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REVIEW ARTICLE

BISPHOSPHONATE-INDUCED OSTEONECROSIS OF THE JAW AND GUIDELINES FOR DIAGNOSIS, STAGING AND DENTAL MANAGEMENT: REVIEW

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ABSTRACT: Recently, bisphosphonates (BPs) have been widely used in medical practice as anti-resorptive agents owing to their anti-osteoclatic action. In addition, these compounds are also used for their analgesic action and their potential anti-tumour effect. Patients treated with BPs may subsequently develop osteonecrosis of the jaw or maxillary bone after minor local trauma including dental work, recently labelled as bisphosphonate osteonecrosis of jaw (BRONJ).The aim of this paper to review this phenomenon, including the diagnosis, staging and current clinical guidelines for dental management of patients in which bisphonate therapy is indicated.

KEYWORDS: Bisphopshonates drugs, Osteonecrosis of jaw, Dental Management.

INTRODUCTION: Bisphosphonate-associated osteonecrosis of the jaw, often abbreviated as BON, BON of the jaw or even BRONJ, is a recently discovered dental phenomenon that may lead to surgical complication in the form of impaired wound healing following oral or periodontal surgery or endodontic therapy.[1] In 2003, the first reports describing osteonecrosis of the jaw in patients receiving bisphosphonates were published. About 95% of these cases occurred among cancer patients receiving high-dose intravenous bisphosphonates. Approximately 5% of the reported cases have been in osteoporosis patients receiving low-dose bisphosphonate therapy.[2]

Osteonecrosis of the jaw is an uncommon condition with many recognized causes. Traditionally, it has been associated with head and neck irradiation. It can also occur in the presence of periodontal disease, local malignancy, chemotherapy, glucocorticoid therapy, or trauma.[2-6]

Recently, however, high-dose intravenous bisphosphonates have been identified as a risk factor for osteonecrosis of the jaw among oncology patients. Low-dose bisphosphonate use in patients with osteoporosis or other metabolic bone disease has not been causally linked to the development of osteonecrosis of the jaw.

Osteonecrosis of the jaw can occur in patients who are not taking bisphosphonates and in patients without traditional risk factors.

What are Bisphosphonate Drugs?: Bisphosphonates are stable analogs of pyrophosphate, which are naturally occurring modulators of bone metabolism and have been synthesized and used since the 19th century but their in –vitro ability to inhibit the precipitation of calcium phosphate was applied clinically in 1960s.They are poorly absorbed by the gastrointestinal tract and excreted largely unchanged by the kidneys but if given IV, about half of the drugs goes to the bone.[7, 8]

BPs are commonly used to treat certain resorptive bone diseases such as osteoporosis, osteitis deformans and hypercalcemia associated with certain malignancies such as multiple

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myeloma and bone metastasis from the breast or prostate. Their principle action is to inhibit resorption of bone by inhibiting osteoclast activity, which results in an increase in the mineral density of bone and a reduction in serum calcium[8] although other actions such as inhibition of angiogenesis have also been reported.[9]

Chemical Structure, Classification and Main indications: Chemically, BPs represents pyrophosphate analogues possessing two variable regions, R_1 and R_2 on the carbon atom of BPs molecule attached to basic P-C-P structure. This allows variations in molecular structure and a range of potency corresponding to the changes in the structure. The group occupying R_1 position, usually hydroxyl, enhances the molecule's affinity to bone (calcium crystals) and the variable group at R_2 position decides its anti-resorptive action, specifically its potency and efficacy.[10]

CLASSIFICATION: Basically, BPs have been classified depending on the presence or absence of nitrogen in their R_2 group.[11]

First-Generation Drugs Non-nitrogen containing BPs (NNBP)	**Second Generation (Aminobisphosphonate Drugs)** Nitrogen containing BPs (NBP)
Bonefos (clodronate) Relative potency of 10 PO and IV formulations **Didronel (etidronate disodium)** Relative potency of 1 PO **Skelid (tiludronic disodium)** Relative potency of 10 PO	**Actonel (risedronate sodium)** Relative potency of 5000 PO **Aredia (pamidronate disodium)** Relative potency 100 IV **Boniva (ibandronate sodium)** Relative potency 10000 PO and IV formulations **Fosamax (alendronate sodium)** Relative potency 1000 PO **Reclast (zoledronic acid)** Relative potency 100000 IV Formulation Infused annually for osteoporosis FDA approval pendin **Zometa (zoledronic acid)** Relative potency 100000 IV

Table 1

Side Effects: Orally administered BPs may induce recurrent ulcers with burning sensation and blisters in the oral cavity, erosive esophagitis, esophageal stenosis, uveitis, gastric ulcerations and abdominal pain.[12-14] However, more serious effects such as bisphosphonate-related osteonecrosis of jaw (BRONJ) is seen most commonly after intravenous NBPs such as pamidronate and zoledronate.[14]

What is BRONJ?: Bisphosphonate Related Osteonecrosis of the Jaw (BRONJ) can be described as" An area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a BPs, and no history of radiotherapy to the craniofacial region".[15]

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Symptoms of BRONJ Include:

Exposed bone;
Localized pain;
Swelling of the gum tissues and inflammation; and
Loosening of previously stable teeth.
BRONJ is usually identified by the appearance of exposed bone in the oral cavity.

Risk Factors for BRONJ: According to recent paper by AAOMS and NSW Heath Guidelines, risk factors for the development of BPs associated ONJ can be grouped as follows.

Risk factors	Literature Of Review
1. Drug related	
Potency of BPs	More potent BPs have more tendency to developed osteonecrosis necrosis of jaw(ONJ)
Route of drug administration	IV route of administration resulting greater drug exposure than the oral route therefore more tendency ONJ if given IV
Duration of therapy	Longer duration appears to be associated with increased risk
2. Local	
Dentoalveolar surgery	Patients receiving IVBPs and having dento-alveolar surgery are seven times more likely to develop ONJ than patients who are not having dentoalveolar surgery.
Anatomic location	BPs associated ONJ is more common in the mandible than in the maxilla and more common in areas with thin mucosa overlying bony prominence (Tori, Bony exostoses and mylohyoid ridge)
Concomitant oral diseases	Cancer patients exposed to IV BPs but sex was not statically associated with ONJ.
3. Demographic System	
Age	With each passing decade- there is a 9% increased risk of ONJ in multiple myeloma patients treated with IV BPs but sex was not statically associated with ONJ**.**
Cancer type	Multiple myeloma breast cancer other cancer and osteopenia /osteoporosis concurrent with cancer are more prone to developed ONJ.
Concomitant risk factors	Renal dialysis, low hemoglobin, obesity, Diabetes, Chemotherapeutic agents. Tobacco users and poor oral hygiene are risk factors but no increased risk associated with alcohol exposure.

Table 2

While the majority of patients on intravenous (IV) and oral bisphosphonates will not develop BRONJ, it is important to understand the risk factors for the disease. They have identified three categories of risk factors for the disease.

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The AAOMS Staging and Treatment Strategies For BPs Associated BRONJ[16]

Staging	Treatment Strategies
At Risk Category; No apparent necrotic bone in patients who have been treated with either oral or IVBPs.	No treatment indicated Patient education
Stage 0: No clinical evidence of necrotic bone, but non- specific clinical findings and symptoms**.**	Systemic management including the use of pain medication and antibiotics.
Stage 1: Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection**.**	Antibacterial mouth rinse Clinical follow-up on a quarterly basis Patient education and review of indications for continued BPs therapy.
Stage 2: Exposed and necrotic bone associated with infection as evidence and erythema in the region of the exposed bone with or without purulent drainage.	Symptomatic treatment with oral antibiotics Oral antibacterial mouth rinse Pain control Superficial debridement to relieve soft tissue irritation.
Stage 3: Exposed and necrotic bone in patients with pain, infection and one or more of the fallowing; Exposed and necrotic bone extending beyond the region of alveolar bone (i.e. infection border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathological fracture. Extra oral fistula Oralantral oral nasal communication Osteolytic extending to the inferior border of the mandible of sinus floor.	Antibacterial mouth rinse Antibiotic therapy and pain control. Surgical debridement resection for longer term palliation of infection and pain.

Table 3

How is BRONJ Treated& Its Dental Management? The treatment plan includes regular and thorough communications between physician, dentist and the surgeon.

General Recommendations: The dentist should inform the patient taking oral bisphonates that:

- There is a very risk (estimated at 0.7 cases per 100000 person years exposure) of developing BRONJ
- There are ways to minimize the risk, but not to eliminate the already low risk;
- There are no diagnostic techniques to identify those at increased risk of developing bone.

Management of Periodontal Diseases: The periodontal literature has suggested that these drugs may be beneficial in modulating host response for management of periodonatal diseases17.The patients with destructive periodontal diseases should receive appropriate forms of nonsurgical

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therapy, if the disease does not resolve, surgical treatment should be aimed primarily at obtaining access to root surfaces, with modest bone recon touring being considered when necessary.(Guided bone regeneration or guided tissue regeneration should be considered in view of the fact that these drugs have been shown to decrease the vascularity of tissues, which may have negative effect on grafted sites).Patient without periodontal disease should be treated with mechanical and pharmaceutical methods to prevent peri-implantitis, with regular monitoring of the patient.

Implant placement and Maintenance: At this time, there are limited data regarding the effects of implant placement in patients taking bisphonates. Therefore, treatment plans for patients taking bisphonates should be considered carefully, since it requires the preparation of the osteotomy site.

Before implant placement, the dentist and the patient should discuss the risks, benefits and treatment alternatives, at the same time this discussion should be documented and written acknowledgment of that discussion and consent for the chosen course of treatment should be obtained.

Maintenance of implants should follow accepted mechanical and pharmaceutical methods to prevent peri-implantitis, with regular monitoring of the patient.

Oral and Maxillofacial Surgery: Patients taking oral bisphonates should be informed of the risk. If extractions or bone surgery are necessary, conservative surgical technique with primary tissue closure should be considered, when possible. Immediately before and after surgical procedures involving bone, the patient should rinse gently with a chlorehexidine- containing rinse. Typically, is used twice a day for two months after surgery.

Although For elective surgical procedures in patients with a duration of drug use exceeding 3 years, discontinuation of the medication 3 months before and 3 months after surgery has been suggested. Because of the reduced angiogenesis, osseous grafts should be used judiciously. As adjunctive therapy to enhance healing, the osseous defect can be covered with a resorbable collagen membrane impregnated with platelet-rich plasma. In some situations, antibiotics listed in Table 3 may be instituted a day or two before and after the surgical procedures, if the antibiotics fail to stop the pain, then hospitalization with IV therapy is indicated.

Antibiotics that may be used to treat unexpected pain, purulence or active sequestration after a dental procedure.

Patient Type	Suggested Drug	Oral Regimen
Patients Not Allergic to Penicillin	Amoxicillin may be combined with Metronidazole	500 mg three times per day for 14 days. 250mg three times per day for 14 days.
Patients Allergic To Penicillin	Clindamycin or Azithromycin	300mg three times per day for 14 days. 250mg one time per day for 10 days.

Table 4

Endodontics: Endodontic treatment is preferable to surgical manipulation if a tooth is salvageable. Routine endodontic technique should be used. Manipulation beyond the apex is not recommended.

Restorative Dentistry and Prosthodontics: All routine restorative procedures can be carried out. Well-fitting dentures can be worn if appropriate care is taken to minimize irritation to soft-tissues. Dentures should be removed and thoroughly cleaned each night.

Orthodontics: The Orthodontic treatment is not contraindicated; progress should be evaluated after 2 to 3 months of active therapy. At that point, therapy can proceed if the tooth movement is occurring predictably with normal forces. Invasive orthognathic surgery, four-tooth extraction cases, and miniscrew anchorage should be avoided, if possible. Because the medication is drawn to sites of active bone remodeling, a drug holiday (or switching to a nonamino bisphosphonate agent) during active orthodontics may be advantageous.

Medically Diseased Conditions: In case of osteoporosis and metastatic cancer patients oral bisphonates are prescribed only when there is an inadequate bone density and once the bone density returns switching to nonamino bisphoshonate is advised.

For individuals scheduled to receive IV aminobisphoshonate therapy as part of their cancer management, should undergo pretreatment dental evaluation and preventive care, with long term, close follow –up.

CONCLUSION: Bisphosphonates are excellent medications for bone diseases and osteoporosis that help relieve bone pain and prevent fractures. However, long-term use of bisphosphonates, particularly IV bisphosphonates for metastatic bone disease, may be associated with a small but real risk of developing osteonecrosis of the jaw. While BRONJ is a new and potentially serious condition, so, it is important to ensure that all patients maintain good dental hygiene and see their dentists semiannually.

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