

Alendronate in Periodontics: An Evolving Trend**Harinder Gupta¹, Navita Budhiraja²**¹Professor and Head, Department of Periodontology, Punjab Government Dental College and Hospital; ²Post Graduate Student, Department Of Periodontology, Punjab Government Dental College and Hospital**Address for Correspondence:**

Dr. Navita Budhiraja, Post Graduate Student, Department Of Periodontology, Punjab Government Dental College and Hospital, Amritsar, Punjab, India.

ABSTRACT:

Periodontitis is an immunoinflammatory disease that causes destruction of tooth supporting tissues. It is characterized by multifactorial etiology involving bacterial biofilm and an inflammatory host response. The inflammatory host response is an important component in periodontal tissue destruction; thus novel therapeutic modalities should be considered that modulates host response. The proven efficacy of bisphosphonates to inhibit osteoclast bone resorption has led to their use as a host modulating agent in the perspective of preventing the alveolar bone loss. Bisphosphonates were also proposed to have osteostimulative properties *in vivo*; thus can be used with bone regenerative materials to potentiate bone regeneration This review describes the mechanism of action and potential use of novel aminobisphosphonate alendronate in periodontal therapy.

Keywords: Alendronate, Bisphosphonates, Bone regeneration, Bone resorption.**INTRODUCTION**

Periodontitis is an immuno inflammatory disease that causes destruction of tooth supporting tissues. Although periodontal diseases are initiated by bacteria that colonize the tooth surface and gingival sulcus, the host response is believed to play an essential role in the breakdown of connective tissue and bone.¹ The inflammatory host response is an important component in periodontal tissue destruction; thus novel therapeutic modalities should be considered that modulates host response. Various host modulating agents have been developed to block different pathways in periodontal disease that includes nonsteroidal anti-inflammatory drugs (inhibition of arachidonic acid metabolites; anti-inflammatory), bisphosphonates (inhibition of alveolar bone resorption), tetracyclines (inhibition of matrix metalloproteinases). Among these agents, bisphosphonates are chemical analogues of pyrophosphate in which the oxygen bridge has been replaced by a carbon with various side chains (P-C-P) (Figure 1). This P-C-P bond is stable, which resists hydrolysis by pyrophosphatase and alkaline phosphatase.² The proven efficacy of

bisphosphonates to inhibit osteoclast bone resorption has led to their use as a host modulating agent in the perspective of preventing the alveolar bone loss.

Alendronate (4-amino 1-hydroxybutylidene bisphosphonate), a second generation aminobisphosphonate is a very potent inhibitor of bone resorption. Alendronate is 200 to 1000 times more active in inhibiting bone resorption than etidronate. Pamidronate is about 10 times less potent than alendronate. Hence alendronate is used in lower concentrations (Figure 2).³ The inhibition of mineralization has not been correlated with the pharmacological dosage of bisphosphonates used in inhibition of bone resorption. Alendronate reduces bone remodeling leading to inhibition of bone resorption and bone formation. But the local bone balance at individual basic multicellular unit (BMU), might be positive; thus explaining the net effect of alendronate on bone formation. Alendronate has a prolonged half life (upto years) and its release occurs significantly in resorptive phase that might provide protection to alveolar bone.⁴

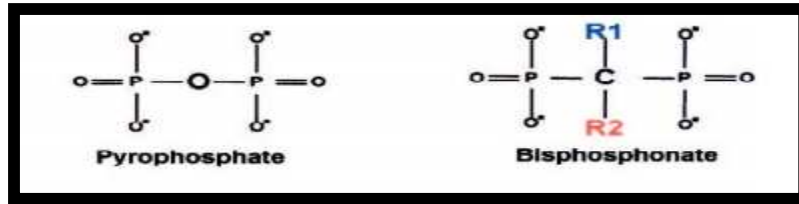


Figure 1: Chemical structure of pyrophosphate and bisphosphonates

	Bisphosphonate	R ₁	R ₂
First Generation	Etidronate: Clodronate:	OH Cl	CH ₃ Cl
Second Generation	Pamidronate: Alendronate:	OH OH	CH ₂ CH ₂ NH ₂ CH ₂ CH ₂ CH ₂ NH ₂
Third Generation	Tiludronate: Risedronate:	H OH	—S— CH ₂ —

Figure 2: Classification of bisphosphonates

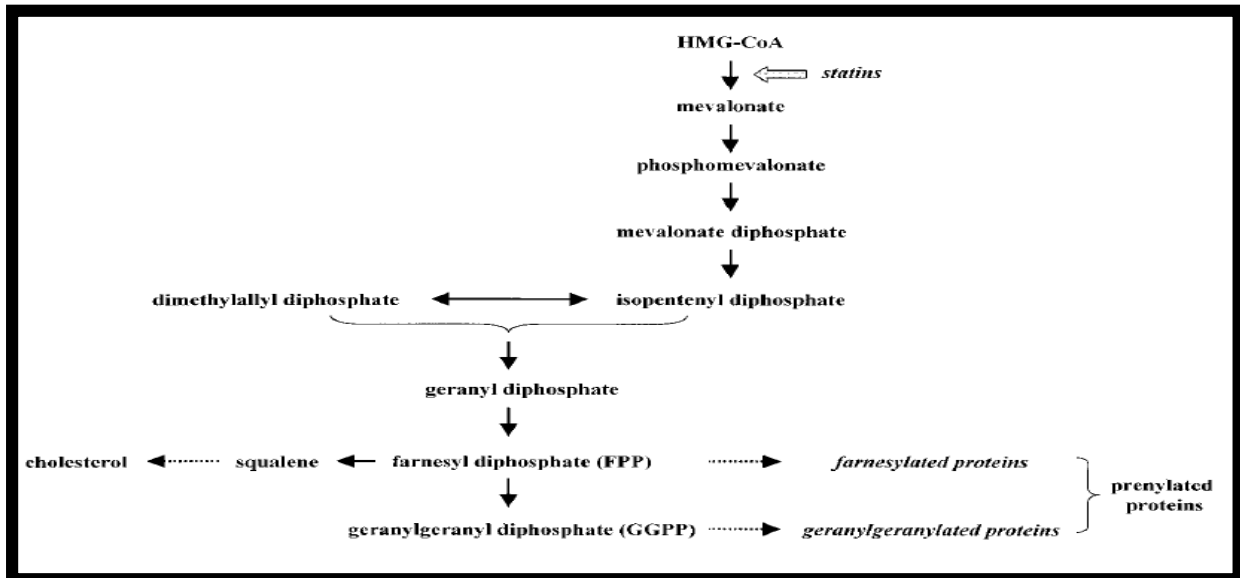


Figure 3: Schematic representation of the mevalonate pathway

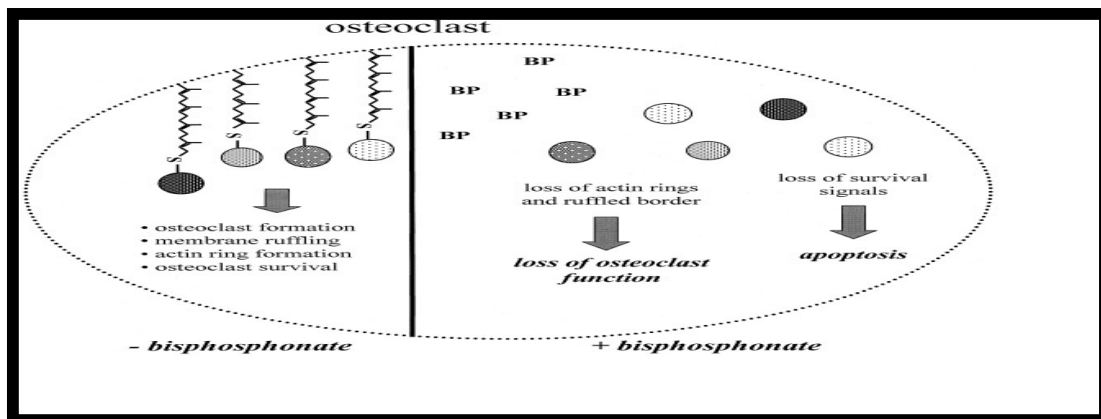


Figure 4: Cellular uptake of bisphosphonates by the osteoclast leads to inhibition of the mevalonate pathway and loss of prenylated proteins, causing loss of osteoclast function and cell death by apoptosis

MECHANISM OF ACTION

Bisphosphonates shows high avidity for Ca^{2+} ; forming the bone-targeting property of these compounds. After administration, bisphosphonates thus bind to the bone mineral. Bisphosphonates has decreased ability to chelate Ca^{2+} ions in the acidic environment of the osteoclast resorptive process (at low Ph).⁵ Bisphosphonates, after being released from bone surfaces, rise to high concentrations locally. After release, bisphosphonates are internalized by osteoclasts. Bisphosphonate affect both bone resorption and bone deposition by various mechanisms.

Bisphosphonate causes bone modulation at various levels. At molecular level there is inhibition of mevalonate pathway. This pathway of sterol synthesis is responsible for the production of isoprenoid lipids such as isopentyl diphosphate (IPP), farnesyl diphosphate (FPP) and geranylgeranyl diphosphate (GGPP). These lipids are required for post-translational lipid modification (prenylation) of small GTPases.⁶ These GTPases are important signaling proteins that regulate a variety of cell processes important for osteoclast function, including control of cell morphology, integrin signaling, trafficking of endosomes, membrane ruffling and apoptosis.⁷

Inhibition of this biosynthetic pathway by nitrogen containing bisphosphonates could lead to interference with generation of GGPP and further loss of prenylation of small GTPases.⁵ This results in disruption of actin cytoskeleton, loss of ruffled border formation, and decrease in acid extrusion (Figure 3,4). These molecular changes causes changes at cellular level. Four mechanisms appeared to be involved at cellular level 1) inhibition of osteoclast recruitment to bone surface; 2) decreased osteoclastic adhesion; 3) induction of osteoclast apoptosis; and 4) reduction of osteoclast activity.⁸

The cumulative effects of cellular changes leads to changes at tissue level. There is a reduction in bone turnover due to decrease in bone resorption. There is a decrease in number

of new bone (multicellular units). Thereby a positive bone balance is maintained in the body. There Is increase in bone mass since bone formation exceeds bone resorption.⁸

It has also been shown that alendronate caused a rise in intracellular calcium levels in an osteoclast-like cell line.⁹ This finding suggests that there might be a receptor present on osteoclasts for bisphosphonates. Additionally downregulation of bone resorption was also correlated with inhibition of matrix metalloproteinases (MMPs), the enzymes involved in extracellular matrix (ECM) degradation in periodontitis.¹⁰

One indirect mode of action suggests that osteoclasts function can be altered by the production of an osteoclast –inhibitory factor secreted by osteoblasts on exposure to bisphosphonates.¹¹ Bisphosphonates prevents osteocyte and osteoblast apoptosis by binding and inhibiting protein tyrosine phosphatase.¹² Reports have demonstrated that bisphosphonates stimulate the formation of osteoblast precursors and mineralized nodules, a phenomena accompanied by increased basic fibroblast growth factor. Alendronate could increase osteoblast and osteoblast progenitor numbers with enhanced expression of bone morphogenic protein-2, type I collagen, and osteocalcin.¹³ Other data shows that abrogation of interleukin-6 production by bisphosphonates in human osteoblastic cells can occur, which could also affect osteoclastic activity.¹⁴

ROLE OF ALENDRONATE IN THE MANAGEMENT OF PERIODNTAL DISEASE

Alendronate was the first drug approved by the FDA in USA , in 1995, to treat osteoporosis and is now used extensively to prevent bone loss, reduce the incidence of vertebral and non-vertebral fracture and to increase bone mineral density. In early 1990's, there was a beginning interest in application of alendronate as a host modulating agent for the treatment of periodontitis associated bone loss. Many animal studies have demonstrated the

efficacy of alendronate in inhibiting the progression of experimentally induced periodontitis. This improvement was also achieved in human clinical trials.

Animal Studies

The major research focus of bisphosphonates in periodontal therapy is determination of their effect on bone resorption along with the clinical parameters. This concept was studied in animal model of experimental periodontitis in monkeys where it was shown that alendronate, when administered intravenously biweekly at a concentration of 0.05 mg/kg, could retard alveolar bone loss in comparison to control group. Interestingly, there was no significant improvement in clinical parameters.¹⁵ Concomitant with this radiographic study, a histological study was performed that confirmed 0.05 mg/kg of alendronate could inhibit bone loss in ligature induced periodontitis.¹⁶ These investigations utilized experimentally induced periodontitis in monkeys, so bisphosphonates were tried in naturally occurring periodontitis. A weekly oral dose of 3 mg/kg of alendronate was administered in beagle dogs to study their efficacy in naturally occurring periodontitis.¹⁷ However, the results were not quite robust, demonstrating only trends in reduction of bone loss in alendronate treated beagle dogs. The reason for less robust response could be attributed to different dose of alendronate in latter study. In addition investigators magnified disease activity by use of ligatures; so possibly a more aggressive disease was present in monkey model.

Many studies have demonstrated the potential effects of bisphosphonates in relation to “Regional accelerated phenomenon” (RAP). This phenomenon was termed in orthopedic surgery by Frost as regional accelerated phenomenon (RAP), beginning with accelerated resorption activity followed by a slow process of bone regeneration. It was shown that alendronate could inhibit bone resorption induced as a result of flap reflection and attendant RAP. It was also put forward

that topical application was ineffective in preventing flap induced bone loss, while intravenous administration was effective.¹⁸ However, subsequent studies demonstrated by the same group using a different topical application vehicle could in fact inhibit flap induced bone loss.^{19,20}

Human Studies

Studies have reported a possible link between systemic use of alendronate and avascular necrosis of the jaw ; therefore systemic use of alendronate for the treatment of periodontitis induced bone loss was limited.²¹ Local delivery avoids adverse effects and patient compliance associated with systemic regimen. Thus various specialized local drug delivery systems were designed to maintain the concentration higher than that achieved by systemic administration. A controlled release injectable gel based delivery of alendronate was investigated. Studies showed successful local application of alendronate for reducing bone resorption following surgery.^{22,23} Alendronate had been combined with dense fibrin matrix of PRF that helped in maintaining its concentration at osseous defect site for a long duration to provide provision for osteoblast differentiation and proliferation.²⁴

The existing literature demonstrates potential effects of alendronate in relation to RAP phenomenon in human trials as well. Alendronate had shown inhibition of flap associated bone resorption and attendant RAP.²⁵ This research gave a new dimension to periodontal therapy by demonstrating that topical delivery of alendronate with the bone regenerative material may potentiate osseous regeneration. This finding provides a clue that bone targeting properties of bisphosphonates can be harnessed along with regenerative materials to potentiate osseous regeneration. Human trials have demonstrated the further benefits of systemic administration of bisphosphonates in adjunct to mechanical therapy. The studies reported that bisphosphonates, in addition to inhibition of

alveolar bone loss, improved clinical parameters.^{26,27} Due to adverse effects associated with systemic regimen local drug delivery was performed. 1% alendronate gel was locally delivered in adjunct to scaling and root planing in patients with chronic periodontitis, chronic periodontitis with diabetes mellitus, aggressive periodontitis and Class II furcation defects. Non surgical therapy along with direct subgingival injection of alendronate avoids additional step of mucoperiosteal flap reflection and bone loss due to associated RAP. Alendronate in adjunct to scaling and root planing resulted in improved clinical and radiographic parameters when compared to scaling and root planing alone.²⁸⁻³¹

NEW ADVANCEMENTS IN BISPHOSPHONATES FOR THE SUCCESS OF IMPLANTS

A study was conducted in dogs demonstrating that dental implants coated with hydroxyapatite and alendronate resulted in an increased early bone formation rate around dental implants.³² Oral administration of alendronate with risendronate improved the success of implant therapies compared with control ones. A 3 year follow up demonstrated that oral bisphosphonates usage was not associated with occurrence of osteonecrosis of the jaw.³³

ADVERSE EFFECTS

There are multitude of adverse effects associated with systemic bisphosphonate therapy. Alendronate is generally well-tolerated after short or long-term usage, but adverse effects like esophagitis and gastric damage have also been reported.³⁴ Alendronate has been shown to be toxic in the upper gastrointestinal tract with many endoscopic studies.³⁵ Alendronate has an acute mucosal damage rate comparable with nonsteroidal anti-inflammatory drugs.³⁶ Abdominal pain, nausea, dyspepsia, constipation and diarrhea are some associated adverse effects.

The most sinister skeletal adverse effect of bisphosphonates is Bisphosphonate related Osteo Necrosis of the Jaws (BRONJ). Patients may be considered to have BRONJ if all of the following three characteristics are present: 1. Current or previous treatment with a bisphosphonate; 2. Exposed bone in the maxillofacial region that has persisted for more than eight weeks; and 3. No history of radiation therapy to the jaws.³⁷ The incidence of BRONJ in patients on oral bisphosphonates varies from 0.01 to 0.04%; the incidence of BRONJ in patients with IV bisphosphonates is about 0.8-12%.³⁸

CONCLUSION

1. The use of alendronate as an adjunct to non-surgical and surgical methods may be a future potential application in periodontal therapy.
2. Alendronate can be used with bone regenerative materials to potentiate bone regeneration. This can add a new dimension to periodontal therapy.
3. Alendronate can be used with anti-inflammatory drugs to achieve more conceivable effects on clinical parameters.
4. However, there is lack of data determining optimal concentration and formulation.
5. BRONJ questions the rationality of using bisphosphonates in periodontal treatment. Nevertheless occurrence of BRONJ is limited. To avoid the side effects local bisphosphonates were locally administered. Long term studies should be done to report the incidence of BRONJ after the local drug delivery.

REFERENCES

- 1.Graves D. Cytokines that promote periodontal tissue destruction. J Periodontol 2008;79(Suppl. 8):1585-91.
- 2.Tenenbaum HC, Shelemay A, Girard B, Zohar R, Fritz PC. Bisphosphonates and periodontics: Potential applications for

- regulation of bone mass in the periodontium and other therapeutic/diagnostic uses. *J Periodontol* 2002;73:813-22.
2. DeRuiter J, Clark R. *Endocrine Module*. Spring 2002.
 3. Martin TJ, Grill V. Bisphosphonates-mechanisms of action. *Aust Prescr* 2000; 23:130.
 4. Rogers MJ, Gordon S, Benford HL, Coxon FP, Luckman SP, Monkkonen J et al. Cellular and molecular mechanisms of action of bisphosphonates. *Cancer* 2000;88:2961-78.
 5. Fisher JE, Rogers MJ, Halasy JM, Lukman SP, Hughes DE, Masarachia PJ, et al. Alendronate mechanism of action: geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption and kinase activation *in vitro*. *Proc Natl Acad Sci USA* 1999;96:133-8.
 6. Zhang FL, Casey PJ. Protein prenylation: Molecular mechanisms and functional consequences. *Annu Rev Biochem* 1996;65:241-69.
 7. Fleisch H. Bisphosphonates. Mechanisms of action. *Endocr Rev* 1998;19:80-100.
 8. Colucci S, Minielli V, Zambonin G, Cirulli N, Mori G, Serra M et al. Alendronate reduces adhesion of human osteoclast-like cells to bone and bone protein-coated surfaces. *Calcif Tissue Int* 1998;63:230.
 9. Teronen O, Heikkila P, Konttinen YT, Laitinen M, Salo T, Hanemaaijer R et al. MMP inhibition and downregulation by bisphosphonates. *Ann N Y Acad Sci* 1999; 878:453-65.
 10. Vitte C, Fleisch H, Guenther HL. Bisphosphonates induce osteoblasts to secrete an inhibitor of osteoclast mediated resorption. *Endocrinology* 1996;137:2324-33.
 11. Lezcano V, Bellido T, Plotkin LI, Boland R, Morelli S. Osteoblastic protein tyrosine phosphatases inhibition and connexin 43 phosphorylation by alendronate. *Exp Cell Res* 2014;15:30-9.
 12. Duque G, Rivas D. Alendronate has an anabolic effect on bone through the differentiation of mesenchymal stem cells. *J Bone Miner Res* 2007;22:1603-11.
 13. Giuliani N, Pedrazzoni M, Passeri G, Girasole G. Bisphosphonates inhibit IL-6 production by human osteoblast-like cells. *Scand J Rheumatol* 1998;27:38-41.
 14. Brunsvold MA, Chaves ES, Kornman KS, Aufdemorte TB, Wood R. Effects of a bisphosphonate on experimental periodontitis in monkeys. *J Periodontol* 1992;63(10):825-30.
 15. Weinreb M, Quartuccio H, Seedor JG, Aufdemorte TB, Brunsvold M, Chaves E. Histomorphometrical analysis of the effects of the bisphosphonate alendronate on bone loss caused by experimental periodontitis in monkeys. *J Periodontal Res* 1994;29(1):35-40.
 16. Reddy MS, Weatherford TW 3rd, Smith CA, West BD, Jeffcoat MK, Jacks TM. Alendronate treatment of naturally occurring periodontitis in beagle dogs. *J Periodontol* 1995;66(3):211-7.
 17. Yaffe A, Fine N, Alt I, Binderman I. Effect of bisphosphonate on alveolar bone resorption following mucoperiosteal flap surgery in the mandible of rats. *J Periodontol* 1995;66:999-1003.
 18. Yaffe A, Izkovich M, Earon Y, Alt I, Lilov R, Binderman I. Local delivery of an aminobisphosphonate prevents the resorptive phase of alveolar bone following mucoperiosteal flap surgery in rats. *J Periodontol* 1997;68:884-9.
 19. Binderman I, Adut M, Yaffe A. Effectiveness of local delivery of alendronate in reducing alveolar bone loss following periodontal surgery in rats. *J Periodontol* 2000;71:1236-40.
 20. 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.
 21. Veena HR, Prasad D. Evaluation of aminobisphosphonate (alendronate) in the management of periodontal osseous defects. *J Indian Soc Periodontol* 2010;14(1):40-5.

- 22.Reddy GT, Kumar TM, Veena KM. Formulation and evaluation of alendronate sodium gel for the treatment of bone resorptive lesions in periodontitis. *Drug Deliv* 2005;12:217-22.
- 23.Kanoriya D, Pradeep AR, Singhal S, Garg V, Guruprasad CN. Synergistic Approach Using Platelet-Rich Fibrin and 1% Alendronate for Infrabony Defect Treatment in Chronic Periodontitis: A Randomized Clinical Trial. *J Periodontol* 2016;87(12):1427-35.
- 24.Gupta J, Gill AS, Sikri P. Evaluation of the relative efficacy of an alloplast used alone and in conjunction with an osteoclast inhibitor in the treatment of human periodontal infrabony defects: A clinical and radiological study. *Indian J Dent Res* 2011;22(2):225-31.
- 25.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, placebo-controlled trial. *J Periodontol* 2001;72(2):204-9.
- 26.Lane N, Armitage GC, Loomer P, Loomer P, Hsieh S, Majumdar S, Wang HY. Bisphosphonate therapy improves the outcome of conventional periodontal treatment: Results of a 12-month, randomized, placebo-controlled study. *J Periodontol* 2005;76:1113-22.
- 27.Sharma A, Pradeep AR. Clinical efficacy of 1% alendronate gel as a local drug delivery system in treatment of chronic periodontitis: a randomized controlled clinical trial. *J Periodontol* 2012;83:11-8.
- 28.Sharma A, Pradeep AR. Clinical Efficacy of 1% Alendronate Gel in Adjunct to Mechanotherapy in the Treatment of Aggressive Periodontitis: A Randomized Controlled Clinical Trial. *J Periodontol* 2012;83:19-26.
- 29.Pradeep AR, Sharma A, Rao NS, Bajaj P, Naik SB, Kumari M. Local drug delivery of alendronate gel for the treatment of patients with chronic periodontitis with diabetes mellitus: a double-masked controlled clinical trial. *J Periodontol* 2012;83:1322-8.
- 30.Pradeep AR, Kumari M, Rao NS, Naik SB. 1% alendronate gel as a local drug delivery in the treatment of degree II furcation defects: a randomized controlled clinical trial. *J Periodontol* 2013;84:307-15.
- 31.Meraw SJ, Reeve CM, Wollan PC. et al. Use of alendronate in peri-implant defect regeneration. *J Periodontol* 1999;70:151-8.
- 32.Jeffcoat MK. Safety of bisphosphonates: controlled studies on alveolar bone. *Int J Oral Maxillofac Implants* 2006;21:349-53.
- 33.Graham DY, Malaty HM, Goodgame R. Primary amino-bisphosphonates: a new class of gastrotoxic drugs-comparison of alendronate and aspirin. *Am J Gastroenterol* 1997;92(8):1322-5.
- 34.Lowe CE, Depew WT, Vanner SJ, Paterson WG, Meddings JB. Upper gastrointestinal toxicity of alendronate. *Am J Gastroenterol* 2000;95(3):634-40.
- 35.Graham DY, Malaty HM. Drug-induced gastric ulcers are caused by more than just NSAIDs: alendronate gastric ulcers. *Gastroenterol* 1998;114.
- 36.Ruggerio SL, Dodson TB, Landesberg R, Mehrotra B. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws-2009 Update. *J Oral Maxillofac Surg* 2009;67(Suppl 1):2-12.
- 37.Brock G, Barker K, Butterworth CJ, Rogers S. Practical considerations for treatment of patients taking bisphosphonates medications: An Update. *Dent Update* 2011;38:313-26.

How to cite this article: Gupta H, Budhiraja N. Recent Alendronate in Periodontics: An Evolving Trend. *Arch of Dent and Med Res* 2017;3(1):38-44.