrations,7 block the transformation of amorphous calcium phosphate into hydroxyapatite10,11 and delay the aggregation of apatite crystals. (12) Bisphosphonates also delay the dissolution of calcium phosphate crystals. 13,14,15

BONE RESORPTION:

BPs are believed to bind osteoclasts and affect their resorptive capability at different levels—tissue level, cellular level and molecular level.

A.TISSUE LEVEL:

At the tissue level, BPs show both decrease in bone formation and resorption, ultimately leading to total reduction in bone turnover. Bone morphologic unit (BMU) is the morphological dynamic unit of turnover while Bone Structural Unit (BSU) is the final morphological entity. Bisphosphonates also act at the individual BMU level by decreasing the depth of the resorption site. 16, 17, 18

B.CELLULAR LEVEL:

Four mechanisms appear to be involved: 1) inhibition of osteoclast recruitment; 2) inhibition of osteoclastic adhesion; 3) shortening of the life span of osteoclasts; and 4) inhibition of osteoclast activity.

Bisphosphonates are also powerful inhibitors of macrophage proliferation, cells that are of the same lineage as osteoclasts. 19 Furthermore, the potency rank of bisphosphonates, when assessed *in vitro*, correlates with effects *in vivo* only when systems are used that detect osteoclast recruitment and not activity alone.20,21 However, there is now excellent evidence that bisphosphonates can inhibit the adhesion of some cells, mainly tumor cells, *in vitro.*22 Recently it has been reported that bisphosphonates induce osteoclast programmed cell death (apoptosis), both *in vitro* and *in vivo*, and both in normal mice and in mice with increased bone resorption.23 After bisphosphonate administration, the number of multinucleated osteoclasts on the bone surface often increases initially, despite a reduced bone resorption;(24,25,26) however, the cells appear inactive.24 It is only later, after chronic administration that the osteoclast number decreases. The cause for the initial increase is that it could reflect a stimulation of osteoclast formation to compensate for the decrease in osteoclast activity.

C. MOLECULAR LEVEL:

The fact that osteoblasts exposed for only 5 min to very low concentrations of bisphosphonates are being stimulated into augmenting the release of an osteoblast recruitment inhibitor 27, 28 speaks in favor of their presence as a linking site. Certain bisphosphonates, such as clodronate and etidronate, also inhibit prostaglandin synthesis by bone cells or calvaria, both *in vitro* and *in vivo.*29,30 Since prostaglandins are involved in bone resorption, this inhibition may play a role in the resorption process. Phosphatases and pyrophosphatases are influenced only at relatively high concentrations 31, 32 or not influenced at all.33 Bisphosphonates inhibit Protein Tyrosine Phosphataseses at very low concentrations and inhibit the formation of osteoclasts *in vitro.*33

D.EFFECT THROUGH OTHER CELLS:

a. OSTEOBLAST LINEAGE CELLS:

The recruitment and activity of osteoclasts under physiological and pathological condition is controlled by cells of osteoblastic lineage. This control was proposed to be due to the production of an as yet unknown activity, generated by osteoblast-lineage cells, and modulating bone resorption,34 and this modulation was thought to be an activation of resorption.35–38 BPs may act by modulating osteoblast-osteoclast interaction.

b. CELLS OF THE MONONUCLEAR PHAGOCYTE AND IMMUNE SYSTEM:

i. In vitro BPs decrease both activity and multiplication of the cells of mononuclear phagocytic lineage.6 With respect to cytokine production, clodronate inhibits lipopolysaccharide-induced interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNFα) production by a macrophage-like cell line (RAW 264).39,40 Pamidronate, however, increases the production of IL-6. 40

ii. In vivo Some patients who receive amino BPs for the first time show transient pyrexia, flu like symptoms, decrease in peripheral lymphocytes, especially the CD3+ T cells, an increase in C-reactive protein, and a decrease in serum zinc.6 The pyrexia was shown to be accompanied by an increase in circulating IL-6 bioactivity.41 In addition to IL-6, TNFα is also increased in the blood after treatment with pamidronate but not clodronate42

c. TUMOR CELLS.

BPs inhibits adhesion of tumor cells in vitro and the potency is very well related with the potency in vivo.

OTHER EFFECTS

The other effects include the following**:6**

- Increase of fatty acid oxidation and amino acid oxidation
- Stimulation of citric acid cycle
- Increase in cellular content of glycogen
- Increase in the production of alkaline phosphatase
- Inhibition of the 1,25-(OH)2D3 induced production of osteocalcin in vivo

STAGING OF BRONJ:

It is necessary to make changes in the staging system in order to make the patients more accurately stratified. AAOMS proposed the use of the following revised staging system in order to direct rational treatment guidelines and collect data to assess the prognosis in patients who have used either IV or oral bisphosphonates.43

- **Patients at risk:** No apparent necrotic bone in asymptomatic patients who have been treated with IV or oral bisphosphonates.
- **Stage0:** Patients with no clinical evidence of necrotic bone, but present with non specific symptoms or clinical and radiographic findings. These nonspecific findings, which characterize Stage 0, may occur in patients with a prior history of Stage 1, 2, or 3 diseases that have healed and have no clinical evidence of exposed bone.
- **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 1 or more of the following: Pathologic fracture, extra oral fistula, or osteolysis extending to the inferior border.

PREVENTION AND MANAGEMENT OF BRONJ:

- Routine dental check-ups and completion of invasive dental procedures before initiating therapy can help in prevention of BRONJ. Practicing preventive dentistry, involving procedures such as oral prophylaxis, dental restorations, educating patient about the risk, and endodontic therapy, and check dentures for irritational foci are also means of BRONJ prevention.
- Conservative debridement of necrotic bone, pain control, infection management, use of antimicrobial oral rinses, and withdrawal of bisphosphonates are preferable to aggressive surgical measures for treating this condition.44 Radical resection appears to be of limited use in cases of osteonecrosis of the jaw and may be contraindicated; the disease may progress despite surgery and cessation of bisphosphonate therapy.45
- Treatment of BRONJ can be according to different patient categories {table 2} 44

  The following recommendations are made by the American Association of Oral and Maxillofacial Surgeons for management of patients on BP therapy and patients with proven ONJ. 43

TABLE 2: MANAGEMENT RECOMMENDATIONS

PATIENT CATEGORY	TREATMENT RECOMMENDATIONS
Group 1: Patients about to begin aminobisphosphonate therapy	• Treat any present oral infection, remove any partially impacted wisdom teeth, nonrestorable teeth or teeth with substantial periodontal bone loss. • Encourage oral health care which includes oral examination every six months
Group 2: Patients without osteonecrosis of the jaws who are receiving intravenous aminobisphosphonate therapy	• Same as given in Group 1 incase drug therapy given < 3 months • For >3 months of drug therapy, rather than surgical procedures, seek conservative alternatives with local and systemic antibiotics. • Follow up to ensure healing.
Group 3: Patients with osteonecrosis of the jaws	• Same as in group 2 with >3 months of drug therapy • Consider additional imaging studies • Perform conservative removal of dead bone if required • Prescribe oral rinses, systemic antibiotic therapy, systemic analgesics, soft acrylic stent • Suggest discontinuation of bisphosphonate therapy until osteonecrosis heals or underline disease progresses

Treatment of patients with established ONJ 43:

- **At risk -** Patients who are at risk of developing BRONJ by virtue of the fact that they have been exposed to a bisphosphonate do not require any treatment. However, these patients should be informed of the risks of developing BRONJ, as well as the signs and symptoms of this disease process.
- **Stage 0 –** Provide symptomatic treatment, and conservatively manage other local factors, such as caries and periodontal disease. Systemic management may include the use of medication for chronic pain and control of infection with antibiotics, when indicated.
- Patients with **stage 1** ONJ: Conservative management with oral rinse such as 0.12% chlorhexidine.
- Patients with **stage 2** ONJ: Manage with antibiotics and antimicrobial oral rinses.
- Patients with **stage 3** ONJ: Surgical debridement/ resection in combination with antibiotic therapy.

Extraction of symptomatic teeth can be performed without any additional risks of worsening the condition.

CONCLUSION

BPs are excellent pharmacological agents indicated for the treatment of malignancy related conditions and skeleton related abnormalities but this one adverse effect of osteonecrosis of jaw has raised a question mark on their use. Further clinical research on this topic is required so as to overcome its disadvantages.

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