Publication Types: Case Reports

Oral implants in patients receiving bisphosphonates: A review and update

María Paz Mínguez Serra [1], César Salort Llorca [2], Francisco Javier Silvestre Donat [3]

(1) Stomatology Unit. Doctor Peset University Hospital (Valencia)
(2) Service of Pharmacy. Mutua de Terrassa Hospital (Barcelona)
(3) Department of Stomatology. Valencia University Medical and Dental School. Head of the Stomatology Unit. Doctor Peset University Hospital (Valencia)(Spain)

Correspondence:
Prof. F.J. Silvestre-Donat
Unidad de Estomatología
Hospital Dr. Peset. Consultas externas
Cl Juan de Garay s/n
46017 – Valencia (Spain)
francisco.silvestre@uv.es

Received: 02/03/2008
Accepted: 25/07/2008

Indexed in:

- *Science Citation Index Expanded*
- *Journal Citation Reports*
- *Index Medicus, MEDLINE, PubMed*
- *Excerpta Medica, Embase, SCOPUS,*
- *Indice Médico Español*

Mínguez-Serra MP, Salort-Llorca C, Silvestre-Donat FJ. Oral implants in patients receiving bisphosphonates: A review and update. Med Oral Patol Oral Cir Bucal. 2008 Dec 1;13(12):E755-60.

http://www.medicinaoral.com/medoralfree01/v13i12/medoralv13i12p755.pdf

Abstract

This rewiew was mad to establish the convenience of dental implant treatment in patients receiving bisphosphonates or programmed to receive such drugs, with a description of their mechanisms of action and the way in which they can affect the mandibular or maxillary bone of dental implant candidates. In turn, a description is provided of the key elements for evaluating the benefit-risk ratio in patients treated with bisphosphonates who require oral surgery. Clinicians must be aware of the potential risk of osteonecrosis in patients treated with bisphosphonates via the oral or intravenous route.

When bisphosphonates are administered via the intravenous route, all invasive oral procedures (including implant surgery) are contraindicated, and should be avoided unless absolutely necessary. The indications are more controversial in the case of bisphosphonates administered via the oral route. There is little literature on the influence of oral bisphosphonates upon bone repair, and there are not many published cases of mandibular or maxillary osteonecrosis among patients that receive such medication.

The use of bisphosphonates is becoming increasingly widespread, and the duration of such treatment is increasing. It would be of interest to design studies to evaluate the risk factors of maxillary osteonecrosis among dental implant patients receiving treatment with oral bisphosphonates, and to define biomarkers capable of indicating the level of risk in the event of oral surgery in patients receiving such drugs.

Key words: *Osteonecrosis, bisphosphonates, implants, oral surgery, osteoporosis.*

Introduction

Success in implant-supported restorations requires due evaluation of the risk factors, with correct patient selection. In this sense, there must be no local or systemic contraindications to implant surgery. Some absolute contraindications to dental implant (DI) rehabilitation are disease processes such as recent myocardial infarction or cerebrovascular stroke, heart valve surgery, immune suppression, blood dyscrasias, active neoplastic disease undergoing treatment, drug abuse, psychiatric disorders and, as a more recent contraindication, intravenous bisphosphonate (BPP) treatment (1).

BPPs are widely used for the treatment of diseases such as multiple myeloma, bone metastases and malignant hypercalcemia (2), as well as for the prevention and treatment of osteoporosis and other skeletal diseases such as Paget's disease (2).

BPPs are endogenous pyrophosphate analogs that prove

comparatively more difficult to metabolize. Their molecular structure comprises two phosphate groups (responsible for the low bioavailability of these drugs) bound to a carbon atom, and two radicals (R1 and R2), which are likewise bound to the central carbon atom. The R1 radical determines affinity for binding to hydroxyapatite, while the R2 radical determines the potency and efficacy of the drug (Figure 1). Minor changes in BPP molecular structure in turn lead to changes in their physicochemical, biological, therapeutic and toxicological properties (3). The BPPs marketed in Spain, and their corresponding brand names, are indicated in Table 1.

BPPs act by fixing to bone hydroxyapatite, inhibiting bone reabsorption by reducing osteoclast activity, facilitating their apoptosis and inhibiting their production from the corresponding hematopoietic precursor cells. They also reduce osteoblast apoptosis and stimulate the secretion of osteoclast recruitment inhibitors. A degree of antiangiogenic activity has also been reported as being responsible for some of the effects of these drugs.

BPPs are well tolerated when adequately administered, though different adverse effects and complications have been associated with their use.

In the case of oral bisphosphonates, the most common side effects are oral erosions, gastric ulcer, esophagitis and esophageal stenosis. The adverse effects of intravenous bisphosphonates are similar, but moreover also include phlebitis, transient febricula, chills, pseudoinfluenza syndrome in the first two days of treatment, and renal failure when intravenous infusion is rapid (4).

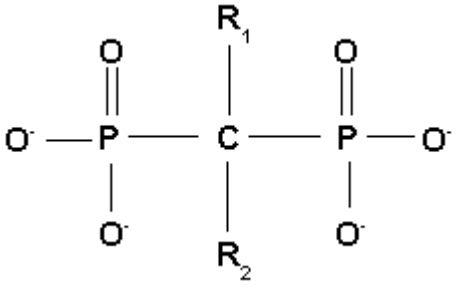

Fig. 1. Basic bisphosphonate chemical structure.

In recent years, the appearance of numerous cases of osteonecrosis (ON) of the maxillas of patients treated with BPPs has drawn considerable attention.

ON induced by bisphosphonates is characterized by the appearance of exposed mandibular or maxillary bone over a period of over 8 weeks in patients receiving or who have received BPPs without radiotherapy of the maxillofacial zone (5).

The diagnosis must be based on the clinical evidence, the radiological findings and the histological analysis. ON presents as an exposure of alveolar bone either spontaneously or secondary to invasive oral surgical procedures. Radiologically, ON can manifest as normal bone, while the histological findings can correspond to bone necrosis with bacterial colonization. A differential diagnosis must be established with bacterial osteomyelitis and osteoradionecrosis (5).

The aim of the present study is to establish the convenience of dental implant treatment in patients receiving bisphosphonates, and to define the key elements for evaluating the benefit-risk ratio in patients treated with bisphosphonates who require oral surgery.

Results

Estefania-Fresco et al. (6) conducted a review of the cases of ON associated to BPPs, published up until 2005, in which an increased appearance of ON was observed in women, and in particular in women over 55 years old. The nitrogenated BPPs developed for parenteral administration and of high potency (pamidronate and zoledronic acid) were the drugs most commonly associated with ON. However, cases were also reported with orally administered BPPs (alendronate and risedronate).

There have been descriptions of ON in patients receiving treatment with BPPs during long periods of time, and also in patients subjected to such therapy for only a few weeks. However, different authors have correlated timing

Table 1. Bisphosphonates marketed in Spain.

DRUG SUBSTANCE	BRAND NAME [1]	ADMINISTRATION
Alendronate [2]	Adrovance®, Alendrocare®, Bifoal®, Fosamax®, Fosavance®	Oral
Risedronate	Acrel®, Actonel®.	Oral
Etidronate	Difosfen® , Osteum®	Oral
Clodronate	Bonefos®.	Oral
Tiludronate	Skelid®	Oral
Ibandronate	Bondenza®, Bondronat®, Bonviva®	Oral / intravenous
Zolendronate	Aclasta®, Zometa®	Intravenous
Pamidronate [2]	Aredia®, Linoten®, Pamifos®.	Intravenous

1 Brand names marketed in Spain

2 In the case of alendronate and pamidronate, generic drugs are also available that include the international nonproprietary name (INN) of the drug substance in the marketed name

of the administration of BPPs to the risk of ON (7-10). The lesions documented have been both spontaneous and secondary to some type of dental treatment. Dental extraction was reported as the most frequent antecedent of ON in patients treated with BPPs via both the intravenous and oral routes. The possibility thus arises that oral surgery and DIs may be factors predisposing such patients to ON (6).

Many studies have addressed this subject (7-12). In the case of patients receiving intravenous BPPs, agreement is clear, and such treatment is regarded as an absolute contraindication to the placement of DIs. However, controversy arises in the case of treatment with oral BPPs.

The Summaries of Product Characteristics of drugs such as Zometa® and Aredia® suggest that dental professionals should adhere to the following protocol when dealing with patients treated with intravenous BPPs:

- Clinical oral examination of oncological patients programmed to start treatment with intravenous BPPs.
- Avoidance of invasive dental procedures during the period of treatment.
- Reporting of the appearance of any case of ON or of serious adverse effects to the company manufacturing the drug product, or to the competent health authorities.

Regarding the use of oral BPPs, and despite the documentation of occasional cases of ON, the United States Food and Drug Administration (FDA) does not advocate modification of the treatment plan in these patients. However, in the concomitant presence of other risk factors such as prolonged therapy, treatment with corticoids, etc., the patient must be warned of the possibility of ON in cases of surgery affecting periosteum or bone.

The Multiple Myeloma Research Foundation recommends that patients treated with intravenous BPPs should wear perfectly fitting dentures; that root canal treatment and fillings should be considered for the preservation of teeth, rather than the placement of DIs (which is considered to be contraindicated); and that the best treatment modality is prevention (9).

Scully, Madrid and Bagán (11) consider that there is no evidence to suggest that bone disorders are a contraindication to DIs, though there is evidence that intravenous BPP therapy is effectively contraindicated – since the prolonged use of BPPs can suppress bone remodeling capacity to the point where bone repair in response to trauma of any kind is practically abolished. Whenever possible, dental extractions must be avoided, as well as any kind of surgery oral—including the placement of DIs. Alternatively, such procedures should be performed before starting treatment with BPP. If surgery proves absolutely necessary while the patient is receiving BPP treatment, due information must be provided of the risks, and strictly aseptic techniques must be used, with atraumatic surgery and healing by first intention whenever possible.

Different authors consider that in patients receiving treatment with BPPs who must undergo surgery, prior withdrawal of these drugs may be advisable. Nevertheless, there is no evidence that the suppression of such treatment is able to prevent the appearance of jaws ON, since the half-life of BPPs is very long.

Osteoporosis and osteopenia are characterized by a reduction in bone mass leading to skeletal fragility and an increased risk of bone fractures. The incidence of these disorders, associated to the increase in life expectancy in the industrialized world and to a growing number of pregnancies in later stages in life, is increasing considerably (13).

The risk factors for osteoporosis can be divided into two groups: non-modifiable and modifiable. The non-modifiable factors include variables such as sex, age, early menopause, small body size or thinness, and racial and hereditary factors. The modifiable risk factors in turn include insufficient calcium ingestion, sedentarism or a lack of physical exercise, smoking and alcohol abuse. Many of these risk factors of osteoporosis are similar to those that influence the failed osteointegration of DIs (14,15).

The usual treatment for osteoporosis includes calcium and vitamin D supplements, BPPs (oral or intravenous), selective estrogen receptor modulators (SERMs; fundamentally raloxifen and tamoxifen), calcitonin, teriparatide and hormone replacement therapy (HRT). Of all these treatment options, only oral BPPs have been shown by randomized, long-term studies to reduce the risk of hip fractures (15).

Osteoporosis is not a major health risk, though its treatment is important for patient quality of life. The prevention and treatment of osteoporosis are important aspects to be taken into account in patients programmed for the placement of DIs (15,16).

The demand for DIs has increased enormously in recent years. A large percentage of the population requiring treatment with DIs are elderly persons over 65 years of age in which osteoporosis is very common (5,17). This increased demand for the placement of DIs in osteoporotic patients treated with BPPs makes necessary for dental professionals to improve their knowledge of this disease, its treatment, and the effects of BPPs upon DI surgery.

Histological studies in humans show that osteoporotic bone suffers a decrease in mechanical resistance, with alterations of the trabecular structure, a lessened mineral content, and an increase in crystallization and in the carbonate/phosphate ratio. The influence of these changes in relation to the success of DI surgery is not fully clear. A number of studies involving patients with osteoporosis have reported a discrete effect of this disease upon the success of DI. In this sense, Friberg et al. (18) placed 70 DIs in 14 osteoporotic patients, with a success rate of over 97% after three years in both the maxillary and in the mandibular region. This study suggests that osteoporosis in itself does not affect the outcome of DI surgery.

Minsk and Polson (19) analyzed a total of 450 maxillary and mandibular DIs placed in 116 postmenopausal women over 50 years of age. The objective of the study was to determine whether hormone replacement therapy reduces the risk of DI failure in postmenopausal women, though the results obtained did not support this hypothesis.

August et al. (20) found that mandibular DI failure occurs with equal frequency in postmenopausal and premenopausal patients. In contrast, the postmenopausal patients showed a greater percentage failure of maxillary implants.

Although these studies do not mention the degree of osteoporosis in the patients, osteoporosis was assumed to imply a high risk of DI failure.

Studies have been made in experimental models of periodontitis induced in animals treated with BPPs, with beneficial effects. Two studies showed low oral doses of these drugs to be beneficial, and defined an optimum dose for the treatment of periodontitis in monkeys (21,22). Likewise, different human studies have shown a positive effect of BPPs in the management of periodontal disease progression (23-25).

Chacon et al. (17) published an in vivo study in rabbits designed to explore the effects of the systemic administration of alendronate upon DI osteointegration, based on the torque values required to remove the implants. Identical titanium DIs were placed bilaterally in the femur and tibia of 20 white New Zealand rabbits, using a standardized surgical protocol. One week after surgery, 10 of the 20 rabbits received alendronate during 5 weeks. The torque values required to remove the DIs were determined using a Tohinichi 15-BTG torque Wrench®. The data analysis showed no statistically significant difference between the group treated with alendronate and the control group. The authors concluded that the oral administration of alendronate in rabbits exerts no significant effects upon the torque needed to remove the DIs six weeks after their placement in the tibia and femur. They also reported the absence of ON, though they pointed out that the surgical beds were not exposed to the oral cavity, and that the conditions were different to those found in clinical practice. The cases of ON in patients treated with oral BPPs have been documented in maxillary and mandibular bone. The effects of BPPs upon bone are probably location-dependent (maxillas), and are influenced by local factors (irritative and infectious).

Altundal et al. (27) conducted a study in albino rats with the purpose of determining the effects of alendronate upon the reabsorption of alveolar bone following tooth extraction. The maintenance of alveolar bone both in height and in volume following the loss of a tooth is essential for successful DI restoration surgery, and it is well known that alendronate is a potent inhibitor of bone reabsorption mediated by osteoclasts. The study concluded that in the alendronate treatment group, the reduction in alveolar bone volume (both buccal and lingual) was significantly lower than in the group treated with saline solution. Likewise, an important reduction was observed in the calcium levels in serum and urine, and the number of osteoclasts revealed marked suppression of bone reabsorption in the group treated with alendronate.

Denissen et al. (28) considered the possibility of applying BPPs locally to improve the quality, osteoconduction and repair of alveolar bone. In different studies, hydroxyapatite DIs have been used in an attempt to maintain alveolar bone following tooth extraction. However, the clinical results have shown that hydroxyapatite requires the introduction of a modification to increase its efficacy. The authors therefore combined the implants with a bone reabsorption inhibitor in the form of BPPs. This study contributes to improve our understanding of the properties of hydroxyapatite DIs as transporters or supports for BPPs, which in turn would act as bone modeling agents. The results obtained suggest that osteoconduction and the repair of alveolar bone around the hydroxyapatite-bisphosphonate complex prove normal.

Jeffcoat (16) carried out two controlled studies with the purpose of demonstrating the safety of oral BPPs in patients with periodontitis and in patients subjected to oral surgery. The first was a double-blind, placebo-controlled trial designed to demonstrate both the efficacy and the safety of oral alendronate at a dose of 70 mg weekly, administered for 11 weeks to patients with moderate or severe periodontal disease. A significant benefit was recorded in terms of alveolar bone height (ABH), defined as the distance between the amelocemental limit and the alveolar crest, in the patients treated with oral alendronate and belonging to the low mandibular bone mineral density group, compared with placebo. However, the difference was not significant in the group of patients with normal bone mineral density values. In no case was jaws ON seen during the two years of follow-up, and the number of teeth lost in the treated group was lower than in the placebo group.

The second study was a parallel-group controlled trial involving patients subjected to DI treatment who had received oral BPPs versus patients with DI who had not received BPPs. All the patients were postmenopausal women with osteoporosis. The patients of the treated group had received BPPs between 1-4 years prior to inclusion in the study. The analysis of the results showed that after three years of follow-up, a full 100% of the DIs placed in the BPP-treated patients were successful, compared with 99.2% of those in the control group – though the difference between the two groups was not statistically significant. The author concluded that the decision to introduce some medical or dental treatment, such as the prescription of oral BPPs or the placement of DIs, requires evaluation of the associated benefit-risk ratio.

Osteoporosis is a serious condition that undoubtedly re-

quires treatment in the absence of major risk factors. In the two studies commented above, no evidence was found to suggest that oral BPPs constitute a risk for alveolar bone ON versus placebo.

Other investigators (29,30) have reported that oral alendronate improves alveolar bone thickness and density at a dose of 70 mg a week. However, the duration of the studies was limited to 6 months; as a result, it cannot be confirmed that the effect persists over the long term.

Very recently, Grant et al. (12) have published the results of the review of 468 implants placed in 115 patients that had been treated with oral BPPs for different disorders. There were no cases of maxillary ON among the reviewed patients, though the authors concluded that there is sufficient evidence to suggest that all patients programmed for DI surgery should be questioned about BPP therapy – including the type of drug, the dose, and the duration of treatment.

Furthermore, it should be considered that all patients administered BPPs for more than three years with concomitant prednisone therapy are at an increased risk of developing ON. As a result, other noninvasive treatment options should be proposed in such patients (12)

Discussion

The placement of dental implants (DIs) induces a series of metabolic changes around the implants that should lead to the formation of bone intrinsically bound to the implant surface. If the bone surrounding the DI presents a medium to high concentration of bisphosphonates (BPPs), these turnover and remodeling processes will be hindered or prevented – with the risk of necrosis of the surrounding bone. The situation is different in the case of patients receiving BPPs who have already undergone DI surgery previously. In this context, it is before starting treatment with BPPs when all the dental procedures necessary for adequate oral health should be provided, with a view to avoiding problems at a later point in time (31).

Clinicians must be aware of the potential risk of osteonecrosis (ON) in patients treated with BPPs via the oral or intravenous route. All the articles consulted in the literature agree that in patients treated with intravenous BPPs, it is necessary to avoid any kind of invasive oral procedure (such as DI placement), unless such techniques are considered absolutely necessary.

If the patient is programmed to receive BPPs, the dental professional must carry out a correct oral exploration to ensure that all teeth amenable to extraction are dealt with before the start of BPP therapy (31). Regarding the placement of DIs in patients receiving intravenous therapy with these drugs, very few data are available to date. Moreover, the risk of postoperative maxillary ON following the cessation of intravenous therapy with BPPs remains uncertain. In recent years, as a result of the appearance of numerous reports of maxillary ON exhibiting a presumed time-dependent relationship, oncologists and pharmacists have begun to debate the time for which intravenous therapy with BPP must be maintained. In this sense, it seems that beyond a period of two years, the efficacy of such therapy does not improve, though the risk of adverse effects increases (10,13).

The principal discussion arises when BPP treatment is administered via the oral route. To date, the literature offers very little information on the influence of oral BPPs upon bone repair, and there are not many published cases of mandibular or maxillary ON in patients receiving treatment of this kind. The American Dental Association suggests no modification in the oral BPP treatment plan when contemplating invasive oral procedures – though if there are other risk factors such as the prolonged use of such drugs, concomitant estrogen or corticoid treatment, or advanced age, the patient must be informed of the potential complications. The number of patients receiving treatment with BPPs is increasing, and the duration of such treatment is also being prolonged. Dental professionals and oral surgeons therefore must be aware that there is a potential risk of ON with the prolonged use of BPP that in turn can be increased by the introduction of invasive procedures such as DI surgery. It would be interesting to conduct further controlled clinical studies to assess treatment with oral BPPs and the appearance of maxillary ON, with a view to establishing clearer guidelines for the treatment of these patients.

Current evidence suggests the avoidance of dental implant procedures in patients that have been receiving intravenous BPPs. In the case of administration via the oral route, caution is required – avoiding these procedures, or indicating them only when absolutely necessary.

References

1. Hwang D, Wang HL. Medical contraindications to implant therapy: part I: absolute contraindications. Implant Dent. 2006 Dec; 15(4):353-60.

2. Fleisch H. Bisphosphonates: mechanisms of action. Endocr Rev. 1998 Feb; 19(1):80-100.

3. Fleisch H. Development of bisphosphonates. Breast Cancer Res. 2002 ;4(1):30-4.

4. Ponte-Fernández N, Estefanía-Fresco R, Aguirre-Urizar JM. Bisphosphonates an oral pathology I. General and preventive aspects. Med Oral Patol Oral Cir Bucal. 2006 Aug 1; 11(6):E396-400.

5. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonates-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg. 2005 Nov; 63(11):1567-75.

6. Estefanía-Fresco R, Ponte-Fernández N, Aguirre-Urizar JM. Bisphosphonates and oral pathology II. Osteonecrosis of the jaws: review of the literature before 2005. Med Oral Patol Oral Cir Bucal. 2006 Nov 1; 11(6):456-61.

7. Bamias A, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: Incidence and risk factors. J Clin Oncol. 2005 Dec 1; 23(34):8580-7.

8. Dimopoulos MA, Kastritis E, Anagnostopoulos A, Melakopoulos I, Gika D, Moulopoulos LA et al. Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of in-

crease risk after treatment with zoledronic acid. Haematologica. 2006 Jul;91(7):968-71.
9. Durie BG, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. N Engl J Med. 2005 Jul 7;353(1):99-102.
10. Ruggiero SL, Mehrotra B, Rosenber TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg. 2004 May;62(5):527-34.
11. Scully C, Madrid C, Bagan J. Dental endosseous implants in patients on bisphosphonate therapy. Implant Dent. 2006 Sep;15(3):212-8.
12. Grant BT, Amenedo C, Freeman K, Kraut RA. Outcomes of placing dental implants in patients taking oral bisphosphonates: a review of 115 cases. J Oral Maxillofac Surg. 2008 Feb ;66(2)223-30.
13. Cosman F, Borges JL, Curiel MD. Clinical evaluation of novel bisphosphonate dosing regimens in osteoporosis: the role of comparative studies and implications for future studies. Clin Ther. 2007 Jun;29(6):1116-27.
14. Jeffcoat M. The assocation between osteoporosis and oral bone loss. J Periodontol 2005. Nov;76(11 Suppl):2125-32.
15. Rosen CJ, Hochberg M, Bonnick SL, McClung M, Miller P, Broy S et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. J Bone Miner Res. 2005 Jan;20(1):141-51.
16. Jeffcoat MK. Safety of oral bisphosphonates: controlled studies on alveolar bone. Int J Oral Maxillofac Implants. 2006 May-Jun;21(3):349-53.
17. Chacon GE, Stine EA, Larsen PE, Beck FM, McGlumphy EA. Effect of alendronate on endosseous implant integration: an in vivo study in rabbits. J Oral Maxillofac Surg. 2006 Jul;64(7):1005-9.
18. Friberg B, Ekestubbe A, Mellström D, Sennerby L. Brånemark implants and osteoporosis: A clinical exploratory study. Clin Implant Dent Relat Res. 2001;3(1):50-6.
19. Minsk L, Polson AM. Dental implant outcomes in post-menopausal women undergoing hormone replacement. Compend Contin Educ Dent. 1998 Sep;19(9):859-62.
20. August M, Chung K, Chang Y, Glowacki J. Influence of estrogen status on endosseus implant osseointegration. J Oral Maxillofac Surg. 2001 Nov;59(11):1285-9.
21. Weinreb M, Quartuccio H, Seedor JG , Aufdemorte TB, Brunsvold M, Chaves E et al. Histomorphometrical analysis of the effects of the bisphosphonate alendronate on bone loss caused by experimental periodontitis in monkeys. J Periodontol Res. 1994 Jan;29(1):35-40.
22. Brunsvold MA, Chaves ES, Kornman KS, Aufdemorte TB, Wood R. Effects of a bisphosphonate on experimental periodontitis in monkeys. J Periodontol. 1992 Oct;63(10):825-30.
23. Takaishi Y, Ikeo T, Miki T, Nishizawa Y, Morii H. Suppression of alveolar bone resorption by etidronate treatment for periodontal disease: 4 to 5-year follow-up of four patients. J Int Med Res. 2003 Nov-Dec;31(6):575-84.
24. Takaishi Y. Treatment of periodontal disease, prevention and bisphosphonate. Clin Calcium. 2003 Feb;13(2):173-6.
25. El-Shinnawi UM, El-Tantawy SI. The effect of alendronate sodium on alveolar bone loss in periodontitis (clinical trial). J Int Acad Periodontol. 2003 Jan;5(1):5-10.
26. Kajiwara H, Yamaza T, Yoshinari M, Goto T, Iyama S, Atsuta I et al. The bisphosphonate pamidronate on the surface of titanium stimulates bone formation around tibial implants in rats. Biomaterials. 2005 Feb;26(6):581-7.
27. Altundal H, Güvener O. The effect of alendronate on resorption of the alveolar bone following tooth extraction. Int J Oral Maxillofac Surg. 2004 Apr;33(3):286-93.
28. Denissen H, Montanari C, Martinetti R, van Lingen A, van den Hoff A. Alveolar bone response to submerged bisphosphonate-complexed hydroxyapatite implants. J Periodontol. 2000 Feb;71(2):279-86.
29. Rocha ML, Malacara JM, Sánchez-Marin FJ, Vazquez de la Torre CJ, Fajardo ME. Effect of alendronate on periodontal disease in postmenopausal women: A randomized placebo-controlled trial. J Periodontol. 2004 Dec;75(12):1579-85.
30. Rizzoli R, Greenspan SL, Bone G 3rd, Schnitzer TJ, Watts NB, Adami S, et al. Two-year results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis. J Bone Miner Res. 2002 Nov;17(11):1988-96.
31. Bagán J, Blade J, Cozar JM, Constela M, García Sanz R, Gómez Veiga F et al. Recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw (ONJ) in cancer patients treated with bisphosphonates. Med Oral Patol Oral Cir Bucal. 2007 Aug 1;12(4):336-40.
32. Wang HL, Weber D, McCauley LK. Effect of long-term oral bisphosphonates on implant wound healing: literature review and a case report. J Periodontol. 2007 mar;78(3):373-6.
33. Berardi D, Carlesi T, Rossi F, Calderini M, Volpi R, Perfetti G. Potential applications of bisphosphonates in dental surgical implants. Int J Immunopathol Pharmacol. 2007 Jul-Sep;20(3):455-65.