RESEARCH PAPER

Targeted Bisphosphonate Application as an Adjunctive Treatment to Scaling and Root Planing

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Abstract

Bisphosphonates are potent antiresorptive agents widely used in the management of osteoporosis, Paget's disease of bone, osteogenesis imperfecta, and skeletal complications associated with malignancies. Their strong affinity for hydroxyapatite and ability to suppress osteoclast-mediated bone resorption make them clinically valuable; however, these same properties have important implications for dental practice. This review examines the pharmacological characteristics, classification, mechanisms of action, pharmacokinetics, pharmacodynamics, and major clinical applications of bisphosphonates, with particular emphasis on their role in dentistry. Bisphosphonates inhibit osteoclast activity through distinct mechanisms, with nitrogen-containing agents primarily targeting farnesyl pyrophosphate synthase within the mevalonate pathway, thereby reducing osteoclast function and bone turnover. In periodontal therapy, locally or systemically administered bisphosphonates have been investigated as adjuncts to scaling and root planing, with evidence indicating potential improvements in periodontal parameters, including reductions in probing pocket depth. Their localized application may provide therapeutic benefits while minimizing systemic adverse effects. Bisphosphonates have also demonstrated potential benefits in implant therapy through localized surface coatings that may enhance osseointegration and preserve marginal bone. Conversely, systemic bisphosphonate therapy may influence orthodontic tooth movement by suppressing bone remodeling. A major dental concern is medication-related osteonecrosis of the jaw (MRONJ), particularly following invasive dental procedures in patients receiving potent intravenous bisphosphonates. Therefore, although bisphosphonates offer significant therapeutic benefits for skeletal and periodontal conditions, their use requires careful dental assessment, individualized risk evaluation, and appropriate preventive management. Understanding their dual therapeutic and adverse effects is essential for safe and effective multidisciplinary patient care.

Keywords: Bisphosphonates; Scaling and Root Planing; Periodontitis; Osteoclast Inhibition; Bone Remodeling; Periodontal Therapy

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INTRODUCTION

Bisphosphonates (BPs) around a century ago were first synthesized as antiscaling compounds by German chemists.[1] Since then, the BPs have evolved to become one of the most successful and widely used groups of drugs in the world, used for improving the treatment of Paget's disease of bone, osteoporosis, metastatic bone disease, multiple myeloma [2,3] Apart from their use for treatment of bony diseases, they are used in non-skeletal applications such as neurodegenerative diseases as well.[4] Recently they are used as bone-targeting carriers for other drugs such as antibiotics, hormones and anti-cancer drugs[5-7]

Structurally, bisphosphonates consist of two phosphonate groups linked by a carbon atom, the general chemical structure of bisphosphonates, with the attached carbon chains (denoted as R and R'), varying depending on the specific type of bisphosphonate is shown in figure 1. [8]

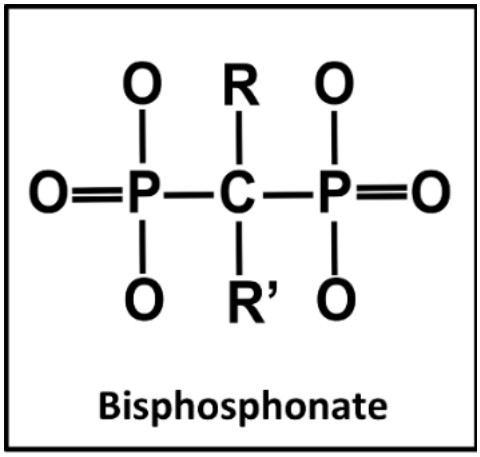
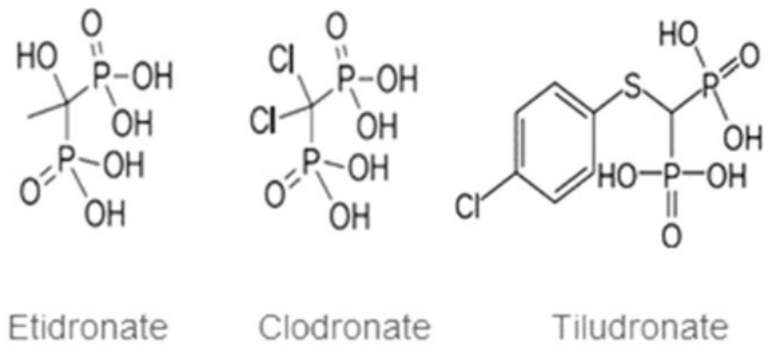


Figure 1: Chemical structure of bisphosphonates. The "R" and "R'" refers to long carbon chains that differ depending on the type of bisphosphonate.

CLASSIFICATION

These drugs are divided into first-generation non-nitrogen-containing (clodronate, etidronate and tiludronate), second and third generation nitrogen-containing (alendronate, risedronate, ibandronate and zoledronate) where third generation differ from the others because they adhere more tightly to hydroxyapatite mineral in bone [9]

1st generation: Non nitrogen containing



2nd generation: nitrogen containing with short alkyl chains

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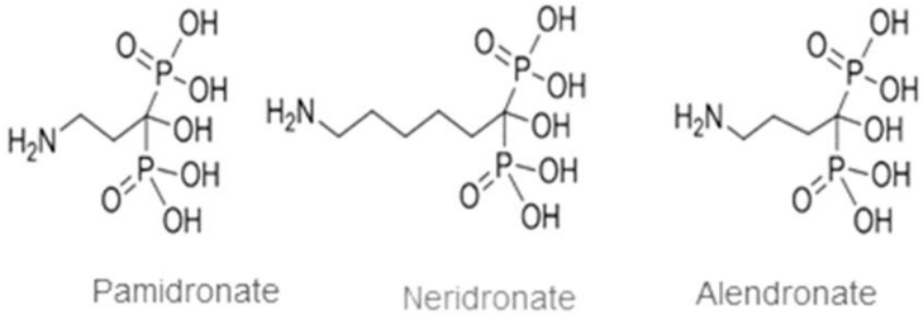
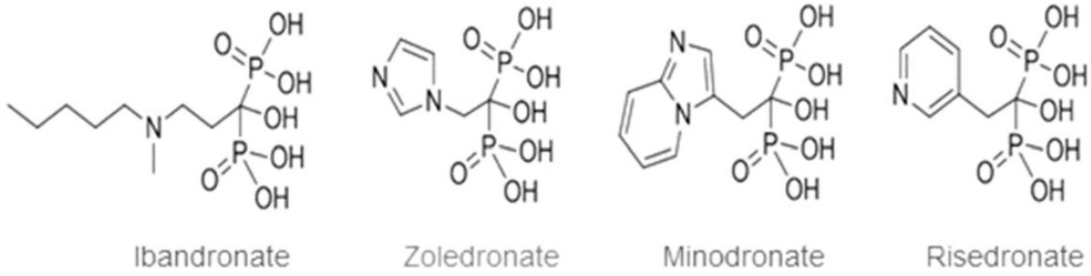


3rd generation: nitrogen containing with branch or ring structure



MECHANISM OF ACTION

All bisphosphonates inhibit bone resorption particularly in areas with active resorption by attaching to hydroxyapatite binding sites on the bone. As osteoclasts resorb bone, the bisphosphonate embedded in the bone is released and impairs the osteoclast's ability to continue bone resorption.[5] One of the novel actions of bisphosphonates has been related to preservation of osteoblasts and osteocyte viability.[10]

Nitrogen-containing bisphosphonates (2nd and 3rd generation)work by inhibiting farnesyl pyrophosphate synthase, which is important in promoting attachment of the osteoclast to the bone. As a result, the osteoclast detaches from the bone surface, thus inhibiting bone resorption.[11]

Non-nitrogen-containing bisphosphonates, on the other hand, are metabolized within the cell to substrates that replace the terminal pyrophosphate moiety of adenosine triphosphate, leading to forming of a nonfunctional molecule that competes with adenosine triphosphate in the energy metabolism of the cell. Due to this osteoclast apoptosis is inhibited , in turn leading to an overall decrease in bone breakdown.[11]

So, overall their mechanism of action can be divided into two primary pathways: inhibition of osteoclast activity and reduction of bone turnover.

1. **Inhibition of Osteoclast Activity**
   Bisphosphonates exert their effects by disrupting the function of osteoclasts, the cells responsible for bone resorption. The nitrogen-containing bisphosphonates with its effect on inhibition of farnesyl pyrophosphate synthase (FPPS), a key enzyme in the mevalonate pathway leads to the impairment of the osteoclast's ability to adhere to the bone surface. As the osteoclasts do not adhere to bone, no ruffled border is formed which is an essential step for bone resorption.[13] Additionally, bisphosphonates induce programmed cell death in osteoclasts, reducing their population and activity.[14]
2. **Reduction in Bone Turnover**
   Bisphosphonates inhibit osteoclast-mediated bone resorption, which can lead to a shift in the bone remodeling process.Moreover, bisphosphonates bind to hydroxyapatite, preventing mineral loss and reducing bone brittleness.[15]

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PHARMACOKINETICS

All oral BPs have a low and highly variable bioavailability, where approximately 99% of any orally administered BP are excreted unchanged into the faeces. This increases to 100% if the drug is ingested with calcium- or magnesium-containing foods, drinks or drugs.[16] Oral BPs are taken up in the stomach, duodenum and ileum by means of paracellular and active transport.[17,18] However, when co-ingested with gastric pH-raising drugs such as ranitidine and omeprazole its bioavailability increases.[16] Also enhancers such as caproic acid increase absorption of BPs.[19]

In the circulation, BPs remain bound to plasma and serum proteins with lower binding in plasma which has been attributed to endogenous displacers. Moreover, this binding is dependent on the type of BP, its concentration, pH, calcium.[17]

BPs without any first phase or second phase metabolism go in the liver. The only pathway of metabolism for BPs is intracellular transformation to cytotoxic ATP analogues of the non-nitrogen-containing BPs etidronate, clodronate and tiludronate.[20] Their elimination is via the kidneys or they are deposited in the calcified tissue. And they are eliminated predominantly through glomerular filtration, with the renal clearance of the drug correlating closely with creatinine clearance [21-23] None of the FDA-approved BPs have been approved for use in patients with a creatinine clearance below 35 mL/min. The general recommendation for the use of BPs in patients on renal replacement therapy is to decrease the BP dose by 50%, increase the infusion time of intravenously administered BPs, and limit the overall number of doses provided.[24]

BPs bind to hydroxyapatite crystals in bone [25] more strongly at sites of new mineral deposition at the "calcification front" in osteoid. They also bind well to resorption sites, presumably because calcium phosphate minerals are exposed during resorption. BPs less avidly bind to sites with little bone turnover. [26,27] In the skeleton, more BP is taken up by trabecular bone than cortical bone, it's because of the higher rate of turnover and greater surface area available in trabecular bone.[28] Thus there is a non-homogeneous distribution of BPs within the skeleton. [28]

The distribution of BP to bone seems to differ from BP to BP. [26,27]Some BPs bind more strongly to hydroxyapatite than others. This difference in BP binding properties were shown to determine not only the extent to which a single BP dose would bind to the skeleton, but also how well BPs penetrate into the canalicular network of bone. In general, however, BPs with weaker bone-binding properties such as risedronate appear to penetrate deeper into the bone than stronger binding BPs such as alendronate.[29]

After binding to the bone, BPs are either released again by dissolution, or are covered within new bone that overlays resorption sites for later release into the circulation during osteoclast-mediated bone resorption, either directly or via osteoclasts.[26,27]

Intracellularly, the nitrogen (N)-containing BPs inhibit farnesyl pyrophosphate synthase (FPPS), which ultimately leads to the loss of function of the osteoclasts.[30] Some of the BP is released into the circulation during resorption from bone, and some may be released after apoptosis and death of osteoclasts. BPs released from bone may undergo re-uptake onto bone surfaces. Thus, these BPs are detected in urine for years after treatment is discontinued.[31]

PHARMACODYNAMICS

A landmark discovery in the 1990s, was made about the first clinical use of bisphosphonates , and how BPs act biochemically within cells. For the N-containing BPs the inhibition of osteoclast-mediated bone resorption is mediated via inhibition of the enzyme, farnesyl pyrophosphate synthase (FPPS), an essential enzyme of the mevalonate pathway and inhibition of this enzyme leads to a decrease in farnesyl pyrophosphate, and geranyl geraniol pyro-phosphate (GGPP), leading to a decreased

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prenylation of signal transduction proteins such as Rac, Ras and Rho, which in turn leads to a loss of function of the osteoclasts.[30,31-34] In addition to osteoclasts, BPs have also been shown to work on other bone cells, osteoblasts as well as osteocytes, by preserving their viability.[10] Some BPs also seem to have direct anti-tumour activity,[35,36] eg Zoledronate might exert its anti-tumour effects through the miR21/PTEN/Akt signalling and Activin signalling pathways.[37,38]

The potential actions of BPs in other indications such as for neurodegenerative diseases are not yet fully explored. Their ability to inhibit calcium crystal growth as well as to inhibit FPP synthase in the mevalonate pathways has been postulated. [39]

The most important clinical outcome parameters for BP treatment are reduction of fracture risk in osteoporosis, skeletal-related events (SREs) in metastatic bone disease and more disease-specific parameters in other diseases such as pain and deformation in Paget's disease of bone, or number of fractures and bone pain in osteogenesis imperfecta.[40]

ROLE OF BISPHOSPHONATES IN CLINICAL PRACTICE

1. Osteoporosis

Osteoporosis is characterized by a decrease in bone mass and a deterioration in the architecture of the bones, which leads to an enhanced fragility of the skeleton and a greater risk of fracture. It is defined as present in women when the bone mass is more than 2.5 SD below that of the young woman (t score). [41]

The clinical manifestations of osteoporosis are fractures, which occurs often spontaneously or after minimal trauma, and their consequences. Osteoporosis is diagnosed and assessed quantitatively by techniques that measure bone mineral density (BMD), most commonly dual X-ray absorptiometry.

Treatment of osteoporosis with bisphosphonate is done. Bisphosphonates prevent the decrease in BMD. With etidronate being the first compound thoroughly investigated.[42] followed by alendronate [43] and later risedronate.[44] Bisphosphonates are active in osteoporotic women, also they are used for elderly women without osteoporosis [45] . Risedronate therapy prevents and partially even reverses the bone loss in glucocorticoid-treated patients .[46] All the bisphosphonates induce a marked decrease in bone turnover when given in doses effective on BMD. Both bone formation and resorption are decreased. Both alendronate and risedronate decrease by about one-half the occurrence of vertebral and nonvertebral fractures in osteoporotic patients. [47,48]Lastly, bisphosphonates do reduce fractures also in children with osteogenesis imperfecta [49]

The treatment regimens for the three main commercialized compounds are the following:[41]
– Alendronate: The dose recommended by the producers is 10 mg orally daily, 5 mg in Japan. It has a similar effect on BMD when given once weekly at 70 mg, so the weekly regimen is used today in many countries.
– Etidronate: The regimen recommended by the producer is 400 mg daily orally for 2 weeks every 3 months.
– Risedronate: The recommended regimen is 5 mg daily orally or 35 mg once weekly.

2. Glucocorticoid-Induced and Transplant-Associated Osteoporosis

Whereas bisphosphonates have become the primary therapeutic choice for treatment of postmenopausal osteoporosis, few recognize that glucocorticoid therapy leads to bone loss. Numerous clinical trials have now determined that bisphosphonates are highly
effective at limiting bone losses in patients receiving glucocorticoids or transplants.[46,50,51]

Multiple studies have documented that both oral and IV bisphosphonate therapy are capable of limiting the bone loss that frequently occurs with either solid organ [52-56] or bone marrow transplant.[57-60]

3. Bisphosphonate Therapy for Children

Bisphosphonates have become the mainstay of therapy for Osteogenesis Imperfecta (OI). A regimen developed by Glorieux of cyclic IV pamidronate (given in 3-day cycles every 2 to 4 months at an annual dose of 9 mg/kg) has been used most successfully, leading to an 88% increase in cortical thickness, a 46% increase in trabecular bone volume and substantial improvement in functional status. [61,62]
More recently, several studies have demonstrated that oral alendronate can also lead to substantial increases in BMD in OI affecting children. [63-65]

4. Paget Disease of Bone

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Bisphosphonates are the cornerstone of therapy for Paget disease of bone, it profoundly suppresses the increased bone resorption underlying the disease. Oral and iv bisphosphonates are all FDA-approved for the treatment of Paget disease of bone replacing previous modalities because of their superior ability to suppress osteoclast activity.[66-69]

5. Bisphosphonates in Malignancy

a. Breast Cancer—For patients with breast cancer metastatic to bone, treatment with IV preparations of pamidronate, zoledronic acid and ibandronate has been shown to substantially relieve skeletal pain and reduce skeletal complications. Of the oral nitrogen containing bisphosphonates, only ibandronate (given in a daily dosage of 50 mg) has been effective in reducing bone pain and limiting skeletal complications of breast cancer.[70-77]

b. Prostate Cancer – recent studies have shown a role of increased bone resorption in metastatic prostate cancer . Among the bisphosphonates, only zoledronic acid has been demonstrated to reduce skeletal bone–related events in men with hormone-refractory prostate cancer.[78-80]

c. Multiple Myeloma- many studies have shown that both pamidronate and zoledronic acid have an important palliative role in reducing the incidence of skeletal bone–related events associated with myeloma and hypercalcemia , these studies provide a substantial base for considering IV bisphosphonates as the center of current therapies to prevent and treat myeloma-associated bone disease.[81-83]

d. Renal cell carcinoma-Use of bisphosphonates in renal cell carcinoma, has been demonstrated to delay the onset and progression of skeletal disease which is due to involvement of secondaries in the bone.[84]

BISPHOSPHONATES AND DENTISTRY

1. Dental implants:

A systemic review has been done and it concludes that patients taking BPs presented a statistically significant higher risk of dental implant failure than patients not taking it. [85] They postulate that it is due to that it may be due to some potential negative effects of BPs such as its ability to inhibits bone remodelling and turnover impairing the osseointegration of dental implants and the repair of microdamage in these patients.[86] Also sites with a poor bone quality and lack of bone volume may negatively affect the implant failure rates as seen in a previous study.[87]

Also in the systemic review it is emphasised that higher implant failure rates are expected in cases with iv administration [85] due to a greater potential for side effects with iv doses of bisphosphonates due to their higher dose and potency.[88]
This effect can further be demonstrated due to the fact that BP loads bone and accumulates in bone 142.8 times faster when administered intravenously in comparison to when given orally. [89]

Also the period that patients have been under BP therapy may also play an important role in the survival of implants.[85] The higher risk of implant failure may also be influenced by the patients' compliance to the BP therapy. [85]

Lastly, the different degrees of potency among different BPs have different potentials to affect bone metabolism and cause adverse effects and that could directly or indirectly have an effect on dental implant survival.[90]

However some of them also have a beneficial effect on implant systems. Bisphosphonates, can be administered systematically or topically, the latter involving localized application, such as coating the surface of dental implants. [91] Studies have shown positive outcomes when bisphosphonates are coated on implants, enhancing osseointegration and

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delaying osteoclast apoptosis, ultimately extending the preservation time of marginal bone around implants.[92-94]

2. **Periodontal treatment:**
Periodontitis is the inflammation of the gingiva caused by bacterial flora, which could lead to the destructive of gingival tissues, or both. It can even cause tooth loss, in more severe cases.[95] Periodontitis is treated via a procedure known as scaling and root planning (SRP), which physically removes the pathogenic microorganisms causing the inflammation.[95] However, a different approach to periodontal treatment is seen by adjunctive bisphosphonate therapy in the treatment of periodontitis, it is due to the bisphosphonates' ability to inhibit proinflammatory cytokines and the resorption of alveolar bone.[96-99] Alternative routes have been used as well such as administration via intravenously or applied locally, in gel-form (often using alendronate specifically) for the purpose of treating periodontitis.[100-101] According to several review articles, a vast number of studies with locally applied showed significant improvements to patients' periodontal conditions, resulting in decreased probing pocket depth.[95,96] Similar results were found for bisphosphonates administered systemically, whether orally or intravenously, with oral bisphosphonates showing greater improvement compared to IVs.[95] Although both systemic and local bisphosphonates demonstrate effectiveness, locally applied bisphosphonates are preferred due to having fewer side effects.[96]

3. **Orthodontics:**
Considering that orthodontic forces promote physical and biological events critical to bone renewal, including recruitment of inflammatory cells, formation of new vessels and tissue remodelling, it is possible that the systemic use of bisphosphonates inhibits the osteo-reabsorption process, and as such bisphosphonates concomitantly with orthodontic treatment influence these events, decreasing tooth movement and delaying orthodontic treatment.[102,103] Most of the studies agreed that the systemic use of bisphosphonates contributed to decrease orthodontic movement.[104-109] The reason for the inhibitory effect of bisphosphonates on orthodontic movement can be attributed to disrupting osteoclast function and maintaining the compression sites of the periodontal ligament, where bone resorption becomes necessary for tooth movement to occur.[108]

However, in a study by Seifi et al , he reported that despite not observing the influence of using bisphosphonate on orthodontic movement, still found that experimental bisphosphonate significantly inhibited the bone and root resorption in rats, assigning a protective and also beneficial tissue effect to this drug.[110]

Variations in the drug dose also exerted an influence on the results of these studies , with larger doses associated with smaller and slower orthodontic movements, and smaller doses associated with larger and faster movements. [106]

CLINICAL CONCERNS ASSOCIATED WITH BISPHOSPHONATE THERAPY

1. **Osteonecrosis of the Jaw**
Medication-related osteonecrosis of the jaw (MRONJ) is a serious side-effect in the therapeutic use of AR drugs such as bisphosphonates .[111] The majority of MRONJ cases occurred in patients receiving intravenous administrations of nitrogen-containing bisphosphonates due to metastatic bone lesions.
Dental infection, teeth extraction and poor oral hygiene are main risk factors for the development of MRONJ. [112,113] Several investigations propose that common infectious diseases e.g. preexisting pathological inflammatory conditions like baseline osteomyelitis and periapical periodontitis are also contributing factors to

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the development of bisphosphonate related osteonecrosis of jaw (BRONJ) following tooth extraction. [114-117]

2. **Atrial Fibrillation**
In addition to the concern for BRONJ, another concern with bisphosphonate therapy, which has recently come to light, is atrial fibrillation. In the HORIZON Pivotal Fracture Trial, in patients were treated annually with IV zoledronic acid, and a statistically significant increase in the incidence of serious atrial fibrillation was noted.[118]

3. **Over-suppression of Bone Turnover**
Because bisphosphonates inhibit osteoclast activity, there has been some concern that prolonged bisphosphonate treatment leads to “frozen bone,” characterized by over suppression of bone remodelling, an impaired ability to repair skeletal microfractures, and increased skeletal fragility.[119]

4. **Hypocalcemia**
Hypocalcemia after mostly after iv bisphosphonate administration and can occur in patients with high rates of osteoclast-mediated bone resorption [120-121]

5. **Acute Inflammatory Response**
Approximately 10% to 30% of patients receiving their first nitrogen-containing bisphosphonate infusion will experience an acute phase reaction, most commonly characterized by transient pyrexia with associated myalgias, arthralgias, headaches, and influenza-like symptoms. This rate declines by more than half with each subsequent infusion, such that a rate of 2.8% was found after the third infusion in the HORIZON trial.[118]

6. **Severe Musculoskeletal Pain**
Although all oral and IV bisphosphonate preparations list musculoskeletal pain as a potential adverse effect in their prescribing information, the US FDA recently issued an alert highlighting the possibility of severe, incapacitating musculoskeletal pain that can occur at any point after initiation of bisphosphonate therapy.[122]

CONCLUSION

In clinical dentistry, bisphosphonates represent a double-edged sword simultaneously being a systemic bliss and a localized bane. They function as a profound medical bliss by preserving skeletal integrity, preventing debilitating fractures, and managing bone malignancies through the powerful inhibition of osteoclastic bone resorption. However, they transform into a formidable dental bane because this same mechanism halts the high-turnover bone remodelling necessary for oral healing, occasionally triggering Medication-Related Osteonecrosis of the Jaw (MRONJ). Thus overall we can conclude that bisphosphonates are a highly effective medical necessity that requires strict dental caution.

REFERENCES

1. Widler L, Jahnke W, Green JR. The chemistry of bisphosphonates: From antiscaling agents to clinical therapeutics. Anticancer Agents Med Chem. 2012;12(2):95-101.
2. Burr D, Russell G. Foreword: bisphosphonates. Bone. 2011;49(1):1.https://doi.org/10.1016/j.bone.2011.05.019
3. Corral-Gudino L, Tan AJ, Del Pino-Montes J, Ralston SH. Bisphosphonates for Paget's disease of bone in adults. Cochrane Database Syst Rev. 2017;12:CD004956.
4. Zameer S, Najmi AK, Vohora D, Akhtar M. Bisphosphonates: Future perspective for neurological disorders. Pharmacol Rep. 2018; 70(5):900-907.
5. Farrell KB, Karpeisky A, Thamm DH, Zinnen S. Bisphosphonate conjugation for bone specific drug targeting. Bone Rep. 2018;9:47-60.
6. Sedghizadeh PP, Sun S, Junka AF, et al. Design, synthesis, and antimicrobial

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evaluation of a novel bone-targeting bisphosphonate-ciprofloxacin conjugate for the treatment of osteomyelitis biofilms. J Med Chem. 2017;60(6):2326-2343.
7. Wang H, Xiao L, Tao J, et al. Synthesis of a bone-targeted bortezomib with in vivo anti-myeloma effects in mice. Pharmaceutics. 2018;10(3):154.
8. Roelofs, A.J.; Ebetino, F.H.; Reszka, A.A.; Russell, R.G.G.; Rogers, M.J. Bisphosphonates: Mechanisms of action. In Principles of Bone Biology; Academic Press: Cambridge, MA, USA, 2008; pp. 1737–1767.
9. Drake MT, Clarke BL, Lewiecki EM. The Pathophisiology and Treatment of Osteoporosis. Clin Ther. 2015;37:1837-50.
10. Bellido T, Plotkin LI. Novel actions of bisphosphonates in bone: preservation of osteoblast and osteocyte viability. Bone. 2011 Jul;49(1):50-5. doi: 10.1016/j.bone.2010.08.008. Epub 2010 Aug 18. PMID: 20727997; PMCID: PMC2994972.
11. Ganesan K, Goyal A, Roane D. Bisphosphonate. [Updated 2023 Jul 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470248/
12. Drake MT, Clarke BL, Khosla S: Bisphosphonates: mechanism of action and role in clinical practice . Mayo Clin Proc. 2008, 83:1032-45. 1
13. Fleisch H: Bisphosphonates: mechanisms of action . Endocr Rev. 1998, 19:80-100. 10.1016/B978-012098652- 1.50180-3
14. Hughes DE, Wright KR, Uy HL, et al.: Bisphosphonates promote apoptosis in murine osteoclasts in vitro and in vivo. J Bone Miner Res. 1995, 10:1478-87. 10.1002/jbmr.5650101008
15. Rodan GA, Fleisch HA: Bisphosphonates: mechanisms of action . J Clin Invest. 1996, 97:2692-96. 10.1172/JCI118722
16. Gertz BJ, Holland SD, Kline WF, et al. Studies of the oral bioavailability of alendronate. Clin Pharmacol Ther. 1995;58(3):288-298. https://doi.org/10.1016/0009-9236(95)90245-7.
17. Lin JH. Bisphosphonates: A review of their pharmacokinetic properties. Bone. 1996;18(2):75-85.
18. Twiss IM, Burggraaf J, Schoemaker RC, et al. The sugar absorption test in the evaluation of the gastrointestinal intolerance to bisphosphonates: Studies with oral pamidronate. Clin Pharmacol Ther.2001;69(6):431-437.
19. McClung MR, Miller PD, Brown JP, et al. Efficacy and safety of a novel delayed-release risedronate 35 mg once-a-week tablet. Osteoporos Int. 2012;23(1):267-276. https://doi.org/10.1007/s00198-011-1791-y
20. Frith JC, Monkkonen J, Auriola S, Monkkonen H, Rogers MJ. The molecular mechanism of action of the antiresorptive and antiinflammatory drug clodronate: Evidence for the formation in vivo of a metabolite that inhibits bone resorption and causes osteoclast and macrophage apoptosis. Arthritis Rheum. 2001;44(9):2201-2210.
21. Berenson JR, Rosen L, Vescio R, et al. Pharmacokinetics of pamidronate disodium in patients with cancer with normal or impaired renal function. J Clin Pharmacol. 1997;37(4):285-290.
22. Bergner R, Henrich DM, Hoffmann M, et al. Renal safety and pharmacokinetics of ibandronate in multiple myeloma patients with or without impaired renal function. J Clin Pharmacol. 2007;47(8):942-950. https://doi.org/10.1177/0091270007301801
23. Skerjanec A, Berenson J, Hsu CH, et al. The pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with varying degrees of renal function. J Clin Pharmacol. 2003;43(2):154-162.
24. Miller PD. Is there a role for bisphosphonates in chronic kidney disease? Semin Dial. 2007;20(3):186-190. https://doi.org/10.1111/j.1525-139X.2007.00271.x
25. Fleisch H, Russell RG, Francis MD. Diphosphonates inhibit hydroxyapatite

Author for Correspondence: , Fatimah Salman Ghazwani

dissolution in vitro and bone resorption in tissue culture and in vivo. Science. 1969;165(3899):1262-1264.
26. Masarachia P, Weinreb M, Balena R, Rodan GA. Comparison of the distribution of 3H-alendronate and 3H-etidronate in rat and mouse bones. Bone. 1996;19(3):281-290.
27. Azuma Y, Sato H, Oue Y, et al. Alendronate distributed on bone surfaces inhibits osteoclastic bone resorption in vitro and in experimental hypercalcemia models. Bone. 1995;16(2):235-245.
28. Weiss HM, Pfaar U, Schweitzer A, Wiegand H, Skerjanec A, Schran H. Biodistribution and plasma protein binding of zoledronic acid. Drug Metabol Dispos. 2008;36(10):2043-2049. https://doi.org/10.1124/dmd.108.021071
29. Roelofs AJ, Stewart CA, Sun S, et al. Influence of bone affinity on the skeletal distribution of fluorescently labeled bisphosphonates in vivo. Bone Miner Res. 2012;27(4):835-847. https://doi.org/10.1002/jbmr.1543
30. Luckman SP, Hughes DE, Coxon FP, Russell RGG, Rogers MJ. Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. J Bone Miner Res. 1998;13(4):581-589. https://doi.org/10.1359/jbmr.1998.13.4.581
31. Khan SA, Kanis JA, Vasikaran S, et al. Elimination and biochemical responses to intravenous alendronate in postmenopausal osteoporosis. J Bone Miner Res. 1997;12(10):1700-1707. https://doi.org/10.1359/jbmr.1997.12.10.1700
32. van Beek E, Pieterman E, Cohen L, Lowik C, Papapoulos S. Farnesyl pyrophosphate synthase is the molecular target of nitrogen containing bisphosphonates. Biochem Biophys Res Commun. 1999;264(1):108-111. https://doi.org/10.1006/bbrc.1999.1499
33. van Beek E, Pieterman E, Cohen L, Lowik C, Papapoulos S. Nitrogen containing bisphosphonates inhibit isopentenyl pyrophosphate isomerase/farnesyl pyrophosphate synthase activity with relative potencies corresponding to their antiresorptive potencies in vitro and in vivo. Biochem Biophys Res Commun. 1999;255(2):491-494. https://doi.org/10.1006/bbrc.1999.0224
34. Rogers MJ. New insights into the molecular mechanisms of action of bisphosphonates. Curr Pharm Des. 2003;9(32):2643-2658.
35. Mathew A, Brufsky A. Bisphosphonates in breast cancer. Int J Cancer. 2015;137(4):753-764. https://doi.org/10.1002/ijc.28965
36. Coleman R, Cameron D, Dodwell D, et al. Adjuvant zoledronic acid in patients with early breast cancer: Final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial. Lancet Oncol. 2014;15(9):997-1006. https://doi.org/10.1016/S1470-2045(14)70302-X
37. Wilson C, Ottewell P, Coleman RE, Holen I. The differential anti- tumour effects of zoledronic acid in breast cancer—Evidence for a role of the activin signaling pathway. BMC Cancer. 2015;15(1):55. https://doi.org/10.1186/s12885-015-1066-7
38. Li Q, Kingman J, Sundberg JP, Levine MA, Uitto J. Etidronate prevents, but does not reverse, ectopic mineralization in a mouse model of pseudoxanthoma elasticum (Abcc6(−/−)). Oncotarget.2018;9(56):30721-30730. https://doi.org/10.18632/oncotarget.10738
39. Cremers S, Drake MT, Ebetino FH, Bilezikian JP, Russell RGG. Pharmacology of bisphosphonates. Br J Clin Pharmacol. 2019 Jun;85(6):1052-1062. doi: 10.1111/bcp.13867. Epub 2019 Feb 28. PMID: 30650219; PMCID: PMC6533426
40. Cremers S, Garnero P. Biochemical markers of bone turnover in the clinical development of drugs for osteoporosis and metastatic bone disease: Potential uses and pitfalls. Drugs. 2006;66(16):2031-2058. https://doi.org/10.2165/00003495-200666160-00001

Author for Correspondence: , Fatimah Salman Ghazwani

41. Fleisch H. Bisphosphonates in osteoporosis. Eur Spine J. 2003 Oct;12 Suppl 2(Suppl 2):S142-6. doi: 10.1007/s00586-003-0622-z. Epub 2003 Sep 16. PMID: 13680318; PMCID: PMC3591825.
42. Watts NB, Harris ST, Genant HK, Wasnich RD, Miller PD, Jackson RD, Licata AA, Ross P, Woodson GC, Yanover MJ, Mysiw WJ, Kohse L, Rao MB, Steiger P, Richmond B, Chesnut CH III (1990) Intermittent cyclical etidronate treatment of post- menopausal osteoporosis. N Engl J Med 323:73–329
43. Liberman UA, Weiss SR, Bröll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downs RW Jr, Dequeker J, Favus M, Seeman E, Recker RR, Capizzi T, Santora AC II, Lombardi A, Shah RV, Hirsch LJ, Karpf DB (1995) Effect of oral alendronate on bone mineral density and the incidence of fractures in post-menopausal osteoporosis. N Engl J Med 333:1437–1443
44. Mortensen L, Charles P, Bekker PJ, Digennaro J, Johnston CC (1998) Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow up. J Clin Endocrinol Metab 83:396–402
45. McClung M, Clemmesen B, Daifotis A, Gilchrist NL, Eisman J, Weinstein RS, El Hajj Fuleihan G, Reda C, Yates AJ, Ravn P (1998) Alendronate prevents postmenopausal bone loss in women without osteoporosis. Ann Intern Med 128:253–261
46. Cohen S, Levy RM, Keller M, Boling E, Emkey RD, Greenwald M, Zizic TM, Wallach S, Sewell KL, Lukert BP, Axelrod DW, Chines AA (1999) Risedronate therapy prevents corticosteroid- induced bone loss. Arthritis Rheum 42: 2309–2318
47. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE (1996) Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 348: 1535–1541
48. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner D, Keller M, Chesnut CH, Brown J, Eriksen EF, Hoseyni MS, Axelrod DW, Miller, PD (1999) Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. JAMA 14:1344–1352
49. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanogu G, Travers R (1998) Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. N Engl J Med 339:947–952
50. Boutsen Y, Jamart J, Esselinckx W, Stoffel M, Devogelaer JP. Primary prevention of glucocorticoid- induced osteoporosis with intermittent intravenous pamidronate: a randomized trial. Calcif Tissue Int 1997;61(4):266–271. [PubMed: 9312195]
51. Ringe JD, Dorst A, Faber H, Ibach K, Sorenson F. Intermittent intravenous ibandronate injections reduce vertebral fracture risk in corticosteroid-induced osteoporosis: results from a long-term comparative study. Osteoporos Int 2003 Oct;14(10):801–807. [PubMed: 14610641]Epub 2003 Aug28
52. Krieg MA, Seydoux C, Sandini L, et al. Intravenous pamidronate as treatment for osteoporosis after heart transplantation: a prospective study. Osteoporos Int 2001;12(2):112–116. [PubMed: 11303710]
53. Coco M, Glicklich D, Faugere MC, et al. Prevention of bone loss in renal transplant recipients: a prospective, randomized trial of intravenous pamidronate. J Am Soc Nephrol 2003;14(10):2669–2676. [PubMed: 14514747]
54. Aris RM, Lester GE, Renner JB, et al. Efficacy of pamidronate for osteoporosis in patients with cystic fibrosis following lung transplantation. Am J Respir Crit Care Med 2000;162(3 pt 1):941–946.[PubMed: 10988110]
55. Grotz W, Nagel C, Poeschel D, et al. Effect of ibandronate on bone loss and renal function after kidney transplantation. J Am Soc Nephrol 2001;12(7):1530–1537. [PubMed: 11423583]

Author for Correspondence: , Fatimah Salman Ghazwani

56. Giannini S, D'Angelo A, Carraro G, et al. Alendronate prevents further bone loss in renal transplant recipients. J Bone Miner Res 2001;16(11):2111–2117. [PubMed: 11697808]
57. Tauchmanova L, Ricci P, Serio B, et al. Short-term zoledronic acid treatment increases bone mineral density and marrow clonogenic fibroblast progenitors after allogeneic stem cell transplantation. J Clin Endocrinol Metab 2005 Feb;90(2):627–634. [PubMed: 15546907]Epub 2004 Nov 16
58. Grigg AP, Shuttleworth P, Reynolds J, et al. Pamidronate reduces bone loss after allogeneic stem cell transplantation. J Clin Endocrinol Metab 2006 Oct;91(10):3835–3843. [PubMed: 16835281]Epub 2006 Jul 11
59. D'Souza AB, Grigg AP, Szer J, Ebeling PR. Zoledronic acid prevents bone loss after allogeneic haemopoietic stem cell transplantation. Intern Med J 2006;36(9):600–603. [PubMed: 16911552]
60. Yao S, McCarthy PL, Dunford LM, et al. High prevalence of early-onset osteopenia/osteoporosis after allogeneic stem cell transplantation and improvement after bisphosphonate therapy. Bone Marrow Transplant 2008 Feb;41(4):393–398. [PubMed: 17994116]Epub 2007 Nov 12
61. Glorieux FH. Experience with bisphosphonates in osteogenesis imperfecta. Pediatrics 2007;119 (suppl 2):S163–S165. [PubMed: 17332237]
62. Rauch F, Travers R, Plotkin H, Glorieux FH. The effects of intravenous pamidronate on the bone tissue of children and adolescents with osteogenesis imperfecta. J Clin Invest 2002;110(9):1293–1299. [PubMed: 12417568]
63. Cho TJ, Choi IH, Chung CY, Yoo WJ, Park MS, Park YK. Efficacy of oral alendronate in children with osteogenesis imperfecta. J Pediatr Orthop 2005;25(5):607–612. [PubMed: 16199940]
64. DiMeglio LA, Peacock M. Two-year clinical trial of oral alendronate versus intravenous pamidronate in children with osteogenesis imperfecta. J Bone Miner Res 2006 Jan;21(1):132–140. [PubMed: 16355282]Epub 2005 Oct 17
65. Akcay T, Turan S, Guran T, Bereket A. Alendronate treatment in children with osteogenesis imperfecta. Indian Pediatr 2008;45(2):105–109. [PubMed: 18310788]
66. Siris E, Weinstein RS, Altman R, et al. Comparative study of alendronate versus etidronate for the treatment of Paget's disease of bone. J Clin Endocrinol Metab 1996;81(3):961–967. [PubMed: 8772558]
67. Siris ES, Chines AA, Altman RD, et al. Risedronate in the treatment of Paget's disease of bone: an open label, multicenter study. J Bone Miner Res 1998;13(6):1032–1038. [PubMed: 9626635]
68. Siris ES. Perspectives: a practical guide to the use of pamidronate in the treatment of Paget's disease. J Bone Miner Res 1994;9(3):303–304. [PubMed: 8191921]
69. Reid IR, Miller P, Lyles K, et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. N Engl J Med 2005;353(9):898–908. [PubMed: 16135834]
70. Hortobagyi GN, Theriault RL, Porter L, et al. Protocol 19 Aredia Breast Cancer Study Group. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. N Engl J Med 1996;335(24):1785–1791. [PubMed: 8965890]
71. Hortobagyi GN, Theriault RL, Lipton A, et al. Protocol 19 Aredia Breast Cancer Study Group. Long- term prevention of skeletal complications of metastatic breast cancer with pamidronate. J Clin Oncol 1998;16(6):2038–2044. [PubMed: 9626201]
72. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer 2000;88(5):1082–1090. [PubMed: 10699899]
73. Rosen LS, Gordon D, Tchekmedyian NS, et al. Long-term efficacy and safety of

Author for Correspondence: , Fatimah Salman Ghazwani

zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. Cancer 2004;100(12):2613–2621. [PubMed: 15197804]

74. Clemons MJ, Dranitsaris G, Ooi WS, et al. Phase II trial evaluating the palliative benefit of second- line zoledronic acid in breast cancer patients with either a skeletal-related event or progressive bone metastases despite first-line bisphosphonate therapy. J Clin Oncol 2006 Oct 20;24(30):4895–4900. [PubMed: 17001071]Epub 2006 Sep 25
75. Body JJ, Diel IJ, Lichinitser MR, et al. MF 4265 Study Group. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. Ann Oncol 2003;14(9):1399–1405. [PubMed: 12954579]
76. Body JJ, Diel IJ, Bell R, et al. Oral ibandronate improves bone pain and preserves quality of life in patients with skeletal metastases due to breast cancer. Pain 2004;111(3):306–312. [PubMed: 15363874]
77. Body JJ, Diel IJ, Lichinitzer M, et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. Br J Cancer 2004;90(6):1133–1137. [PubMed: 15026791]
78. Garnero P, Buchs N, Zekri J, Rizzoli R, Coleman RE, Delmas PD. Markers of bone turnover for the management of patients with bone metastases from prostate cancer. Br J Cancer 2000;82(4):858–864. [PubMed: 10732759]
79. Saad F, Gleason DM, Murray R, et al. Zoledronic Acid Prostate Cancer Study Group. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002;94(19):1458–1468. [PubMed: 12359855]
80. Saad F, Gleason DM, Murray R, et al. Zoledronic Acid Prostate Cancer Study Group. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst 2004;96(11):879–882. [PubMed: 15173273]
81. Berenson JR, Lichtenstein A, Porter L, et al. Myeloma Aredia Study Group. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. N Engl J Med 1996;334:488–493. [PubMed: 8559201]
82. Berenson JR, Rosen LS, Howell A, et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases [published correction appears in Cancer. 2001;91(10):1956]. Cancer 2001;91(7):1191–1200. [PubMed: 11283917]
83. Rosen LS, Gordon D, Kaminski M, 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(5):377–387. [PubMed: 11693896]
84. Lipton A, Zheng M, Seaman J. Zoledronic acid delays the onset of skeletal-related events and progression of skeletal disease in patients with advanced renal cell carcinoma. Cancer 2003;98(5): 962–969. [PubMed: 12942563]
85. Sulaiman N, Fadhul F, Chrcanovic BR. Bisphosphonates and Dental Implants: A Systematic Review and Meta-Analysis. Materials (Basel). 2023 Sep 5;16(18):6078. doi: 10.3390/ma16186078. PMID: 37763356; PMCID: PMC10532755.
86. Mashiba T., Hirano T., Turner C.H., Forwood M.R., Johnston C.C., Burr D.B. Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J. Bone Miner. Res. 2000;15:613–620. doi: 10.1359/jbmr.2000.15.4.613.
87. Chrcanovic B.R., Albrektsson T., Wennerberg A. Bone Quality and Quantity

Author for Correspondence: , Fatimah Salman Ghazwani

and Dental Implant Failure: A Systematic Review and Meta-analysis. Int. J. Prosthodont. 2017;30:219–237. doi: 10.11607/ijp.5142.
88. Perazella M.A., Markowitz G.S. Bisphosphonate nephrotoxicity. Kidney Int. 2008;74:1385–1393. doi: 10.1038/ki.2008.356.
89. Marx R.E. A decade of bisphosphonate bone complications: What it has taught us about bone physiology. Int. J. Oral Maxillofac. Implants. 2014;29:e247–e258. doi: 10.11607/jomi.te61.
90. Cremers S.C., Pillai G., Papapoulos S.E. Pharmacokinetics/pharmacodynamics of bisphosphonates: Use for optimisation of intermittent therapy for osteoporosis. Clin. Pharmacokinet. 2005;44:551–570. doi: 10.2165/00003088-200544060-00001.
91. Najeeb, S.; Zafar, M.S.; Khurshid, Z.; Zohaib, S.; Hasan, S.M.; Khan, R.S. Bisphosphonate releasing dental implant surface coatings and osseointegration: A systematic review. J. Taibah Univ. Med. Sci. 2017, 12, 369–375. [CrossRef]
92. Najeeb, S.; Zafar, M.S.; Khurshid, Z.; Zohaib, S.; Hasan, S.M.; Khan, R.S. Bisphosphonate releasing dental implant surface coatings and osseointegration: A systematic review. J. Taibah Univ. Med. Sci. 2017, 12, 369–375. [CrossRef]
93. Jobke, B.; Milovanovic, P.; Amling, M.; Busse, B. Bisphosphonate-osteoclasts: Changes in osteoclast morphology and function induced by antiresorptive nitrogen-containing bisphosphonate treatment in osteoporosis patients. Bone 2014, 59, 37–43. [CrossRef] [PubMed]
94. Abtahi, J.; Henefalk, G.; Aspenberg, P. Randomised trial of bisphosphonate-coated dental implants: Radiographic follow-up after five years of loading. Int. J. Oral Maxillofac. Surg. 2016, 45, 1564–1569.
95. Muniz, F.; Silva, B.F.D.; Goulart, C.R.; Silveira, T.M.D.; Martins, T.M. Effect of adjuvant bisphosphonates on treatment of periodontitis: Systematic review with meta-analyses. J. Oral Biol. Craniofac. Res. 2021, 11, 158–168.
96. Akram, Z.; Abduljabbar, T.; Kellesarian, S.V.; Abu Hassan, M.I.; Javed, F.; Vohra, F. Efficacy of bisphosphonate as an adjunct to nonsurgical periodontal therapy in the management of periodontal disease: A systematic review. Br. J. Clin. Pharmacol. 2017, 83, 444–454. [CrossRef]
97. Badran, Z.; Kraehenmann, M.A.; Guicheux, J.; Soueidan, A. Bisphosphonates in periodontal treatment: A review. Oral Health Prev. Dent. 2009, 7, 3–12.
98. Chen, J.A.-O.; Chen, Q.A.-O.; Hu, B.A.-O.; Wang, Y.A.-O.; Song, J.A.-O. Effectiveness of alendronate as an adjunct to scaling and root planing in the treatment of periodontitis: A meta-analysis of randomized controlled clinical trials. J. Periodontal Implant. Sci.2016, 46, 382–395.
99. Li, C.L.; Lu, W.W.; Seneviratne, C.J.; Leung, W.K.; Zwahlen, R.A.; Zheng, L.W. Role of periodontal disease in bisphosphonate-related osteonecrosis of the jaws in ovariectomized rats. Clin. Oral Implant. Res. 2016, 27, 1–6.
100. Dutra, B.C.; Oliveira, A.; Oliveira, P.A.D.; Manzi, F.R.; Cortelli, S.C.; Cota, L.O.M.; Costa, F.O. Effect of 1% sodium alendronate in the non-surgical treatment of periodontal intraosseous defects: A 6-month clinical trial. J. Appl. Oral Sci. 2017, 25, 310–317.
101. Gupta, A.; Govila, V.; Pant, V.A.; Gupta, R.; Verma, U.P.; Ahmad, H.; Mohan, S. A randomized controlled clinical trial evaluating the efficacy of zoledronate gel as a local drug delivery system in the treatment of chronic periodontitis: A clinical and radiological correlation. Natl. J. Maxillofac. Surg. 2018, 9, 22–32.
102. Allen MR, Erickson AM, Wang X, Burr DB, Martin RB, Hazelwood SJ. Morphological assessment of basic multicellular unit resorption parameters in dogs shows additional mechanisms of bisphosphonate effects on bone. Calcif Tissue Int. 2010;86(1):67- 71. http://doi.org/10.1007/s00223-009-9315-x. PMid:19953232.

Author for Correspondence: , Fatimah Salman Ghazwani

103. Araújo AS, Fernandes AB, Maciel JV, Santos JN No, Bolognese AM. New methodology for evaluating osteoclastic activity induced by orthodontic load. J Appl Oral Sci. 2015;23(1):19-25. http://doi.org/10.1590/1678-775720140351. PMid:25760264.
104. Salazar M, Hernandes L, Ramos AL, Salazar BO, Micheletti KR, Paranhos LR, et al. Effect of alendronate sodium on tooth movement in ovariectomized rats. Arch Oral Biol. 2015;60(5):776-81. http://doi.org/10.1016/j.archoralbio.2015.02.003. PMid:25766470.
105. MP, Dos Santos GMT, et al. Zoledronic acid and alendronate sodium and the implications in orthodontic movement. OrthodCraniofac Res. 2017;20(3):164-9. http://doi.org/10.1111/ocr.12192. PMid:28653350.
106. Nakaš E, Lauc T, Tiro A, Džemidžić V, Zukanović A, Franić M, et al. Dose- and time-dependent effects of clodronate on orthodontic tooth movement. Bosn J Basic Med Sci. 2017;17(1):23-8. http://doi.org/10.17305/bjbms.2017.1715. PMid:28086064.
107. Kaipatur NR, Wu Y, Adeeb S, Stevenson TR, Major PW, Doschak MR. Impact of bisphosphonate drug burden in alveolar bone during orthodontic tooth movement in a rat model: a pilot study. Am J Orthod Dentofacial Orthop. 2013;144(4):557-67. http://doi.org/10.1016/j.ajodo.2013.06.015. PMid:24075664.
108. Karras JC, Miller JR, Hodges JS, Beyer JP, Larson BE. Effect of alendronate on orthodontic tooth movement in rats. Am J Orthod Dentofacial Orthop. 2009;136(6):843-7. http://doi.org/10.1016/j.ajodo.2007.11.035. PMid:19962607.
109. 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(5):469-73. http://doi.org/10.1093/ejo/26.5.469.
110. Seifi M, Asefi S, Hatamifard G, Lotfi A. Effect of local injection of Zolena, zoledronic acid made in Iran, on orthodontic tooth movement and root and bone resorption in rats. J Dent Res Dent Clin Dent Prospects. 2017;11(4):257-64. http://doi.org/10.15171/ joddd.2017.045. PMid:29354254.
111. Troeltzsch, M., Woodlock, T., Kriegelstein, S., Steiner, T., Messlinger, K., Troeltzsch, M., 2012. Physiology and pharmacology of nonbisphosphonate drugs implicated in osteonecrosis of the jaw. J. Can. Dent. Assoc. 78, c85.
112. Pichardo, S.E.C., van der Hee, J.G., Fiocco, M., Appelman-Dijkstra, N.M., van Merkesteyn, J.P.R., 2020. Dental implants as risk factors for patients with medication-related osteonecrosis of the jaws (MRONJ). Br. J. Oral Maxillofac. Surg. 58 (7), 771–776. https://doi.org/10.1016/j.bjoms.2020.03.022.
113. Coropciuc, R., Coopman, R., Garip, M., Gielen, E., Politis, C., Van den Wyngaert, T., Beuselinck, B., 2023. Risk of medication-related osteonecrosis of the jaw after dental extractions in patients receiving antiresorptive agents - a retrospective study of 240 patients. Bone 170, 116722. https://doi.org/10.1016/j.bone.2023.116722
114. Otto, S.; Troltzsch, M.; Jambrovic, V.; Panya, S.; Probst, F.; Ristow, O.; Ehrenfeld, M.; Pautke, C. Tooth extraction in patients receiving oral or intravenous bisphosphonate administration: A trigger for BRONJ development? J. Craniomaxillofac. Surg. 2015, 43, 847–854.
115. Soutome, S.; Otsuru, M.; Hayashida, S.; Murata, M.; Yanamoto, S.; Sawada, S.; Kojima, Y.; Funahara, M.; Iwai, H.; Umeda, M.; et al. Relationship between tooth extraction and development of medication-related osteonecrosis of the jaw in cancer patients. Sci. Rep. 2021, 11, 17226.
116. Saia, G.; Blandamura, S.; Bettini, G.; Tronchet, A.; Totola, A.; Bedogni, G.;

Author for Correspondence: , Fatimah Salman Ghazwani

Ferronato, G.; Nocini, P.F.; Bedogni, A. Occurrence of bisphosphonate-related osteonecrosis of the jaw after surgical tooth extraction. J. Oral Maxillofac. Surg. 2010, 68, 797–804.

117. Song, M.; Alshaikh, A.; Kim, T.; Kim, S.; Dang, M.; Mehrazarin, S.; Shin, K.H.; Kang, M.; Park, N.H.; Kim, R.H. Preexisting periapical inflammatory condition exacerbates tooth extraction-induced bisphosphonate-related osteonecrosis of the jaw lesions in mice. J. Endod. 2016, 42, 1641–1646.
118. Black DM, Delmas PD, Eastell R, et al. HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356(18):1809–1822.
119. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc. 2008 Sep;83(9):1032-45. doi: 10.4065/83.9.1032. PMID: 18775204; PMCID: PMC2667901.
120. Whitson HE, Lobaugh B, Lyles KW. Severe hypocalcemia following bisphosphonate treatment in a patient with Paget's disease of bone. Bone 2006 Oct;39(4):954–958. [PubMed: 16769264]Epub 2006 Jun 12
121. Jones SG, Dolan G, Lengyel K, Myers B. Severe increase in creatinine with hypocalcaemia in thalidomide-treated myeloma patients receiving zoledronic acid infusions [letter]. Br J Haematol 2002;119(2):576–577. [PubMed: 12406106]
122. US Food and Drug Administration. Information on bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa). Jan 72008[Accessed July 18, 2008].http://ovha.vermont.gov/for-providers/i3a_fda_gov_cder_drug_infopage_bisphosphonates_default.pdf

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