POTENTIAL APPLICATIONS OF BISPHOSPHONATES IN PERIODONTAL DISEASES

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***Abstract*: Periodontitis is a plaque induced host inflammatory response characterized by tissue destruction and alveolar bone loss.The extent of the alveolar bone loss depends on the host response stimulated by bacterial infection. Alveolar bone loss is a hallmark of periodontitis progression and its prevention is a key clinical challenge in periodontal disease treatment. Bone destruction is mediated by the host immune and inflammatory response to the microbial challenge. Bisphosphonates are widely utilized in the management of systemic metabolic bone disease due to their ability to inhibit bone resorption.Their affinity to bone and their ability to increase osteoblastic differentiation and inhibit osteoclast activity, leads to the possible use of bisphosphonates in the management and regulation of periodontal diseases. The aim of this review is to assess the potential applications of Bisphosphonates in the management of periodontal disease.**

***Keywords*: Bisphosphonates, Periodontal diseases, Alveolar bone loss, Osteoclastic activity, Antiresorptive therapy**

INTRODUCTION:

Periodontal disease is induced by bacterial plaque that stimulates a host response in the adjacent gingiva that leads to the destruction of connective tissue and bone.The progression of periodontal disease may be affected by systemic conditions significantly increases the risk for periodontal disease with bone loss as a major criterion. It is generally understood that successful management of periodontal disease and its sequelae should be focused on elimination of etiologic factors that play an important role in the initiation and progression of this group of diseases. Thus, a major focus of periodontal research has been directed towards the reduction and elimination of pathogenic bacteria that are thought to cause periodontitis (1).

Osteoporosis is the most common disease of bone metabolism encountered in implant patients, and almost one-third of patients over age 60 are affected. Dental professionals involved in implant therapy will increasingly manage patients who are currently or potentially at risk for osteoporosis. These patients would roughly be anyone who has experienced a drop in bone marrow density of 10% greater than what is normal (2).

Osteoporosis is defined as a bone mineral density level more than 2.5 standard deviations below the mean of normal, young women (3,4). Currently, there are four approved treatments for postmenopausal osteoporosis: (1) estrogen replacement therapy, (2) selective estrogen receptor modulators, (3) calcitonin, and (4) bisphosphonates. Medical treatment with bisphosphonate drugs which are potent antiresorptive agents, also has become standard practice in benign and malignant diseases involving bone resorption.

The discovery and development of the bisphosphonates as a major class of drugs for the treatment of bone diseases represents a fascinating story that has its origins in studies of biological calcification processes.(5,6,7). There are many books and review articles available that describe the chemistry, pharmacology, and clinical applications of bisphosphonates. Bisphosphonates (BP) inhibit osteoclast action and thereby bone resorption. It can be administered via oral or intravenous routes.(8,9) Oral bisphosphonates are commonly used in the treatment of osteoporosis, Paget's disease, and osteogenesis imperfecta . On the other hand, intravenous bisphosphonates are used primarily for the treatment of osteolytic tumors, hypercalcemia of malignancy, multiple myeloma, bone metastases from solid tumors, and for treatment of other tumors(10).

PHARMOCOLOGY OF BISPHONATES:

Bisphosphonates are traditionally divided into nitrogen-containing (N-) and non-nitrogen-containing (non-N-) categories. Nitrogen-containing bisphosphonates, such as Zolendronate, are potent inhibitors of osteoclastic bone resorption through inhibition of synthesis of farnesyl pyrophosphate, a key enzyme in the mevalonate pathway(11,12). Bisphosphonates are structurally similar to pyrophosphate, a normal product of human metabolism present in serum and urine that has calcium-chelating properties. Pyrophosphate modulates mineralization by binding to crystals of hydroxyapatite in vitro and in vivo, but is not a very stable molecule in vivo and undergoes rapid hydrolysis of its labile P-O-P bond as a result of pyrophosphatase and even alkaline phosphatase activity.If a carbon atom replaces the linking oxygen atom in the pyrophosphate molecule, a bisphosphonate is formed.The analogues are completely resistant to enzymatic (alkaline phosphatase, pyrophosphatase) hydrolysis and are extremely stable from a chemical perspective. Like pyrophosphate, bisphosphonates bind to the hydroxyapatite crystals of bone and prevent both their growth and dissolution (13,14,15).

MECHANISM OF ACTION-BISPHOSPHONATES:

As we all know that bisphosphonates have been used as antiresorptive agent, it's mechanism plays a major role in illustrating the action. Several modes of action have been investigated including bisphosphonate mediated inhibition of the development of osteoclasts, induction of osteoclastic apoptosis, reduction of osteoclastic activity, prevention of the development of osteoclasts from hematopoietic precursors and stimulation of production of an osteoclast inhibitory factor(16). It has also been shown that the bisphosphonate alendronate caused a rise in intracellular calcium levels in an osteoclast like cell line. This finding is of great interest since it could suggest the presence of a receptor for bisphosphonates on osteoclasts(14).

It is evident that bisphosphonates may affect bone remodeling through direct action on osteoclasts(17,18). A more indirect mode of action suggests that osteoclast function can be altered by the production of an osteoclast inhibitory factor secreted by osteoblasts following expo- sure to bisphosphonates(19).In addition to their obvious effects on bone-resorbing cells, studies carried out in our laboratory clearly demonstrate that the bisphosphonate 1-hydroxyethylidene-1, 1-bisphosphonate (HEBP) has osteostimulative properties both in vitro and in vivo as demonstrated by HEBP-mediated increases in matrix formation and, on cessation of HEBP treatment, increased mineralized bone formation(20). Notably, bisphosphonates bound to bone mineral are released during bone resorption by osteoclasts. This could lead to a localized accumulation of bisphosphonate, which could directly perturb osteoclastic activity or indirectly target osteoblasts and macrophages, resulting in decreased osteoclastic chemotaxis and activity(21).

In contrast to their ability to induce apoptosis in osteoclasts, which contributes to the inhibition of resorptive activity, many studies suggest that bisphosphonates may protect osteocytes and osteoblasts from apoptosis induced by glucocorticoids. Recent evidence suggests that the inhibition of osteocyte apoptosis by bisphosphonates is mediated through the opening of connexion of hemichannels and activation of extracellular signal-regulated kinases(22)The possibility that bisphosphonates used clinically may get access to osteocytes differentially depending on their mineral-binding affinities and inherent structural properties needs to be studied for further discovery of possibilities(23).

MANAGEMENT OF PERIODONTAL BONE LOSS:

It is evident that bisphosphonates are used in the management of many bone lesions and disorders. But it also plays a major role in the management of periodontal associated diseases. It was demonstrated that the bisphosphonate alendronate, when administered intra- venously biweekly at a concentration of 0.05 mg/kg, could retard bone loss around affected teeth in comparison to controls(13).Interestingly, although bone loss was reduced with alendronate, periodontal pocketing was not. This suggests that although bone loss might be retarded, from a clinical perspective, the effects of bisphosphonate treatment might be difficult to detect or appreciate(9)In fact, another possibility, especially in the case of the nitrogen-containing bisphosphonates such as alendronate, suggests that this class of bisphosphonate might upregulate inflammatory processes in vivo through stimulation of IL-1 and IL-6(24). This could suggest that in the periodontal pocket, higher doses of alendronate may augment the inflammatory host response. Studies focusing on local applications might be more successful in controlling the actual drug concentration and, hence, regulating or inhibiting alveolar bone resorption(25).

Further studies also demonstrated that radiolabeled bisphosphonates can be used as a diagnostic tool to detect changes in the metabolic activity at skeletal sites, bone loss associated with periodontal disease, and cessation of bone loss following treatment with the anti-inflammatory agents like flurbiprofen(26). These findings suggested it is conceivable that early intervention or more aggressive therapy can be initiated if and when radiolabeled bisphosphonate uptake demonstrated with nuclear scanning indicates that bone loss is occurring(11,16).

BISPHOSPHONATES THERAPY AND DENTAL IMPLANTS

Osseointegration, which is measured by the percentage of contact between the surface of the implant and the bone, can be affected not only by the characteristics of the implant and surgical procedure but also by patient-dependent variables that can affect the quantity and quality of bone(27). To achieve the osseointegration of implants is necessary to secure their adequate primary stability. Thus, osteoporosis, characterized by bone loss, alteration of the microstructure and the reduction in the regenerative capacity of bone, has been considered a possible contraindication for dental implant placement(6,7).

In the treatment of osteoporosis, the oral bisphosphonates or intravenous pharmacological agents are the choice, because as result to their mechanism of action, they are effective in increasing bone mineral density. In the last 5 years a new complication has been described associated with treatment with bisphonates which is osteonecrosis of the jaw (ONJ), which consists of the appearance of foci of bone necrosis with exposure of maxillary or jaw bone and which has a slow healing process(19). The fact that osteonecrosis associated with the treatment takes place in the oral cavity and especially in the jaw could be explained by the constant microtrauma caused by the forces of chewing, which make the bone be constantly remodeling and bisphosphonates reach there concentrations higher than in other parts of the body. The necessity of repairing and remodeling of bone increases when conducting any dentoalveolar intervention(28).

Due to the antiangiogenic effect of bisphosphonates and the constant presence of microorganisms in the mouth that cause cavities and periodontal disease, the risk of infection of the affected area increases considerably.Then, pain appears and dehiscence of the alveolar mucosa progresses in addition to bone exposure. Implant placement and osseointegration during the last three years of treatment with oral bisphosphonates, without the presence of other diseases or medications shows lower success rate when compared to patients without bisphosphonates therapy(4,5).

DISCUSSION:

Clinical trials in humans using clinical and radiographic outcome variables demonstrated a statistically significant decrease in the proportion of teeth with alveolar bone loss at 9 months after use of alendronate (Rocha et al. 2001; Reddy et al. 2003)(29). A long-term (2 years)clinical trial using 70 mg alendronate once weekly in patients with moderate or severe periodontal disease was recently published (Jeffcoat 2006)(30).This double-blind placebo controlled study on 335 patients studied the effect of this medication on alveolar bone loss, and a significant gain in alveolar bone height was demonstrated in the alendronate group in comparison with the placebo group in patients with a low bone mass density at baseline(1,7).No side effect was reported during the 2-year study period.

Clodronate, alendronate, ibandronate, pamidronate and zoledronic acid have been tested in experimental studies using histological that is bone contact to implant and bone mineral density and mechanical outcomes that is bone implant shear strength(15,16).The results confirmed the capacity of the BPs in increasing significantly the bone density and the pull-out forces necessary to remove the implant. These experimental studies, however, confirm that the effectiveness of BPs in increasing bone mass around implants can only be attained at high doses (Astrand & Aspenberg 2002a, 2002b; Eberhardt et al. 2005, 2006)(31),even at doses up to 50 times the dosage used in the treatment of osteoporosis (Skoglund et al. 2004; Chacon et al. 2006)(19).In order to avoid the systemic administration of BPs and the use of such high doses, topical application of BPs has also been investigated in experimental models (Peter et al. 2005, 2006)(8). Because BPs specifically bind to hydroxyapatite (HA), implants coated with HA or other calcium coatings have been used in this investiga- tions (Kajiwara et al. 2005; Peter et al. 2005)(3).Many experimental and clinical studies show that bisphosphonates conserve bone architecture and strength.

There have been isolated reports of adynamic bone associated with bisphosphonate usage, but long-term use of the bisphosphonates in the therapy of osteoporosis seems to be safe. Case reports of induction of osteopetrosis like lesions in children who were treated with excessive doses of pamidronate have been published. Bisphosphonates have revolutionized osteoporosis treatment and confer considerable anti-fracture benefits that outweigh the small risk of Osteonecrosis of jaw(25).

Whilst bisphosphosnates have potential positive applications, in periodontology in particular, this is balanced against the risk of substantial risk of Osteonecrosis of jaw, a potentially debilitating condition, predominantly in patients receiving intravenous bisphosphonates for cancer. Based on the present knowledge of bisphosphonates, the use of bisphosphonates in periodontal research shows a promising method of managing periodontal diseases by modifying the host response. Published studies tend to demonstrate that bisphosphonates prevent or at least reduce the alveolar bone loss in comparison with control subjects(21).

Even though human studies have shown a significant improvement of the periodontal treatment outcome using bisphosphonates, there is a lack of data determining the optimal prescription concentration and formulation(24). Besides that, by changing the prescribed family of bisphosphonate molecule, a variation in the effects of the periodontal healing can be observed. In particular, the new bisphosphonate, TRK-530, seems to be promising as it combines anti-inflammatory and bone resorption-inhibitory properties(11). The outcome of many cases suggest that, the patient taking bisphosphonates should be warned relating to possible future implant failure and osteonecrosis of the jaw. We all know that Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and have been widely used in the management of skeletal metastases and for the treatment of primary and secondary osteoporosis(15).

As bisphosphonates significantly reduce bone turnover, it is not surprising that a patient receiving BPs may have a problem with dental implant integration. Some studies have directly examined the outcomes of dental implants in individuals with and without

exposure to oral bisphosphonates. Although cases of spontaneous Osteonecrosis have been described, it is typically triggered by local trauma, almost always in the context of oral procedures, particularly dental extractions and the insertion of dental implants (Yarom et al. 2007)(5). Although a number of studies (Madrid & Sanz 2009; Javed & Almas 2010) have concluded that dental implant placement in patients receiving bisphosphonates through the oral route does not imply a risk of Osteonecrosis of jaw.

Wang et al. reported the case of osteonecrosis of the jaw (ONJ) associated with bisphosphonate therapy in cancer patients. These cancer patients were undergoing many treatments with chemotherapy drugs, corticosteroids, and then also bisphosphonates.The majority of reported cases of bisphosphonates associated with Osteonecrosis of jaw have been diagnosed a er invasive dental procedures such as tooth extraction(3,4).Less commonly Osteonecrosis of jaw appears to occur spontaneously in patients taking the bisphosphonates.

Further, Hoff et al. suggested that the fact should not be overlooked that bisphosphonates offer major therapeutic benefits to individuals with metastatic and metabolic bone disease. Bisphosphonate therapy should remain an important medical treatment yet there are a number of implications for dentistry. Dental therapy for the increasing numbers of aging women being prescribed bisphosphonates in treatment for post-menopausal osteoporosis should focus on prevention of ONJ by management of dental disease. It is clinically necessary to understand the effect on dental implant success of skeletal low bone mineral density and treatment for osteoporosis with oral bisphosphonates(1,7).

Most investigations conclude that no compelling theoretical or practical basis exists to expect osteoporosis to be a risk factor for osseointegrated dental implants. There are numerous examples of bisphosphonates having effects on cells and tissues outside the skeleton. The effects on osteoclast precursors, tumor cells, macrophages, and T cells are examples and in all cases are probably explained by sufficient bisphosphonates enter- ing cells to inhibit the mevalonate pathway(6). A well-recognized adverse effect of the nitrogen-containing bisphosphonates is that they cause an acute-phase response in vivo which can lead to induction of fever and “flu-like” symptoms in patients. These effects are transient and occur predominantly on first exposure to the drug, especially with intravenous administration. The mechanism has been attributed to release of pro inflammatory cytokines, and the mechanism has been further unraveled by showing that it involves selective receptor-mediated activation of T cells, leading to their proliferation and activation.The bisphosphonate effect involves the mevalonate pathway in vitro and can be overcome by using statins(23).

One of the other early clinical uses of bisphosphonates was as agents for bone imaging, “bone scanning,” for which they still remain outstandingly useful for detecting bone metastases and other bone lesions(29). The application of pyrophosphate and simple bisphosphonates as bone scanning agents depends on their strong affinity for bone mineral, particularly at sites of increased bone turnover, and their ability to be linked to a gamma emitting technetium isotope(15).

In terms of commercial success, the use of bisphosphonates in oncology has been preeminent. Many cancers in humans are associated with hypercalcemia (raised blood calcium) and increased bone destruction . Bisphosphonates are remarkably effective in the treatment of bone problems associated with malignancy and are now the drugs of choice(31).

CONCLUSION:

The recent elucidation of the likely mode of action of bisphosphonates within cells opens up the possibility of exploiting the subtle and potentially important differences between the classes of bisphosphonates and individual compounds. Patients with osteoporosis have no contraindications to dental implant placement. The steps to take before starting a surgical implant will be no different from people without osteoporosis. Nevertheless, proper oral hygiene prior to intervention will be highly advised. Although the risk of ONJ in subjects treated with BP is very low, patients should be informed and must sign consent with the inclusion of this specific point.

Bisphosphonates represent a class of pharmacological agents that have potentially important applications in periodontics and the treatment of metabolic bone diseases. It is also conceivable that in the future, not only will such drugs be used to prevent bone loss observed in periodontal diseases and even around implants, but also to possibly stimulate new bone formation. Thus, bisphosphonates could be used in conjunction with regenerative therapies, and even for stimulation of bone growth into and around endosseous implants . Whether early or later biomechanical advantages or disadvantages exist vis-a-vis implant retention remains to be seen. For example, the early osteoid phase of healing would likely reduce initial implant stability, while over the longer term, increased bone ingrowth could lead to greater implant stability and retention success. In any case, it would appear that bisphosphonate use in periodontics, both from a diagnostic and therapeutic perspective, provides a potentially exciting avenue for future exploration.

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