REVIEW ARTICLE

Bisphosphonates: An Emerging Trend in Dentistry

Vivek K Bains, Vivek Gupta, G P Singh, Sudhir S Patil and Robin Srivastava

ABSTRACT

Aim: To discuss the basic mechanism alongwith the clinical implications of Bisphosphonates (BPs) in dentistry.

Summary: Bisphosphonates (BPs) are a class of drugs that prevent the loss of bone mass, used to treat osteoporosis and similar diseases. These are compounds used in the treatment of many skeletal disorders such as bone metastases, osteoporosis, Paget's disease etc. and promote the processes of inflammation and destruction by decreasing bone remodeling and exerting antiangiogenic and apoptotic effects.Their clinical application has recently increased in dentistry. BPs have paradoxical effects in the oral cavity, having potential beneficial effects, whilst also increasing the risk of osteo necrosis of jaw. Implant patient who has been taking an oral bisphosphonate for osteoporosis is at the possible risk of developing osteo necrosis of jaw after implant placement. Its various harmful and beneficial effects have been discussed in this paper.

Keywords: Alendronate, Bone Metabolism, Diphosphonate, Bisphosphonate-associated Osteonecrosis of the jaw (BON).

INTRODUCTION

Bisphosphonates (also called diphosphonates) are a class of drugs that prevent the loss of bone mass, and used in the treatment of many skeletal disorders such as bone metastases, osteoporosis, Paget's disease etc.[1] They are called bisphosphonates (BPs) because they have two phosphonate (PO_3) groups**.** These are structurally similar to natural pyrophosphate (PP), which is a normal product of human metabolism that has a calcium chelating property and is seen in serum and urine (Fig. 1).[2]

Department of Periodontology, Saraswati Dental College & Hospital, Lucknow (UP), India.
Address for Correspondence:
Dr. Vivek Gupta,
B-Block, 5/130, Indiranagar,
Lucknow-226016 (UP), India.
Contact No: +91-9839124338, E-mail: drvivek10feb@gmail.com
Date of Submission : 12-05-2011
Reviews Completed : 05-07-2011
Date of Acceptance : 05-07-2011

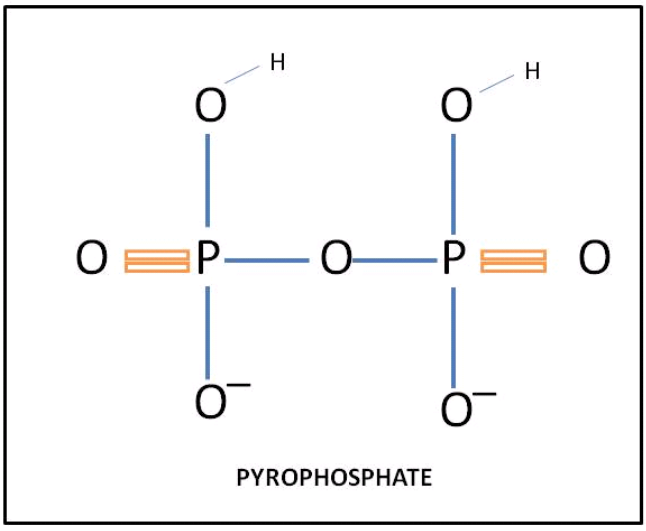

Figure 1: Pyrophosphate

All the geminal BPs and PPs have a funadmental 'planar W' (O-P-C-P-O) configuration that provides bidentate binding to calcium with methylidene BP and the stronger tridentate binding via the hydroxyl group of hydroxymethylidene BP (Fig. 2).[3] PP, in contrast to its analogs that are hydrolytically stable, is an unstable molecule in vivo, and its labile P-O-P bond undergoes rapid hydrolysis by pyrophosphatase and alkaline phosphatase activity.[4]

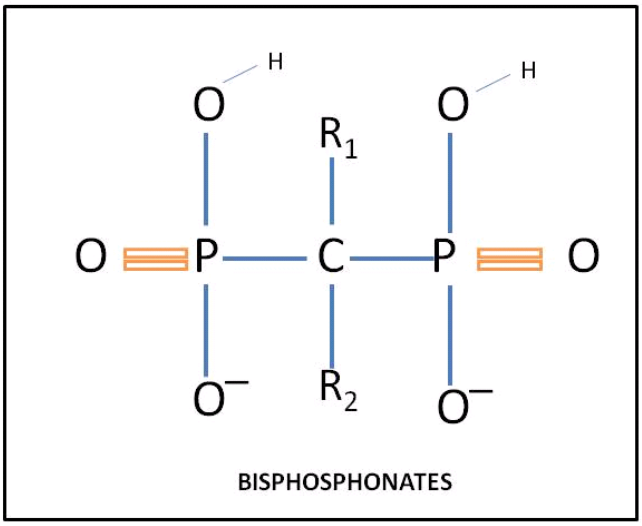

Figure 2: Bisphosphonate

These drugs have a high attraction for hydroxyapatite and rapidly included into all parts of the skeleton.[5] Also, in addition to decreasing hypercalcemia of malignancy, they are used as inhibitors of osteoclastic activity to alleviate bone pain that results from the release of biochemical mediators in metastatic bone disease.[6] Despite the beneficial effects, drug-induced osteonecrosis of jaw is an important complication in patients treated by BPs on long-term basis.[7] Because of its adverse effects, increasing trends of its application in dentistry locally or systemically and its interaction with various dental treatments should be critically reviewed. Present review is intended to discuss the basic mechanism alongwith the clinical implications of BPs in dentistry.

METHODS

We searched the dental literature with Medline/PubMed with an emphasis on peer-reviewed dental journals. MeSH (Medical Subject Headings) terms used were "bishphosphonate" and "dentistry". Pertinent articles on the topic and abstracts of relevant papers were scrutinised thoroughly. Relavent literature for "bisphophonate" in common textbooks on pharmacology, periodontology, oral implantology, oral and maxillofacial surgery; bibliographies of papers and review articles together with appropriate peer reviewed journals were also analyzed for additional information.

LITERATURE REVIEW

In 1897, Von Baeyer and Hoffmann[8] reported the synthesis of the first geminal (central) bisphosphonates, 1-hydroxy-1, 1-ethylidene bisphosphonate disodium salt, but marketable usage for these compounds took place only after their reported use for detergent solutions as complexing agents for calcium and magnesium by Blazer and Worms.[3]

Scientists of Procter and Gamble (P & G) were investigating the calcium chelating agents, which were found to be effective in removing calculus, and chelated enamel calcium causing surface etch damage.[9] Henkel Corporation of Germany, introduced a potential builder for detergency, 1-hydroxy-1, 1-ethylidene bisphosphonate disodium salt (EHDP, etidronate) that could chelate calcium and magnesium in the water blocking re-deposition of soil in the wash, to Procter & Gamble, and this extremely effective chelator of calcium found to cause no damage to the highly polished dental enamel surface.[3]

BPs were originally used in industry, mainly as corrosion inhibitors or as complexing agents in the textile, fertilizer, and oil industries.[10] First human use of a geminal bisphosphonate, etidronate, was reported by Bassett *et al*.[10] in 1969 for the treatment of Myositis Ossficans Progressiva (MPO) and Smith *et al*.[11] were the first to report the evidence of the effectiveness of the bisphosphonates for the treatment of Paget's disease of bone. Since then, bisphosphonates have been approved for the treatment of Paget's disease of bone, hypercalcemia of malignancy using intravenous form, multiple myeloma, or detecting soft tissue calcifications, and for the prevention and treatment of postmenopausal osteoporosis as well as hetreotopic ossification due to total hip replacement or spinal cord injury.[3]

Pharmacological Properties of Bisphosphonates

In bisphosphonates, two phosphonate groups are attached to a geminal (central) carbon that replaces the oxygen in pyrophosphate,[12] which is used as an ingredient in toothpaste to control calculus formation.[13] Three dimensional structure of this pyrophosphate analog, is capable of chelating divalent cations (Ca^{2+}), thus having a strong affinity for bone surfaces undergoing remodeling.[12] Bisphosphonates forms an ultra-thin layer by chemisorbtion to the calcium of hydroxyapatite in bones and teeth.[3] Concentration gradient of bisphosphonate in the extracellular fluid is high, but due to the stronger adsorption of the bisphosphonate on the inorganic HA than on the organic osteoid it is approaching zero (Quantitative Adsorption Ratio; HA: Osteoid=40:1).[3,14] Highly negatively charged, bisphosphonates are membrane impermeable and are incorporated into the bone matrix by fluid-phase endocytosis.

Working profile of each bisphosphonate is determined by its unique side chain. The potency and side effects of the compound are changed by the substitution of different side chains for hydrogen at locations R1 and R2. Amongst modified side chains, hydroxyl group at R1 enhances the binding to bone, whereas the cellular effects of bisphosphonates and their relative efficacies as inhibitors of bone resorption may be regulated by R2 structure and 3-dimensional structure.[6]

The bisphosphonates metabolism of bone modulation occurs at 3 levels.[6] At *tissue* level there is decrease in bone turnover due to decrease in bone resorption and decrease in number of new bone (multicellular units). Thereby, a positive bone balance is maintained in the body. At *cellular* level there is; decrease in osteoclast recruitment, increased osteoclast apoptosis, decreased osteoclast adhesion, decrease depth of resorption site, decrease in release of cytokines by the macrophages, and increase in osteoblasts differentiation and number. At *molecular* level there is inhibition of Mevalonate pathway which is an important cellular metabolic pathway present in all higher eukaryotes and many bacteria. It is important for the production of dimethylallyl pyrophosphate (DMAPP)and isopentenyl pyrophosphate (IPP), which serve as the basis for the biosynthesis of molecules used in processes as diverse as terpenoid synthesis, protein prenylation, cell membrane maintenance, hormones, protein anchoring, and N-glycosylation. It is also a part of steroid biosynthesis and can result in disturbed cell action and induction of apoptosis, and decreased post

translational prenylation of Guanosine triphosphate (GTP)-binding proteins.[6]

Different mode of actions of BPs has been suggested includes: Bisphosphonate-mediated inhibition of the development of osteoclasts, induction of osteoclastic apoptosis,[15] reduction of activity,[16] prevention of the development of osteoclasts from hematopoietic precursors;[17] and stimulation of production of an osteoclast inhibitory factor.[18] It has also been shown that the bisphosphonate alendronate caused a rise in intracellular calcium levels in an osteoclast-like cell line.[19] This finding is of great interest since it could suggest the presence of a receptor for bisphosphonates on osteoclasts. There are various brands of bisphosphonates available in market with varying degree of potency for inhibition of osteoclastic activity. Pyrophosphate drugs are potent inhibitors of osteoclast activity that also have anti-angiogenic effects. The drugs have a high affinity for hydroxyapatite and are rapidly incorporated into all parts of the skeleton and have a very long half-life. Relative potencies of the agents depend on their formulation.

Bisphosphonates have been divided under various generations; the first generation of bisphosphonates include etidronate which was initially used to inhibit ectopic calcification and later was used as to prevent resorption, the second generation bisphosphonates like Ciodronate were used as drugs to prevent bone resorption rather than preventing mineralization to occur, and the third generation drugs had greater potency then first and second generation bisphosphonates (Table 1).[12,20] Amongst various BPs, nitrogen containing bisphosphonates (nBPs) that inhibit farnesyl disphosphonate (FPP) synthetase in the mevalonate pathway, exert intense pharmacodynamic effects long after their blood levels reach zero, and approximately half of any nBP doses reaches the skeleton with an early half life of 10 days and a terminal half-life of about 10 years. FPP synthetase is responsible for isoprenylation of small GTPase as well as geranylgeranylation of Rho and Rac, which promote an array of activities in the osteoclasts that control bone resorption. At low concentrations, the fundamental activities which are related to bone mineral dissolution and collagen degradation, that involve the cytoskeleton, vesicular trafficking, and membrane ruffling are inhibited. At somewhat high concentrations, osteoclast differentitation is inhibited and at concentration of 100 μM, osteoclast apoptosis is induced by Rho and Rac.[21]

Being highly polar compounds, BPs are poorly absorbed after oral ingestion with the bioavailability of less than 5%.[22,23] In order to reduce the interference with the food, timing of meal is important, and to increase the amount of BPs introduced to bone intravenous administration of the drug can also be adviced.[22] Once in the blood stream, almost the entire drug dose is either eliminated in urine or absorbed by the bone,[24]

Table 1: Generations of Bisphosphonates

Drugs	Properties
1st Generation e.g. Etidronate, Medronate, Clodronate, Tiludronate.	Minimally modified side chains (R1 R2) or contain a chlorophenyl group. Can cause bone demineralisation. Apoptosis account for antiresorptive effect. Metabolised into a nonhydrolyzable ATP analog that accumulates within oteoclasts and induces apoptosis. Least potent.
2nd Generation e.g. Alendronate, Pamidronate, Ibandronate.	Aminobisphosphonates, contain nitrogen group (amino terminal) in the side chain. Primarily inhibits bone resorption rather than preventing mineralization. Antiresorptive activity involves inhbition of components of the cholestrol biosynthesis pathway. (G & G) Directly inhibit multiple steps in the pathway from mevalonate to cholestrol and isoprenoid lipids (as geranylgeranyl diphosphonate) that are required for the prenylation of proteins that are important for osteoclast function. They are 10-100 times more potent than 1st generation.
3rd Generation eg. Risedronate, Zoledronate	Contain nitrogen atom within a heterocyclic ring. These are upto 10,000 times more potent than 1st generation.

and in owing to its negative charge and chemical structure, it can be retained as long as ten years.[25] During bone remodelling, BPs are released into the acidic environment of the resorption lacunae where they impede osteoclast bone resorptive action.[26] Osteoclasts take up bisphosphonates from resorption lacunae in the bone matrix, and the bisphosphonates then trigger the osteoclasts to undergo apoptosis.[27]

Bone is normally able to adapt to functional changes through specialized cells, represented by osteoblasts, osteoclasts, and lining cells. This drug is potent inhibitors of osteoclast activity that also have anti-angiogenic effects.[5] Since bone damage is caused by increased numbers and activity of these osteoclast bone cells, bisphosphonates reduce new bone damage and allow an opportunity for bone healing to occur. Bisphosphonates therefore have several beneficial effects, including:[28] Preventing further bone damage; Reducing bone pain and the need for painkillers; Correcting and preventing hypercalcemia (higher than normal levels of calcium in the blood); Reducing the need for radiotherapy; Reducing pathologic fractures due to myeloma (i.e., fracture at a site where myeloma has weakened the bone); Improving quality

of life; and Improving the chances of healing and recovery of strength of the bone.[28]

Adverse Effects of Bisphosphonates

The various toxic effects of BPs can be divided into: *Common* that include renal toxicity, acute-phase reactions, gastrointestinal toxicity; *Rare* as hypocalcemia (symptomatic), ocular complications (retinitis, uveitis, scleritis), asthma (aspirin-sensitive), erythema, phlebitis, altered taste, central nervous system side effects; and *Emerging* as osteonecrosis of the jaw.[29] Besides above mentioned effects, nBPs may inhibit angiogenesis by reducing circulating levels VEFG (vascular endothelial growth factor), and is also found to be associated with accumulation of microcracks at or somewhat above osteoporosis doses in dogs.[21]

Numerous studies and reports have revealed the renal toxic action of the bisphosphonates.[30-34] Varying renal histopathology of acute tubular necrosis associated with individual bisphosphonates may depend on the degree to which the drugs accumulate in the renal parenchyma, which, in turn, depends on the drugs' pharmacokinetics and pharmacodynamics. Renal toxicity for intravenous bisphosphonates determined by the dosage, frequency and speed of infusion, but, so far renal complications following therapeutic oral bisphosphonates have not been reported.[29]

Acute-phase reactions, characterised by number of flu-like signs and symptoms, particularly subfebrile temperature (38°C/100.4°F), leukocytosis, exhaustion, and muscle and bone pain, occur only with intravenously administered aminobisphosphonates (zoledronic acid, ibandronate, and pamidronate), usually after the first infusion.[35-37] Transient increase in pyrogenic cytokines (IL-6, TNF-alpha) may cause acute-phase reactions.[38] Although it is not life-threatening, these reactions may sometimes causing treatment withdrawal and symptoms generally resolve within 48 hours that respond well to nonsteroidal anti-inflammatory drugs and antipyretics.[29]

Bisphosphonate-induced adverse effects in the Gastrointestinal (GI) tract are naturally seen only after oral therapy and lifethreatening complications are extremely rare, however, if adverse GI reactions persist, then intravenous route may be preferred.[29] All levels of the GI tract can be affected, from the lower esophagus to the colon, although ulceration in the esophagus, stomach, and duodenum can occur, mucositis, flatulence, and diarrheoa are more common.[39-41]

*Osteonecrosis of the jaw or Bisphosphonate-Associated Osteonecrosis (BON)***:** The term osteonecrosis (Osteo = bone + necrosis = cell or tissue death) simply means death of bone tissue; bone die in any part of the body if its blood supply is cut off and the cells can't get oxygen or food.[1] Marx,[42] Milgliorati,[43] and Ruggiero *et al*.[44] were amongst the pioneers to describe BON in association with bisphosphonate treatment. BON has similarities with the almost disappeared condition, and presently only reported in Chinese firework factory workers, "phossy jaw" first observed in the 19th century in individuals exposed to white (yellow) phosphorus.[29,45,46]

Clinical presentation of BON includes soft tissue swelling and exposed, necrotic bone that has persisted for more than eight weeks[47,48] in patients who have taken or be currently using BPs, while there is no other perplexing conditions (eg. radiotherapy of jaw, alcoholism etc).[26] The vast majority of BON cases occur in cancer patients who have received high-potency aminobisphosphonates given intravenously to decrease the osteolytic effects of multiple myeloma or malignancies that have metastasized to bone.[5]

With female sex perdilection (3:2), BON is more commonly identified in mandible (posterior lingual side near mylohyoid ridge) alone followed by maxilla and then in both maxilla and mandible.[26,50] Not all patients taking BPs develop BON and frequency of occurrence of BON is between 1% and 12%,[49-51] and less than 1% in patients on oral BPs.[49] There are putative risk factors that may predispose the BON condition which include: age; tobacco use and alcoholism; route of administration (intravenous); Cumulative dosage and potency of bisphosphonates; medical conditions like diabetes, coagulopathy, blood dyscrasias, malignancy; dentoalveolar surgery, intraoral trauma, periodontal disease, poor oral hygiene, poorly fitting dentures, prominent mandibular lingual ridge, mylohyoid ridge and tori; cancer and anticancer therapy, glucocorticoid and estrogen theray; and low mineral density of skeletal systems.[26] All aminobisphosphonates may cause osteonecrosis of jaw with long-term use.[52]

Usually jaw necrosis is characterized clinically by chronically exposed jawbone and including suppuration and sequestration. These lesions do not respond to treatment or intensive antibiotic therapy and repeated jaw surgery.[26,53] Osteonecrosis of jaw may develop due to dentogenic portals of pathogen entry (eg, periodontal disease and periapical granuloma) or to prosthetic pressure points, leading to endosteal infiltration of the jawbone. Bisphosphonates promote the processes of inflammation and destruction by decreasing bone remodelling and exerting antiangiogenic and apoptotic effects,[54] The presence of persistent alveolar sockets after teeth extractions is an important radiographic sign in the jaws associated with BON.[55] Individual with BON often have difficult chewing, speaking and swallowing and severity is comparable to osteonecrosis after radiotherapy to the head and neck.[29]

Implications of Bisphosphonates in Dentistry

Many studies have shown the potential of topical BPs application to enhance osseointegration of dental implants.[46,56-58] Its application on dental implants, with or without calcium phosphate layer promoted implant-bone contact[57,58] and increased the amount of bone peripheral to implants in dogs.[59] Zuffetti *et al*.[20] reported that bisphosphonate-treated implant showed more contact with newely formed bone than the control implant. However, despite these potential benefits, it may contribute the development of BON. Implant patient who has been taking an oral bisphosphonate for osteoporosis is the possible risk of developing osteonecrosis of jaw after implant placement. Oral BPs have been reported to be associated with implant failure[59,60] and Cheng *et al*.[61] reported this risk to be 0.88% of the patients receiving oral BPs. The risk is real as bisphosphonates bind to hydroxyapatite and have a very long half-life; it is likely that the length of time a patient has been taking oral bisphosphonates is important in determining the level of risk. Since oral bisphosphonates slowly accumulate in bone with time, an osteoporosis patient who has been taking the drug for one year is at a lower risk of developing osteonecrosis of jaw or implant failure than someone who has been on the drug for many years. In general, it is not recommended that implants be placed in patients who have been on the drug for more than 3 years. Prolonged use of bisphosphonates is a contraindication to implant placement.[62]

The use of systemic BPs has shown to reduce alveolar bone loss in large animal models which were experimentally induced or had naturally occurring periodontitis without significantally affecting clinical periodontal parameters.[63] Controlled clinical trials in humans showed the efficacy of alendronate in reducing the alveolar bone loss relative to placebo and in one study the effect was seen in subgroup with low mandibular bone density.[64-67] Kaynak[68] did a study on male rats and stated when systemic administration of 0.5 mg/kg was effective enough for preventing alveolar bone loss and in modulating tissue factors. These finding indicate that alendronate is a valuable therapeutic medicine which can be used for the treatment of periodontal disease either alone or in combination with regenerative components like anti-inflammatory drug, bone graft, material and guided tissue regeneration or even with dental implants.[68] Lane *et al*.[69] suggested that BPs treatment improves the clinical outcome of non-surgical periodontal therapy and may be an appropriate adjunctive treatment to severe periodontal bone loss. A newely developed BPs, TRK-530 (disodium dihydrogen [4-(methylthio) phenylthio] methanebisphosphonate), has recently been shown to have anti-inflammatory, anti-bone-resorbing activity as well as dose dependent local anticalculogenic action.[70] Houshmand *et al*.[71] in an in-vivo study evaluated boosting effect of nBP (Pamidronate disodium) on osteoconductive material and revealed improved bone healing process as a result of reducing the number of osteoclasts and increasing the amount of trabeculae in regenerated tissue.

BPs having high affinity for calcium phosphate crystals and that inhibit osteoclast activity, also appear to inhibit MMP activity through a mechanism that involves chelation of cations,[72,73] however, minimal effects was demonstrated on clinical parameters.[74] Topically administered bisphosphonates have been reported to reduce the resorption of root associated with orthodontic tooth movement and alveolar bone resorption following periodontal surgery.[75,76] BPs also reported to modulate cementoblast behavior in an in-vitro study through the regultaion of gene expression, and thus has the potential for cementum formation and mineralisation modifiers.[13] BNs however, have paradoxical effects in the oral cavity, having potential beneficial effects on periodontal disease, whilst also increasing the risk of osteonecrosis of jaw and hence, the ethical issues inherent in undertaking such trials are likely to limit further trials in humans.[46] Future randomized, controlled, longitudinal studies that evaluate therapies for the treatment of osteoporosis should also examine the effectiveness of the treatment on periodontal disease parameters.[74]

For the maintenance of alveolar bone after tooth extraction, submerged hydroxyapatite implants have been attempted. Denssen *et al*.[77] suggested that normal osteoconduction and repair occurred in alveolar bone around the highly bisphophonate-complexed hydroxyapatite implant. However, the long term effect of the presence of BPs in the healed alveolar bone remained unclear.

Bisphosphonates are very effective in managing osteogenesis imperfecta in children, but no cases of osteonecrosis of jaw have been reported, suggesting extractions are not contraindicated in these children. Young age might possibly be a protective factor for prevention of osteonecrosis of jaw.[78-80] Caution is advised with invasive diode laser therapy, miniscrew skeletal anchorage devices, mucosal trauma from retainers, orthognathic surgery and tooth extraction. It has also been proposed that patients discontinue their bisphosphonate therapy for a period of time prior to orthodontic treatment.[81] this concept would require further investigation as the half life of bisphosphonates is approximately 10 years. It has been seen in an experimental study involving local administration of bisphosphonates in rats that there is a positive role for topical bisphosphonates in orthodontic treatment, inhibiting undesirable movement of anchor teeth and inhibiting post-treatment relapse in a dose dependent manner.[82,83] Extrapolation of these animal models to humans requires special care as there is a risk of osteonecrosis of jaw. Endodontic treatment is the preferred

treatment over extraction to minimize osteo necrosis of jaw risk. Due to bisphosphonate suppression of bone turnover, the periapical rarefaction may not decrease in size in a manner comparable to patients with normal bone turnover. Strathy *et al*.[84] described the development of osteo necrosis of jaw in the region of teeth requiring endodontic treatment in patients on long-term BPs.[29] Endodontic treatment has not been considered as a direct risk for osteonecrosis of jaw, but care has to be taken to minimize trauma due to rubber dam placement and filling beyond the apex, apicoectomy is contraindicated as any type of injury in patients on long term bisphosphonate therapy is a positive risk factor for BON. Orthodontic elastics should be used to promote atraumatic extraction. Extractions should always be performed as atraumatically as possible with direct closure of the socket by suturing and antibiotic prophylaxis considered especially in immunocompromised patients.[46] Similarly prosthodontic appliances should be adjusted for fit to avoid mucosal irritation. Levin *et al*.[85] reported a case of pressure wound in the margins of a removable maxillary denture in 66 year old female on oral alendronate sodium treatment for eight years.

Table 2: American Association of Oral and Maxillofacial Surgeons (AAOMS) staging system for BON.[47]

Stage 0	No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms
Stage 1	Exposed/ necrotic bone in asymptomatic patients without evidence of infection
Stage 2	Exposed / necrotic bone associated with infection as evidenced by pain and erythema in region of exposed bone with or without purulent discharge.
Stage 3	Exposed/ necrotic bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone resulting in pathological fracture, extraoral fistula, oral antral/ oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor.

DISCUSSION AND CONCLUDING REMARKS

Physicians and dentists alike must become increasingly aware of impaired oral healing following the use of BPs given for malignancy-related osteopenias,[86] and more effective communication process between prescribing physicians, dentists and patients using BPs, is needed.[49] Based on a case report of post-surgical complications, Soileau[86] suggested that oral/ dental examination should be performed before commencement of BP therapy as recommended for radiation therapy. To reduce any surgical complications after the instigation of BP therapy, precautionary treatment inclusive of periodontal, prosthetic and endodontic therapy, combined with appropriate dental extractions should be instituted.[29] Dental recall examinations should be performed throughout the course of BP therapy and once the therapy has been initiated, patients should be recalled every six months to ensure optimal oral health. Additionally, most of the times, this drug-induced osteonecrosis of jaw (BON), is detected not by a medical oncologist, but rather upon presentation for dental evaluation.[86] Published data revealed increasing reports of osteonecrosis associated with the nBPs, and oral surgeons most frequently have seen and treated such cases, which if remains untreated can lead complications like pansinusitis in untreated maxillary osteonecrosis.[85] Bone remodelling is severely affected in patients taking long term bisphosphonates therapy, therefore such patients are poor candidates for bone grafting, sinus lift and ridge augmentation procedure. Hence, American Association of Oral and Maxillofacial Surgeons (AAOMS)[47] suggested that patients be adequately informed of the potential risk of compromised bone healing and the risk of developing BON (Table 2), and clinicians should follow-up patients carefully until surgical wounds are healed completely.[85] Although, the incidence of BON is much lower in patients receiving oral BPs therapy than patients receiving intravenous BPs therapy. However, such patients often requiring routine dental care should be treated cautiously, as oral BPs use has been found associated with a small risk of developing oral osteonecrosis that occur spontaneously or after the patient has undergone dental surgery.[85] Any established BON patient needing surgical procedures should be referred to an oral and maxillofacial surgeon, who may consult other qualified specialists as appropriate. The role of hyperbaric oxygen [HBO] and vascularized tissue transfers in the reconstructive management of bisphosphonate-related osteonecrosis of the jaw have yet to be revealed in BON cases.[1]

In addition to radiographic imaging, a complete blood count may help in assessing the state of the patient in terms of possible infection. Assays to monitor bone turnover, such as N-telopeptide (NTx) and C-telopeptide (CTx) levels, which are reduced by BPs may help in future risk and diagnosis of BON.[87] Suppression of bone turnover can be an indicator for increased bone mineral density (BMD) and can possibly be related to its effects from bisphosphonates.[88]

For a patient who has been taking an oral BP longer than three years, it should be discontinued, 3 months before and 3 months after the surgial procedure, if approved by the patient's physician. Serum CTx should be greater than 150 pg/mL before any surgical procedure, and rechecked at the time of surgery.[87] Non-surgical periodontal therapy is preferred. Any dentoalveolar surgical procedure (i.e. extractions, implants or apical surgery) should be avoided since the surgical sites will likely result in additional areas of exposed necrotic bone,

however, loose teeth, loose sequestra segments, but without exposing uninvolved bone. Similarly, to avoid trauma to the adjacent soft tissues, sharp bony edges should be removed. Systemic antibiotic therapy as well as chlorhexidine rinse, immediately before and after any inevitable surgical procedure for perioperative prophylaxis,[89] while establishing and maintaing meticulous oral hygiene, is essential. Furthermore, it should always be kept in mind, that knowledge base for bisphosphonate-associated BON is rapidly increasing, and it is likely that the current recommendations made by various societies[88,90,91] may change over time.

Thus it can be concluded that;

- Physicians and dentists should be fully updated regarding the potential complications in the management of patients on BPs.
- Effective communication process between prescribing physicians, dentists and patients on BPs, is needed.
- BON is much lower in patients receiving oral BPs as compared with patients receiving intravenous BP therapy and good oral hygiene, accompanied by regular dental care using non-invasive procedures, is the best way to minimise this risk, if it exists.

REFERENCES

1. Walia MS, Arora S, Singal B. Jaw Osteonecrosis a Risk Factor in Bisphosphonate Therapy - A Dental Concern. J Oral Health Comm Dent 2010; 4: 72-7.
2. Rodan GA. Mechanisms of action of bisphosphonates. Annu Rev Pharmacol Toxicol 1998; 38: 375-88.
3. Francis MD, Valent DJ. History of bisphosphonates in treating bone disease. J Musculoskelet Neuronal Interact 2007; 7: 2-8.
4. Shinozaki T, Pritzker KP. Regulation of alkaline phosphatase: Implications for calcium pyrophosphate dehydrate crystal dissolution and other alkaline phosphatase functions. J Rheumatol 1996; 23:677-83.
5. Armitage GC, Lundgren T. Risk Assessment of the Implant Patient. Clin Periodontol Implant Dent 2008; 5: 634-51.
6. Tenenbaum HC, Shelemay A, Girard B, Zohar R, Fritz PC. Bisphosphonates and Periodontics: Potential application for regulation of bone mass in the periodontium and other theraputic and diagnostic uses. J Periodontol 2002; 73: 813-22.
7. Robinson NA, Yeo JF. Bisphosphonates- A word of caution. Ann Acad Med Singapore 2004; 33: S48-49
8. Von Baeyer H, Hofmann KS. Acetodiphosphorigasauer. Ber 1897; 30: 1973.
9. Francis MD, Gray JA, Griebstein WJ. The formation and influence of surface phases on calcium phosphate solids. Adv Oral Biol 1968; 3: 83-120.
10. Bassett CA, Donath A, Macagno F, Preisig R, Fleisch H, Francis MD. Diphosphonates in the treatment of myositis ossficans. Lancet 1969; 2(7265): 845.
11. Smith R, Russell RG, Bishop M. Diphosphonates and Paget's disease of bone. Lancet 1971; 1 (7706): 945-7.
12. Goodman and Gillman's The Pharmacological Basis of Therapeutics. Brunton LL, Lazo JS, Parker KL, eds. 11th ed, McGraw Hill Medical Publicating Division, New Delhi, 2006, 1666-8.
13. Chun Y-HP, Foster BL, Lukasavage PA, Berry JE, Zhao M, Tenenbanum HC, *et al*. Bisphosphonate modulates cementoblast behavior *in vitro*. J Periodontol 2005; 76: 1890-1900.
14. Francis MD, Horn PA, Tofe AJ. Controversial mechanism of technetium-99m deposition on bone. J Nucl Med 1981; 22: 72.
15. Hughes DE, Wright KR, Uy HL, Sasaki A, Yoneda T, Roodman GD, *et al*. Bisphosphonates promote apoptosis in murine osteoclasts *in vitro* and *in vivo*. J Bone Miner Res 1995; 10: 1478-87.
16. Sato M, Grasser W. Effects of bisphosphonate on isolated rat osteoclasts as examined by reflected light microscopy J Bone Miner Res 1990; 5: 31-40.
17. Hughes DE, MacDonald BR, Russell RG, Gowen M. Inhibition of osteoclast-like cell formation by Bisphosphonates in long-term cultures of human bone marrow. J Clin Invest 1989; 83: 1930-5.
18. Vitte C, Fleisch H, Guenther HL. Bisphosphonates induce osteoblasts to secrete an inhibitor of osteoclast mediated resorption. Endocrinol 1996; 137: 2324-33.
19. Colucci S, Minielli V, Zambonin G, Cirulli N, Mori G, Serra M, *et al*. Aledronate reduces adhesion of human osteoclast-like cells to bone and bone protein-coated surfaces. Calcif Tiss Int 1998; 63: 230-5.
20. Zuffetti F, Bianchi F, Volpi R, Trisi P, Fabbro MD, Capelli M, *et al*. Clinical application of bisphosphonates in implant dentistry: histomorphometric evaluation. Int J Periodontics Restorative Dent 2009; 29: 31–9.
21. Kimmel DB. Mechanism of action, pharmacokinetics and pharmacodynamic profile, and clinical applications of nitrogen-containing bisphosphonates. J Dent Res 2007; 86: 1022-33.
22. Chapurlat RD, Delmas PD. Drug insight: bisphosphonates for postmenopausal osteoporosis. Nat Clin Pract Endocrinol Metab 2006; 2: 211-9.
23. Conte P, Guarneri V. Safety of intravenous and oal bisphosphonates and compliance with dosing regimens. Oncologist 2004; 9 (Suppl 4): 28-37.
24. Rogers MJ. From molds and macrophages to mevalonate: a decade of progress in understanding the molecular mode of action of bisphosphonates. Calcif Tissue Int 2004; 75: 451-61.
25. Kasting GB, Francis MD. Retention of etidronate in human, dog, and rat. J Bone Miner Res 1992; 7: 513-22.
26. Mariotti A. Bisphosphonates and osteonecrosis of the jaws. J Dent Edu 2008; 72: 919-29.
27. Russell RG, Rogers M, Frith JC, Luckman SP, Coxon FP, Benford HL.The pharmacology of bisphosphonates and new insights into their mechanisms of action. J Bone Miner Res 1999; 14(suppl 2): 53–65.
28. Understanding Bisphosphonate Therapy ©2006, International Myeloma Foundation, North Hollywood, California (Available Online at www.myeloma.org. Accessed on 04-07-2011).
29. Diel IJ, Bergner R, Grötz KA. Adverse Effects of Bisphosphonates: Current Issues. J Support Oncol 2007; 5: 475-82.
30. Plosker GL, Goa KL. Clodronate: a review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. Drugs 1994; 47: 945–82.
31. Adami S, Zamberlan N. Adverse effects of bisphosphonates: a comparative review. Drug Saf 1996; 14: 158–70.
32. Markowitz GS, Appel GB, Fine PL, Fenves AZ, Loon NR, Jagannath S, *et al*. Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. J Am Soc Nephrol 2001; 12: 1164–72.

33. Markowitz GS, Fine PL, Stack JI, Kunis CL, Radhakrishnan J, Palecki W, *et al*. Toxic acute tubular necrosis following treatment with zoledronate (Zometa). Kidney Int 2003; 64: 281-9.
34. Chang JT, Green L, Beitz J. Renal failure with the use of zoledronic acid. N Engl J Med 2003; 349: 1676-8.
35. Hortobagyi GN, Theriault RL, Lipton A. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. J Clin Oncol 1998; 16: 2038–44.
36. Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, *et al*. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind comparative trial. Cancer J 2001; 7: 377–87
37. Pecherstorfer M, Jilch R, Sauty A, Horn E, Keck AV, Roth LZ, *et al*. Effect of first treatment with aminobisphosphonates pamidronate and ibandronate on circulating lymphocyte subpopulations. J Bone Miner Res 2000; 15: 147–54.
38. Carmagnola D, Celestino S, Abati S. Dental and periodontal history of oncologic patients on parenteral bisphosphonates with or without osteonecrosis of the jaws: a pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008; 106: e10–5.
39. De Groen PC, Lubbe DF, Hirsch LJ, Daifotis A, Stephenson W, Freedholm D. Esophagitis associated with the use of alendronate. N Engl J Med 1996; 335: 1016–21.
40. Watts N, Freedholm D, Daifotis A. The clinical tolerability profile of alendronate. Int J Clin Pract Suppl 1999; 101: 51–61.
41. Marshall JK. The gastrointestinal tolerability and safety of oral bisphosphonates. Expert Opin Drug Saf 2002; 1: 71–8.
42. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic J Oral Maxillofac Surg 2003; 61: 1115-7.
43. Milgliorati CA. Bisphosphonates and oral cavity avasular bone necrosis. J Clin Oncol 2003; 21: 4253-4.
44. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 2004; 62: 527-34.
45. Dearden W. The causation of phosphorus necrosis. Br Med J 1901; 17: 408-10.
46. Borromeo GL, Tsao CE, Darby IB, Ebeling PR. A review of the clinical implications of bisphosphonates in dentistry. Aust Dent J 2011; 56: 2-9.
47. American association of oral and maxillofacial surgeons' position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2007; 65: 369-76. (www.aaoms.org)
48. Migliorati CA, Casigila J, Epstein J, Jacobsen PL, Siegel MA, Woo SK. Managing the care of patients with bisphosphonate-associated osteonecrosis. J Am Dent Assoc 2005; 136: 1658-68.
49. Migliorati CA, Mattos K, Palazzolo MJ. How patients' lack of knowledge about oral bisphosphonates can interfere with medical and dental care. J Am Dent Assoc 2010; 141: 562-6.
50. Woo S-B, Hellstein JW, Kamar JR. Systemic review: bisphosphonates and osteonecrosis of the jaws. Ann Inetrn Med 2006; 144: 702-4.
51. Khosla S, Burr D, Cauley J, Depster DW, Ebeling PR, Felsenberg D *et al*. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2007; 22: 1479-91.
52. Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. J Clin Oncol 2003; 21: 4277–84.
53. Groetz KA, Al-Nawas B. Persisting alveolar sockets-a radiologic symptom of BP-ONJ? J Oral Maxillofac Surg 2006; 64: 1571-2.
54. Wood J, Bonjean K, Ruetz S, Bellahcène A, Devy L, Foidart JM, *et al*. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. J Pharmacol Exp Ther 2002; 302: 1055–61.
55. Groetz KA, Al-Nawas B. Persisting alveolar sockets—a radiologic symptom of BP-ONJ? J Oral Maxillofac Surg 2006; 64: 1571–7.
56. Meraw SJ, Reeve CM. Quantitative analysis of peripheral implant bone and influence of alendronate sodium on early bone regeneration J Periodontol 1999; 70: 1228-33.
57. Meraw SJ, Reeve CM, Wollan PC. Use of alendronate in perimplant defect regeneration. J periodontol 1999; 70: 151-8.
58. Yoshinari M, Oda Y, Inoue T, Matsuzaka K, Shimono M. Bone response to calcium phosphate-coated and bisphosphonate immobilised titanium implants. Biomaterials 2002; 23: 2879-85.
59. Jeffcoat MK. Safety of oral bisphosphonates: controlled studies on alveolar bone. Int J Oral Maxillofac Implants 2006; 21: 349–53.
60. Bell BM, Bell RE. Oral bisphosphonates and dental implants:a retrospective study. J Oral Maxillofac Surg 2008; 66: 1022–4.
61. Cheng A, Daly CG, Logan RM, Stein B, Goss AN. Alveolar bone and the bisphosphonates. Aust Dent J 2009; 54: S51-61.
62. Starck WJ, Epker BN. Failure of osseointegrated dental implants after diphosphonate therapy for osteoporosis: A case report. Int J Oral Maxillofac Implants 1985; 10: 74–8.
63. Badran Z, Kraehenmann MA, Guicheux J, Soueidan A. Bisphosphonates in periodontal treatment: a review. Oral Health Prev Dent 2009; 7: 3–12.
64. El-Shinnawi UM, El-Tantawy SI. The effect of alendronate sodium on alveolar bone loss in periodontitis (clinical trial). J Int Acad Periodontol 2003; 5: 5–10.
65. Jeffcoat MK, Cizza G, Shih WJ, Genco R, Lombardi A. Efficacy of bisphosphonates for the control of alveolar bone loss in periodontitis. J Int Acad Periodontol 2007; 9: 70–6.
66. Rocha M, Nava LE, Vazquez de la Torre C, Sanchez-Marin F, Garay-Sevilla ME, Malacara JM. Clinical and radiological improvement of periodontal disease in patients with type 2 diabetes mellitus treated with alendronate: a randomized, placebocontrolled trial. J Periodontol 2001; 72: 204–9.
67. Rocha ML, Malacara JM, Sanchez-Marin FJ, Vazquez de la Torre CJ, Fajardo ME. Effect of alendronate on periodontal disease in postmenopausal women: a randomized placebo controlled trial. J Periodontol 2004; 75: 1579–85.
68. Kaynak D, Meffert R, Bostanci H, Gunhan O, Ozkaya G. A histopathological Investigation on the effect of systemic administration of bisphosphonates alendronate on resorptive phase following mucoperiosteal flap surgery in rat mandible, J Periodontol 2003;74:1348-54.
69. Lane N, Armitage GC, Loomer P, Hsieh S, Majumdar S, Wang H-Y, *et al*. Bisphosphonate therapy improves the outcome of conventional periodontal treatment: results of a 12-month, randomised, placebo-controlled study. J Periodontol 2005; 76: 1113-22.
70. Sikder MNH, Itoh M, Iwatsuki N, Shinoda H. Inhibitory effect of a novel bisphosphonate, TRK-530, on dental calculus formation in rats. J Periodontol 2004; 75: 537-45.

71. Houshmand B, Rahimi H, Ghanavati F, Alisadr A, Eslami B. Boosting effects of bisphosphonates on osteoconductive materials: a histologic *in vivo* evaluation. J Periodont Res 2007; 42: 119-23.

72. Fleisch H. Bisphosphonates: Pharmacology and use in the treatment of tumor-induced hypercalcaemic and metastatic bone disease. Drugs 1991; 42: 919-44.

73. Nakaya H, Osawa G, Iwasaki N, Cochran DL, Kamoi K, Oates TW. Effects of bisphosphonate on matrix metalloproteinase enzymes in human periodontal ligament cells. J Periodontol 2000; 71: 1158-66.

74. Informational Paper. Modulation of the Host Response in Periodontal Therapy J Periodontol 2002; 73: 460-70.

75. Igarashi K, Adachi H, Mitani H, Shinoda H. Inhibitory effect of the topical administration of a bisphosphonate (risedronate) on root resorption incident to orthodontic tooth movement in rats. J Dent Res 1996; 75: 1644-9.

76. Yaffe A, Golomb G, Breuer E, Binderman I. The effect of topical delivery of novel bisacylphosphonates in reducing alveolar bone loss in the rat model. J Periodontol 2000; 71: 1607-12.

77. Denssen H, Montanari C, Martinetti R, van Lingen A, van den Hooff A. Alveolar bone response to submerged bisphosphonate-complexed hydroxyapatite implants. J Periodontol 2000; 71: 279-86.

78. Brown JJ, Ramalingam L, Zacharin MR. Bisphosphonate-associated osteonecrosis of the jaw: does it occur in children? Clin Endocrinol (Oxf) 2008; 68: 863–67.

79. Malmgren B, Astrom E, Soderhall S. No osteonecrosis in jaws of young patients with osteogenesis imperfecta treated with bisphosphonates. J Oral Pathol Med 2008; 37: 196–200.

80. Schwartz S, Joseph C, Iera D, Vu D-D. Bisphosphonates, osteonecrosis, osteogenesis imperfecta and dental extractions: a case series. J Can Dent Assoc 2008; 74: 537–42.

81. Rinchuse DJ, Rinchuse DJ, Sosovicka MF, Robison JM, Pendleton R. Orthodontic treatment of patients using bisphosphonates: a report of 2 cases. Am J Orthod Dentofacial Orthop 2007; 131: 321–6.

82. Adachi H, Igarashi K, Mitani H, Shinoda H. Effects of topical administration of a bisphosphonate (risedronate) on orthodontic tooth movements in rats. J Dent Res 1994; 73: 1478–86.

83. Liu L, Igarashi K, Haruyama N, Saeki S, Shinoda H, Mitani H. Effects of local administration of clodronate on orthodontic tooth movement and root resorption in rats. Eur J Orthod 2004; 26: 469–73.

84. Sarathy AP, Bourgeois SL Jr, Goodell GG. Bisphosphonate associated osteonecrosis of the jaws and endodontic treatment: two case reports. J Endod 2005; 31: 759–63.

85. Levin L, Laviv A, Schwartz-Arad D. Denture-related osteonecrosis of the maxilla associated with oral bisphosphonate treatment. J Am Dent Assoc 2007; 138: 1218-20.

86. Soileau KM. Oral post-surgical complications following the administration of bisphosphonates given for steopenia related to malignancy. J Periodontol 2006; 77: 738-43.

87. Lam DK, Sandor GKB, Holmes HI, Evans AW, Clokie CML. A review of bisphonate-associated osteonecrosis of the jaws and its management. J Can Dent Assoc 2007; 73: 417-22. (Avaliable online at www.cda-adc.ca/jcda. Accessed on July 5, 2011).

88. Bisphosphonate associated necrosis of the jaw. Endodontics Collegues for excellence. Winter 2007. (Available online at www.aae.org Accessed on July 5, 2011).

89. Li, Dai, Head, McKee, Tran. Point of Care. What is the recommended dental management for patients who are receiving intravenous bisphosphonate therapy? J Can Dent Assoc 2008; 74: 618-620. (Avaliable online at www.cda-adc.ca/jcda. Accessed on July 5, 2011).

90. American dental association council on scientific affairs. Dental management of patients receiving oral bisphosphonate therapy: exert panel recommendations. J Am Dent Assoc 2006; 137: 1144-50.

91. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Mehrotra B. American Association of Oral and Maxillofacial Surgeons Position Paper: Bisphosphonate-Related Osteonecrosis of the Jaws—2009 Update. J Oral Maxillofac Surg 2009; 67 (Suppl 1): 2-12.