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# BISPHOSPHONATES AND PERIODONTICS

**Dr. Vidya Priyadarshini*[1], Dr. Snigdha Maity [2], Dr. Anupama Amruthesh [3]**

[1,2] Dept of Periodontology, JSS Academy of Higher Education & Research, JSS Dental College and Hospital, Bannimantap, Mysuru, Karnataka- 570015.

[3]. Dept of Periodontology, SJM Dental College and Hospital,PB road, Chickpet Chitradurga , Karnataka- 577501

**Corresponding author:**

Dr. Vidya Priyadarshini*

Dept of Periodontology JSS Academy of Higher Education & Research JSS Dental College and Hospital Bannimantap, Mysuru Karnataka- 570015

drvidyapd77@gmail.com

Phone number: 9739029250

Orcid: 0000-0002-5052-2996

**Abstract**

Bisphosphonates which inhibit bone resorption are the group of drugs widely used in the management of systemic metabolic bone disease such as bone metastases, osteoporosis, Paget's disease etc. Their ability to induce osteoblastic differentiation and inhibit recruitment of osteoclasts, bisphosphonates have provided a management strategy where it can be used alone or in conjunction with regenerative materials around bone defects both in periodontitis as well as around implants. The objective of this review article is to discuss about various groups of bisphosphonates, their actions and their potential use in the field of periodontics.

**Keywords:** Bisphosphonates, Drugs, Periodontitis

## Introduction

Periodontitis is a chronic inflammatory disease of supporting structures of teeth that results in progressive destruction of periodontal ligament and alveolar bone. The rationale of periodontal therapy aims in eliminating infection and regenerating, remodelling and restoring the lost attachment apparatus. This is accomplished by local and systemic therapy or both. Systemic therapy may be employed as an adjunct to local measures to prevent the post treatment bacteraemia [1].

In the late twentieth century, the concept of host modulation in dentistry was first introduced by William and Golub et al. to modulate the host response to the pathogens and other stimuli. Host modulation therapy potentially down regulates the destructive aspects and upregulates the protective aspects of host response by modulating osteoblast and osteoclast functions without affecting normal tissue turnover [2].

A variety of different drug classes have been evaluated as host modulation agents. Bisphosphonate is among one of them. Bisphosphonate was first synthesized as a substitute for pyrophosphate in 1950. Its ability to increase bone mass was discovered in 1966 [3]. In 1990, it was introduced in the treatment of osteoporosis and osteolytic tumors [4,5]. They act by inhibiting the osteoclastic activity that leads to decreased bone resorption, increased bone remodelling and less bone turnover [3]. Bisphosphonates have been evaluated for having high affinity for hydroxyapatite and anti-collagenase properties that is useful in the treatment of periodontitis [6].

The overall goals of this review are to discuss the pharmacology and mechanism of action of Bisphosphonates and their potential use in periodontics.

## Bisphosphonates (BPs) and its structure :

Bisphosphonates are synthetic molecules with a structure similar to inorganic pyrophosphates (P-O-P bond) [7] (Fig 1).

Pyrophosphates are endogenous regulators of bone mineralisation, which can be found naturally in the blood serum, with capacity to chelate calcium and regulate the bone mineralisation process [8]. Bisphosphonates are resistant to enzymatic and chemical breakdown. They present an affinity to the mineral phase of the bone due to their chelating properties for calcium. Bisphosphonate consist of two phosphate groups covalently bonded to central carbon (P-C-P bond). The central carbon has two side chains. The short R1 and long R2 chains that influence the chemical properties and pharmacokinetics (Fig 2) [9].

The R2 side chain and 3 dimensional structure determines the cellular effects of Bisphosphonates and its efficiency as bone inhibitors. The R1 and R2 chains are substituted for hydrogen that changes the potency and side effect profile of the compound [10].

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BPs exists in three generations (Fig 3).

The first generation has alkyl side chains (etidronate), used to prevent resorption. The second generation includes amino-BPS with an amino-terminal side chain (alendronate) to prevent bone resorption by preventing mineralization to occur. The third generation BPs (zoledronate) has a cyclic side chain, has greater potency than first and second generation BPs.11(Table 1).

**Mechanism of action :**

Osteoclasts (bone-resorbing cells) are different from haematopoietic stem cells. They are multinucleated cells that attaches to the bone matrix. After adhering to the bone surface, osteoclast develop deep foldings of plasma membrane called as ruffled border, where protons (H+), Cathepsin K and Matrix metalloproteinases (MMPs) are released to resorb the mineral part, as well as the organic matrix of the bone (Fig 4) [12,13]. An overproduction of osteoclasts by the fusion of their precursors and/or their activation by pro-inflammatory cytokines (IL-1β, TNF-α and PGE2) is responsible for the bone loss occurring in periodontal diseases. Therefore, the use of a drug that inhibits the osteoclast function and/or formation seems promising in periodontal treatment. Several modes of action have been investigated that includes bisphosphonate-mediated inhibition of the development of osteoclasts, induction of osteoclastic apoptosis, reduction of activity, prevention of development of osteoclasts from haematopoietic precursors, and stimulation of production of an osteoclast inhibitory factor [10].

a. Effect on osteoclasts:

Upon administration of BPs, it binds to the bone mineral. When Osteoclasts initiates the resorptive process, BPS are released due to highly acidic local environment, which are taken up by osteoclasts. bisphosphonates then trigger the osteoclasts to undergo apoptosis [14]. It has also been shown that the nitrogen containing BPS (nBPs) results in a rise in intracellular calcium levels in an osteoclast-like cell line. This finding suggested, the presence of a receptor for BPs on osteoclasts. Inside the osteoclasts, nBPs inhibit farnesyl disphosphonate (FPP) synthetase enzyme of the mevalonate pathway. FPP synthetase is responsible for isoprenylation which promote an array of activities in the osteoclasts that control bone resorption [7].This exert an intense pharmacodynamic effects long after the blood levels of nBPS reach zero. Approximately half of any nBP doses reaches the skeleton with an early halflife of 10 days and a terminal half-life of about 10 years.(Fig 5)

**a.** Effect on osteoblasts:

Apart from direct action of BPs on osteoclasts, there is an indirect mechanism of alteration of osteoclast by inducing the production of an osteoclast-inhibitory factor, secreted by osteoblast upon exposure of BPs [15]. Bisphosphonates inhibit osteocyte and osteoblast apoptosis, by interfering with the phosphorylated fraction of extracellular-signal-regulated kinases [16] A report has demonstrated that, BPs stimulate the formation of osteoblast precursors and mineralized nodules, thus helping in promoting early osteoblastogenesis [17]. Along with the previous finding, BPs have shown to decrease the expression of the receptor activator of NF-kB ligand (RANKL) and increase the expression of the RANKL decoy receptor, osteoprotegerin (OPG) in human osteoblastic cells [18].

**b.** Other actions:

- Distinct effect of alendronate on the transendothelial migration of human peripheral blood mononuclear cells have been studied in vitro.Bisphosphonates not only affect bone metabolism but also the inflammatory responses since both osteoclasts and macrophages belong to the mononuclear phagocytic system [19].
- Since bone damage is caused by increased activity of osteoclasts, bisphosphonates with its anti-angiogenic effect, reduce new bone damage and gives an opportunity for occurrence of bone healing. Thus, preventing further bone damage, reducing bone pain and the need for analgesics [20].
- Alendronate is capable of inhibiting matrix metalloproteinases (MMPs)[21] , and inhibition of prostaglandin synthesis [22] that causes degradation of supporting structures in periodontitis through a mechanism that involves chelation of cations.
- BPs has strong affinity for calcium phosphate in bone and helps in management of calcium disorders. This helps in inhibition of hydroxyapatite aggregation, dissolution and crystal formation. Hence Bisphosphonates are used in preventing hypercalcemia, reducing pathologic fractures due to myeloma and improving quality of life [20].

  At the cellular level, bisphosphonates have been shown to increase biosynthesis of collagen by inhibiting collagenase enzyme, necessary to prevent periodontitis [6].

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**Bisphosphonates in periodontal therapy**

a. Animal Studies

The major focus of BPs in periodontal therapy is to determine its effect on bone resorption by studying the clinical parameters in experimental animal models. After the induction of periodontitis, BPS were administrated locally and systemically as adjuvants to the conventional periodontal therapy and compared with the control group where administration of BPs were excluded [23-32].

Various animal studies have been done which suggested that low dose of Bisphosphonate administered for short period are better compared to high doses for longer period.25 This may be because the nitrogen containing BPs such as alendronate in high doses might upregulate inflammatory process in in-vivo through stimulation of IL-1 and IL-6 and hence prevent the periodontal wound healing process. It has also been suggested that alendronate could reduce the collagen production and thus, by this process, block the reconstitution of the extracellular matrix of injured periodontal tissues [31].

Studies have shown an obvious benefit of BPs as adjuvants to the mechanical and surgical periodontal treatment as well as on experimental periodontitis that resulted in reduced alveolar bone resorption. Bisphosphonates are equally effective when delivered locally during implant placement [23-32] (Table 2).

b. Human studies

With regard to human trials, all the existing literature demonstrate benefit of the locally and systemic administration of BPs in adjunct to non-surgical periodontal therapy compared with mechanical debridement alone.

This benefit is mainly in reducing the alveolar bone loss and the preservation of the alveolar bone height along with improvement in clinical parameters [33-36]. On the other hand, some clinical trials failed to show a significant improvement in terms of the clinical parameters, [37,39] whereas in other studies BPs supported the periodontal healing, thus reducing probing pocket depth and tooth mobility [29,40]. Bisphosphonates also play a significant role in the immunocompromised patients like type 2 diabetes mellitus where surgical periodontal therapies are contraindicated [36,40]. (Table 3)

In addition to the above mentioned beneficial effect of Bisphosphonates in preventing bone loss in chronic and aggressive periodontitis, many other studies have focused on the effectiveness of Bisphosphonates in relation to regional accelerated phenomenon (RAP) [41]. In terms of this, another study showed that the Bisphosphonate alendronate could inhibit bone resorption following mucoperiosteal flap elevation and showed positive result on RAP. The investigators noted that topical administration of Bisphosphonate was ineffective in inhibiting bone resorption while its intravenous administration was quite effective [42]. However, later on the same researchers demonstrated the topical administration of the drug can inhibit periodontal bone loss [32].

**Conclusion**

Our review concludes that bisphosphonates are potentially effective in improving clinical outcomes of periodontitis. Several studies have shown the potency of bisphosphonates in alveolar bone fill and gaining clinical attachment level. It is expected that in the future, they will help in stimulating the bone formation around the endosseous implants in cases of periimplantitis too.

This review has entirely focused on the beneficial effect of bisphosphonates. Since every drug has adverse effects on long-term systemic use, its potential risk/benefit ratio should be weighed.

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**Tables**

Table 1: Generations of bisphosphonates

| Drugs | Properties |
|---|---|
| 1st Generation<br>e.g.<br>Etidronate<br>Medronate<br>Clodronate | • Minimally modified side chains (R1 and R2) or contain a chlorophenyl group<br>• Can cause bone demineralisation<br>• Apoptosis account for antiresorptive effect<br>• Metabolised to form adenosine triphosphate (ATP) analog that |

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| | |
|---|---|
| Tiludronate | interferes with energy production and causes osteoclast apoptosis<br>• Least potent |
| 2nd Generation<br>e.g.<br>Alendronate<br>Pamidronate<br>Ibandronate | • Aminobisphosphonates, contain nitrogen group in the side chain<br>• Inactivation of ATP<br>• Causes osteoclast cytoskeletal disruption<br>• Impairment of osteoclast recruitment<br>• Induction of osteoblasts to produce osteoclast-inhibiting factor<br>• They are 10-100 times more potent than 1st generation |
| 3rd Generation<br>eg.<br>Risedronate,<br>Zoledronate | • Contain nitrogen atom within a heterocyclic ring<br>• These are up to 10,000 times more potent than 1st generation |

Table 2: Studies of bisphosphonates on animal models

| Authors | Study | BP used | Administration | Effect on bone resorption |
|---|---|---|---|---|
| Kwon et al (2017)[23] | Implant | Zoledronic acid | Local drug delivery through Ti implants | ↑Local bone formation<br>↑Implant stability<br>↑Osseointegration |
| Lee et al (2011) [24] | Implant | Ibandronate | Bp coated on implant surface | ↑Bone-formation marker expression<br>↑Formation of the adjacent bone<br>↑Osseointegration |
| Cetinkaya et al (2008) [25] | Experimental periodontitis | Risedronate | Orally in different dosage | ↑Bone formation<br>↓Resorption in low dosage<br>No inhibitory effect in high dosage<br>↑Impairment of bone formation and angiogenesis in high doses |
| Goya et al (2006) [26] | Experimental periodontitis | Olpadronate | Topical | ↓Alveolar bone resorption<br>↓Oscteoclast maturation and number |
| Buduneli et al (2005) [27] | Experimental periodontitis | Alendronate | IV injection | ↓ Alveolar bone loss<br>↑Serum osteocalcin |
| Yaffe et al (2003) [28] | In bone marrow | Alendronate | IV injection | ↑Inhibition of bone loss<br>↓es bone density |
| Kaynak et al (2003) [29] | Mucoperiosteal flap surgery | Alendronate | Subcutaneous injection | ↑Prevention of alveolar bone loss<br>↑Modulating tissue factors<br>Can be used alone or with regenerative components |

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| | | | | |
|---|---|---|---|---|
| Mitsuta et al (2002) [30] | Experimental periodontitis | Clodronate | Topical | ↓Osteoclastic bone resorption |
| Yamaguchi et al (2000) [31] | IL-1 deficient mice | Amino bisphosphonate | Intraperitoneal injection | ↑Immune inflammatory reaction<br>↓Collagen production |
| Yaffe et al (1997) [32] | Mucoperiosteal flap surgery | Amino bisphosphonate | Local delivery | ↓Alveolar bone résorption |

Table 3: Studies of bisphosphonates on humans

| Authors | Study | BP used | Administration | Effect on clinical parameters |
|---|---|---|---|---|
| Pradeep et al (2013)[33] | Adjunct to non-surgical periodontal therapy in class II furcation | Alendronate | Locally delivered | ↑Pocket depth reduction<br>↑Relative vertical clinical attachment level gain<br>↑Relative horizontal clinical attachment level gain<br>↑Bone fill |
| Sharma and Pradeep (2012) [34] | Adjunct to non-surgical periodontal therapy | Alendronate | Locally delivered | ↑Pocket depth reduction<br>↑Clinical attachment level gain<br>↑Bone fill |
| Sharma and Pradeep (2012) [35] | Adjunct to non-surgical periodontal therapy in aggressive periodontitis | Alendronate | Locally delivered | ↑Pocket depth reduction<br>↑Clinical attachment level gain<br>↑Bone fill |
| Pradeep et al (2012) [36] | Adjunct to non-surgical periodontal therapy for intrabony defect in type 2 diabetes mellitus patients | Alendronate | Locally delivered | ↑Pocket depth reduction<br>↑Clinical attachment level gain<br>↑Bone fill |
| Graziani et al (2009) [37] | Adjunct to non-surgical periodontal therapy | Neridronate | IM | Test and control site showed no significant changes in short term administration |
| Lane et al (2005) [38] | Adjunct to non-surgical periodontal therapy | Alendronate or Risedronate | orally | ↓Pocket depth<br>↓Bleeding on probing<br>↑Clinical attachment level |

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| | | | | |
|---|---|---|---|---|
| El-Shinnawi and El-Tantawy (2003) [39] | Adjunct to non-surgical periodontal therapy | Alendronate | orally | No effect on clinical parameters<br>↑Alveolar bone density |
| Rocha et al (2001) [40] | Adjunct to non-surgical periodontal therapy with type 2 diabetes mellitus patients | Alendronate | orally | ↑Alveolar bone crest height<br>Improvement in clinical parameters |

**Figure**

Figure 1: Chemical structure of Pyrophosphate

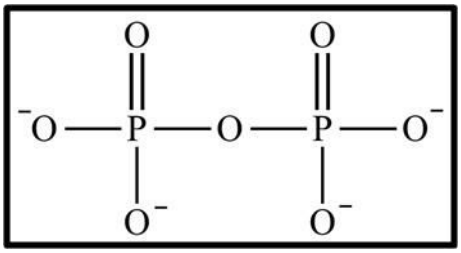

Figure 2: Chemical structure of Bisphosphonate

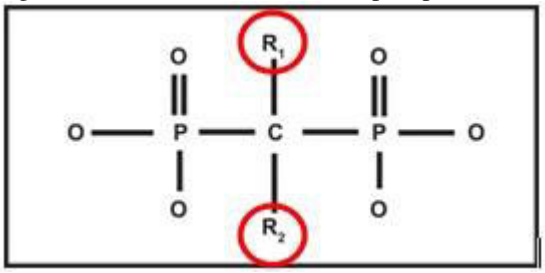

Figure 3: Different generation of BPs. The first generation of BPs has alkyl side chains (etidronate). The second generation included amino-BPs with an aminoterminal side chain (alendronate), and a cyclic side chain characterises the third-generation BPs (zoledronate)

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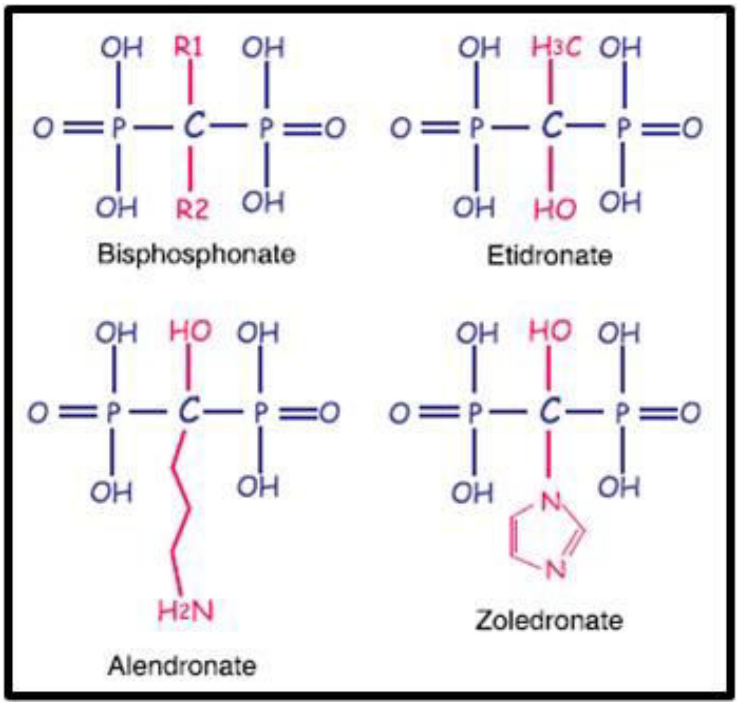


Figure 4: Mechanism of bone resorption

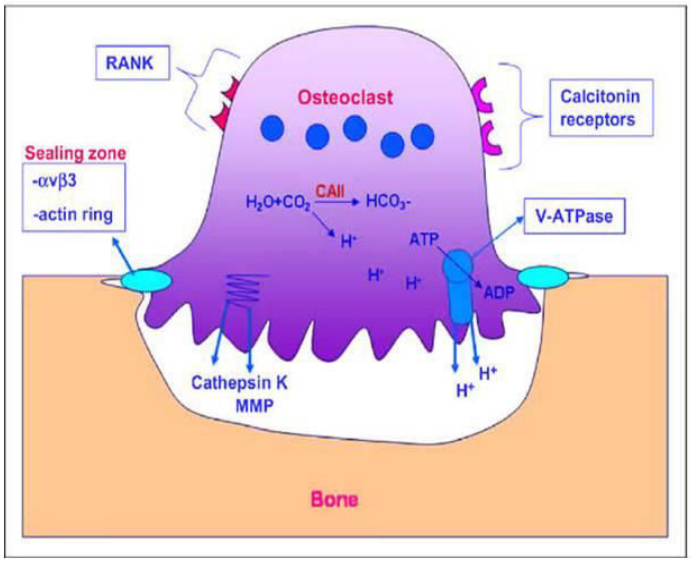


Figure 5: Schematic representation of mevalonate pathway

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