BISPHOSPHONATE THERAPY AND JAW OSTONECROSIS: AN OVERVIEW
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ABSTRACT

BACKGROUND
Bisphosphonates are anti-resorptive agents that have been used for more than a decade, for the treatment of metabolic bone diseases, such as osteoporosis and osteopenia, and to control the skeletal complications associated with metastatic bone disease. Despite their proven efficacy as anti-resorptive drugs, a devastating side-effect, ‘Bisphosphonate Related Osteonecrosis of the Jaws’ (BRONJ), has been documented over the last decade. This article aims to provide an overview of bisphosphonates and BRONJ, to improve the awareness among practitioners.

KEYWORDS
Bisphosphonates; Osteonecrosis; BRONJ; Anti-resorptive; Hypercalcemia.

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BACKGROUND
Bisphosphonates represent an integral part of the overall anti-neoplastic management of patients with malignant bone diseases. They involve high doses and frequency of drug administration and are mainly administered intravenously. Bisphosphonates are extensively used nowadays in the treatment of skeletal metastasis from a variety of cancers, including prostate, breast, lung, renal, bladder and multiple myeloma.1

REVIEW OF LITERATURE
Bisphosphonates are synthetic analogues of the naturally occurring pyrophosphate molecule. Their structural backbone is made up of phosphorus- carbon-phosphorus, which has strong affinity for binding to hydroxyapatite. They differ from one another in the substitution of the active side chains. They are broadly classified into nitrogen-containing and non-nitrogen containing bisphosphonates based on the presence of a nitrogen side chain on the pyrophosphate group; the nitrogen containing being more potent.2

Bisphosphonates can be chemically grouped into two main categories based on side chains.3 The first category is the group containing nitrogen (which prevents metabolization; allowing them to accumulate with ongoing effects) and are considered more potent. Elendronate, risedronate, pamidronate, ibandronate and zoledronate are all members of this category. The medications inhibit farnesyl pyrophosphate synthesis and block the mevalonate pathway in osteoclasts. The second group of medications is without the nitrogen side chain; and is considered less potent. This category includes etidronate, clodronate, and tiludronate. (Table 1)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Nitrogen-Containing Bisphosphonates</th>
<th>Non-nitrogen Containing Bisphosphonates</th>
</tr>
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<tbody>
<tr>
<td>Etidronate</td>
<td>Elendronate</td>
<td>Etidronate</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Pamidronate</td>
<td>Clodronate</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Zoledronate</td>
<td>Tiludronate</td>
</tr>
<tr>
<td>Potency</td>
<td>More potent</td>
<td>Less potent</td>
</tr>
</tbody>
</table>

Current Indications of Bisphosphonate Therapy
These medications are widely used among many medical disciplines with remarkable improvement in the overall quality of life in several conditions, including osteoporosis, Paget's disease, immobilization due to malignancy-related hypercalcemia, fibrous dysplasia and osteolytic bone lesions of malignant myeloma and malignant diseases in which bone resorption is the main component of the disease.

Bisphosphonate strategies, similar to those used to treat post-menopausal osteoporosis, are the intervention of choice for patients with low bone mineral density or rapid bone loss, along with adequate calcium and vitamin D intake and a healthy lifestyle. There is a strong preclinical rationale for bisphosphonates to prevent metastasis, primarily through inhibition of the vicious cycle of metastasis within the microenvironment. Recent data suggest that adjuvant bisphosphonates, at least in some patient subgroups, may modify the course of the disease and disrupt the metastatic process, reducing the risks of disease recurrence. There is also an emerging evidence for direct and indirect anti-tumor activity of bisphosphonates and potential synergy with anti-cancer drugs.4
The established practice of including bisphosphonate administration in the therapy of osseous lesions for multiple myeloma and solid tumors is based on the results of randomized clinical trials demonstrating the efficacy of the bisphosphonates in decreasing the risk of skeletal related events. The American Society of Clinical Oncology has established guidelines for the inclusion of the intravenous bisphosphonates in both breast cancer and multiple myeloma. Pamidronate received US Food and Drug Administration (FDA) approval for hypercalcemia of malignancy in 1991, for multiple myeloma in 1995, and for osteolytic metastases from breast cancer in 1996. Zoledronic acid was first approved for hypercalcemia of malignancy in 2001 and in 2002 gained approval for broad use in bone metastases. (Table 2) It is estimated that approximately 1.9 million people have been treated with pamidronate and 1.0 million with zoledronic acid.5

### Table 2. Bisphosphonate use in Oncology

<table>
<thead>
<tr>
<th>Drugs Used</th>
<th>Dosage</th>
<th>Indications in Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid</td>
<td>4 mg i.v Monthly/every 3 months</td>
<td>Multiple myeloma (anti-myeloma effect) Bone metastases from solid tumours Hypercalcemia of malignancy</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>6 mg i.v every 4 weeks</td>
<td>Bone metastases Multiple myeloma</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>60–90 mg i.v every 4 weeks</td>
<td>Hypercalcemia of malignancy Lytic metastases from solid tumours Multiple myeloma</td>
</tr>
</tbody>
</table>

Bisphosphonates are used to treat patients with multiple myeloma to reduce pain and the risk of skeletal-related events. Approximately 60% of patients with multiple myeloma have lytic lesions at the time of diagnosis. Bisphosphonates are also used to treat patients with solid tumors. Many solid tumors can metastasize to the bone, most commonly, breast and prostate cancers. Bone metastases cause many complications that significantly increase the morbidity in these patients, including pathologic bone fractures, the need for surgery or radiation therapy for symptomatic relief, electrolyte disturbances, hypercalcemia, cancer-treatment related bone loss, nerve compression and neurologic dysfunction.6

In breast cancer, chemotherapy can induce premature ovarian failure, which is a risk factor for decreased bone density; in prostate cancer, androgen deprivation therapy is a risk factor for decreased bone density.7 A review of patients with metastatic breast cancer before the routine use of bisphosphonates revealed that more than 50% developed skeletal-related events during their disease course.8 Data suggest that in patients with breast cancer not treated with a medication to inhibit osteoclast activity, a skeletal-related event is observed every 3 to 4 months on an average in patients with lytic bone lesions.9

Bisphosphonates are also used as part of the treatment regimen for other solid tumour malignancies, such as lung, kidney, stomach, bladder, uterus, thyroid, colon and rectal cancers. Other important uses for bisphosphonates include the treatment of osteoporosis and hypercalcemia. Hypercalcemia is a common metabolic complication associated with malignancy. About 20% of hypercalcemic patients have bone metastases that produce prostaglandins like PGE that erode bone and cause local osteolytic hypercalcemia. The hypercalcemia in the rest of the patients appears to be due to elevated circulating levels of Parathyroid Hormone-related Protein (PTHrP) and is known as humoral hypercalcemia of malignancy. The tumours responsible for the hypersecretion include cancers of the breast, kidney, ovary and skin.

Elevated calcium and alkaline phosphatase levels in blood suggest lytic bone lesions in a patient with cancer. Most common cancers associated with hypercalcemia are breast cancer, lung cancer and multiple myeloma. Less than 25 years ago tumor-induced hypercalcemia was often a lethal complication of cancer. Nowadays, it can be treated easily and successfully in at least 90% of cases with bisphosphonates and aggressive hydration. Prevention of tumor-induced hypercalcemia is one of the objectives of long-term therapy with bisphosphonates in patients with tumor bone disease. The use of bisphosphonates in placebo-controlled trials has shown that the incidence of hypercalcemic episodes is reduced by more than one half.10

### Antiresorptive Action of Bisphosphonates

Bisphosphonates (BP) attach to hydroxyapatite binding sites on bony surfaces, especially those surfaces undergoing active resorption. They inhibit the resorption of bone by accumulating in resorption lacunae located near osteoclasts. At the time of bone resorption, bisphosphonates are released locally and absorbed by osteoclasts; this inhibits osteoclast maturation and leads to apoptosis.11 Bisphosphonates impair the osteoclasts’ ability to form ruffled border, to adhere to bony surface and to produce protons necessary for continuous bone resorption.7 Bisphosphonates also reduce osteoclast activity by decreasing osteoclast progenitor development and recruitment and also promote osteoclast apoptosis. Bisphosphonates appear to have a beneficial effect on osteoblasts. It has been shown to prevent osteocyte and osteoblast apoptosis in glucocorticoid induced osteoporosis. Since bone resorption and formation are coupled in normal bone remodeling, inhibition of bone resorption by bisphosphonates has an indirect effect on bone formation, which in turn decreases.12

### Adverse Effects of Bisphosphonates

In comparison to most other cancer treatments, adverse events related to bisphosphonate therapy are generally mild and infrequent; thus, the benefits of treatment in indicated patients will almost always outweigh the risks. Although extensive data demonstrate the beneficial effects of bisphosphonates, several cases of bisphosphonate related
osteonecrosis of the jaws (BRONJ) have been reported which is a critical complication that is exceptionally hard to treat.

The adverse reactions of BPs are described as low-grade and are almost never severe. (Table 3) Gastrointestinal effects occur in 2-10% of patients after oral administration. Intravenous administration of aminobisphosphonates in 20-40% of cases show an acute-phase immune response caused by osteoclast secretion of tumour necrosis factor-alpha (TNFα) and interferon-gamma (INFγ), which in turn triggers the proliferation of interleukin-6 (IL-6). This results in flu-like symptoms with fever and bone pain. Acetaminophen or ibuprofen can be administered to prevent or treat flu-like symptoms.13 Common adverse effects noted with pamidronate include gastrointestinal symptoms like nausea, vomiting, anorexia, diarrhoea, constipation, skin rash, transient bone pain, arthralgia, myalgia, generalized pain and reactions at the infusion site. The most common adverse effects noted with zoledronic acid are the infusion-related flu-like symptoms that are typically self-remitting, nausea, fatigue, anaemia, bone pain, constipation, fever, vomiting and dyspnea. Kidney is the route of excretion of these drugs and hence adverse reactions are greater in patients with impaired renal function. Uncommon adverse effects that have been reported are orbital inflammation, jaw osteonecrosis (Bisphosphonate Related Osteonecrosis of the Jaws, BRONJ), atypical subtrochanteric and diaphyseal femoral fractures, renal tubular disorders, focal segmental glomerulosclerosis, musculoskeletal pain and hypocalcemia.14

There have been isolated reports of renal impairment and acute renal failure after zoledronic acid administration, particularly in patients with multiple myeloma but also rarely in those treated for osteoporosis and those receiving concurrent diuretic therapy. This occurrence may be related to rapid infusion of zoledronic acid. To reduce this side effect it is recommended that 4 mg dose of zoledronic acid be administered as an infusion over a period of at least 15 minutes. Prior to each zoledronic acid infusion, serum creatinine should be measured and the patients have to be adequately hydrated. In patients taking other nephrotoxic drugs or diuretics, periodic post-infusion measurement of serum creatinine should be considered. Zoledronic acid is not recommended for use in patients with creatinine clearance ≤35 mL/min. An acute phase reaction occurs within three days after zoledronic acid administration with symptoms such as fever, fatigue, bone pain and flu-like symptomatology. These symptoms typically resolve spontaneously within a few days. Rare cases of uveitis, scleritis, episcleritis, conjunctivitis and orbital inflammation have also been reported. Adverse effects with ibandronate injections are similar to those of other bisphosphonates apart from anaphylaxis, local reactions at injection site, hypocalcaemia, rash, dermatitis, dizziness, headache and renal toxicity.15

Patients on intravenous bisphosphonate therapy are prescribed calcium and vitamin D supplementation as hypocalcaemia has been reported as an associated adverse event. Hypocalcaemia is more likely to occur in those individuals with vitamin D deficiency and, therefore, can be minimized by vitamin D and calcium supplementation. Individuals with vitamin D deficiency (25 (OH) D <20 ng/mL (50 nmol/L)) should be treated prior to the infusion, until the serum 25 (OH)D level is above 25 to 30 ng/mL (62 to 75 nmol/L. Some clinicians also advise patients to increase calcium supplementation (doubling of usual dose) for five to seven days starting on the day of the infusion as this may also minimize hypocalcaemia, although there are no data to support this practice. Prior to receiving intravenous bisphosphonates, patients should be assessed for hypocalcaemia, vitamin D deficiency, and renal impairment by measuring serum calcium, creatinine, and 25 (OH) D.16

### Table 3. Adverse Effects of Bisphosphonates

<table>
<thead>
<tr>
<th>Effect</th>
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<tbody>
<tr>
<td>Infusion-related flu-like symptoms</td>
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<tr>
<td>Bisphosphonate Related Osteonecrosis of the Jaws</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
</tr>
<tr>
<td>Renal impairment and renal failure</td>
</tr>
<tr>
<td>Anaphylaxis</td>
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<tr>
<td>Gastrointestinal symptoms</td>
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<tr>
<td>Eye symptoms</td>
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<tr>
<td>Local reactions at injection site</td>
</tr>
<tr>
<td>Atypical subtrochanteric and diaphyseal femoral fractures</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
</tr>
<tr>
<td>Non-specific symptoms: rash, headache, dizziness</td>
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</tbody>
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### Bisphosphonate Related Osteonecrosis of the Jaws (BRONJ)

Phosphorus necrosis of the jaws (‘phossy jaws’) was reported in the 19th and 20th century in workers producing ‘strike-anywhere’ or ‘Lucifer’ phosphorus-based matches. These matches were invented by John Walker in 1827 with its basic part being white phosphor. The exposure of the workers to this compound resulted in ‘phossy jaws’ mainly around ‘rotten teeth’.17 Marx published the first reports of Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) in a letter in 2003, which described 36 cases.18 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 on low-dose bisphosphonate therapy.19 Ruggiero et al.,20 described 63 cases of ONJ from their oral surgery practice from 2001 to 2003. These patients were predominantly female (71%) and typically presented with bone pain, nonhealing extraction sockets, or exposed bone, primarily in the mandible (63%). Nearly all patients (86%) had previous dental procedures.

The American Association of Oral and Maxillofacial Surgeons, in its position paper in 2014,21 recommended changing the nomenclature of bisphosphonate-related osteonecrosis of the jaw (BRONJ) to medication-related osteonecrosis of the jaw (MRONJ) due to the growing number of osteonecrosis cases involving the maxilla and
mandible associated with other antiresorptive (denosumab) and anti-angiogenic (bevacizumab) therapies. Based on case series, case-controlled and cohort studies, estimates of the cumulative incidence of BRONJ range from 0.8%-12%. The incidence of ONJ in cancer patients exposed to zoledronate has been reported as 0.7 to 6.7%. In patients with cancer exposed to Denosumab, the risk of MRONJ ranges from 0.7 to 1.9% and 0.2% in those exposed to bevacizumab. These incidences were based primarily on case reports. The appearance of BRONJ appears to be related to the cumulative dose, the duration of treatment, the type of bisphosphonates used, with a positive correlation for higher doses, longer durations of therapy and nitrogen-containing bisphosphonates.

According to the AAOMS,22 patients may be considered to have MRONJ if all of the following characteristics are present:

- Current or previous treatment with antiresorptive or antiangiogenic agents.
- Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks.
- No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.

BRONJ lesions may remain silent until the occurrence of a triggering event, such as an invasive dental procedure, infection or mechanical trauma to the jawbone as well as the concomitant use of immunosuppressive drugs and chemotherapy. The clinical manifestations of BRONJ vary from necrotic bone exposure (ranging from a few millimetres in size to larger areas), which may or may not be symptomatic, simple swellings of the soft tissues and abscesses, to more complex cases presenting with fistulas and diffuse pain.

Management strategies of BRONJ include the discontinuation of bisphosphonate administration in addition to treatment by medical therapy or minimally invasive surgical therapy. Various adjunctive treatments such as hyperbaric oxygen therapy, laser therapy, ozone therapy, teriparatide, fluorescence-guided debridement, treatment with growth factors (platelet-rich plasma (PRP) or bone morphogenetic protein 2 (BMP2)), and ultrasonic therapy have been mentioned.22,23,24

**Physician Awareness about Bisphosphonates and BRONJ**

BRONJ is a relatively new entity described in the last decade and the treating physicians and the dental professionals are not very much aware of this complication in patients on bisphosphonates. History of bisphosphonate use for osteoporosis or metastatic cancer should make the dentists wary of the risk of osteonecrosis of jaws. The physicians prescribing bisphosphonates for osteoporosis, metastatic bone disease or hypercalcemia may not be very observant about the oral health of these patients and complications such as jaw osteonecrosis may go undetected. At the same time, details of bisphosphonate use may not come to the notice of the treating dental professionals, either due to incomplete history or the patient himself being ignorant of the possible side effects of the drug, due to which the history is not contributory. Pathophysiology of BRONJ is still unclear but poor oral hygiene and oral health and invasive dental procedures have been proposed as risk factors. Hence, good knowledge of the drug, its indications and adverse effects is essential for possible prevention, early detection and management of this not so common complication. This would in turn help them to identify patients at risk and educate them on the prevention and management of BRONJ and make them aware of the signs and symptoms associated.

**CONCLUSION**

Bisphosphonate is a novel antiresorptive medication used in several benign and malignant bone lesions and hypercalcemia. Therapy with bisphosphonates is very effective and significantly improves the quality of life. Apart from the minor adverse effects, a rare but morbid complication of this therapy is BRONJ. A better understanding of the disease and early identification is essential in the management of BRONJ.

**REFERENCES**


