

**Expert Panel Recommendations:
Dental Management of Patients on Oral
Bisphosphonate Therapy**

Report of the Council on Scientific Affairs

*American Dental Association
June, 2006*

ACKNOWLEDGEMENTS

Members of the Expert Panel

Beatrice J Edwards, MD, FACP
Department of Medicine and Orthopaedic Surgery. Feinberg School of Medicine
Northwestern University

John W. Hellstein, DDS, MS
Department of Oral Pathology, Radiology/Medicine
University of Iowa

Peter L. Jacobsen, PhD, DDS
Department of Pathology and Medicine
Arthur A. Dugoni School of Dentistry
University of the Pacific

Steven Kaltman, DMD, MD
Department of Oral Surgery
Nova Southeastern University College of Dental Medicine

Angelo Mariotti, DDS, PhD
Department of Periodontology
Ohio State University College of Dentistry

Cesar A. Migliorati, DDS, MS, PhD
Department of Diagnostic Sciences – Oral Medicine Nova Southeastern
University College of Dental Medicine

1 Introduction

1.1 Background

Reports of osteonecrosis (also called osteochemonecrosis and bisphosphonate-associated osteonecrosis) of the jaw associated with the use of the bisphosphonates, zoledronic acid (Zometa) and pamidronate (Aredia), began to surface in 2003.^{1,2} Zoledronic acid and pamidronate are intravenous (i.v.) bisphosphonates used to reduce bone pain, hypercalcemia of malignancy and skeletal complications in patients with multiple myeloma, breast, lung and other cancers and Paget's disease of bone. The majority of reported cases of bisphosphonate-associated osteonecrosis of the jaw (BON) have been diagnosed after dental procedures such as tooth extraction. Less commonly BON appears to occur spontaneously in patients taking these drugs.³

As of early 2006, cases of BON had also been reported in individuals taking orally administered nitrogen-containing bisphosphonates, used for the treatment of osteoporosis.³⁻⁵ To date, the total number of reported cases of BON associated with alendronate (Fosamax) is approximately 170 worldwide according to Merck and Co., Inc. (C. Arsvær, oral communication, March 2006), approximately 20 associated with risedronate (Actonel) according to Procter and Gamble (M. Schorr, oral communication, March 2006) and approximately 1 with ibandronate (Boniva) according to Roche (J. Travis, oral communication, March 2006). For alendronate (the most commonly prescribed oral bisphosphonate), this translates into a spontaneous BON incidence (or rate at which new cases occur) of approximately 0.7 cases per one hundred thousand person-years exposure. To date, a true cause-and-effect relationship has not been established. The table below lists all oral and i.v. bisphosphonates currently on the market in the U.S.

Orally administered bisphosphonates

Brand Name	Manufacturer	Generic Name
Actonel	Procter & Gamble Pharmaceuticals	risedronate
Boniva	Roche Laboratories	ibandronate
Fosamax	Merck & Co.	alendronate
Fosamax Plus D	Merck & Co.	alendronate
Skelid	Sanofi Pharmaceuticals	tiludronate
Didronel	Procter & Gamble Pharmaceuticals	etidronate

Intravenously administered bisphosphonates

Brand Name	Manufacturer	Generic Name
Aredia	Novartis	pamidronate
Zometa	Novartis	zoledronic acid
Bonefos	Schering AG	clodronate

Limited data on reported cases has not allowed for identification of other risk factors for developing this complication. Extrapolating from cases described in oncology patients on i.v. bisphosphonate therapy, it might be possible that using oral glucocorticoids for chronic conditions^{5,6} and estrogen⁶ may increase the risk for BON. In cancer patients receiving i.v. bisphosphonate therapy, the median time from starting therapy to developing BON was 25 months.⁷ In addition, being older (over 65 years) also may increase risk.^{7,8} The most common dental comorbidity in these patients is, reportedly, clinically and radiographically apparent periodontitis.⁵

In light of the uncertainty surrounding the incidence of BON and concomitant risk factors, dentists have questioned how to manage patients on oral bisphosphonate therapy. This expert panel was assembled to develop guidance for dentists treating these patients.

1.2 Incorporating expert panel recommendations into clinical decision making

The dentist, knowing the patient's health history and vulnerability to oral disease, is in the best position to make treatment recommendations in the interest of each patient. For this reason, *expert panel recommendations are intended to provide guidance, and are not a standard of care, requirements or regulations based on scientific evidence.* The recommendations are a resource for dentists to use in their practice, in addition to the dentist's own professional judgment, the information available in the dental and medical literature, and information from the patient's treating physician. The recommendations must be balanced with the practitioner's professional judgment and the individual patient's preferences and needs.

Through the development of expert panel recommendations, areas for which there is little evidence were identified. In order to address these gaps in the evidence, topics for future research are included in this document.

1.3 Expert panel

Panelists were selected based on their expertise in the relevant subject matter and on their respective dental or medical specialty. Panelists were required to sign a disclosure stating that neither the panelist nor his or her spouse or dependent children had a significant financial interest that would reasonably appear to affect the development of these recommendations.

1.4 Rationale for development of expert panel recommendations on managing patients on oral bisphosphonate therapy

A precautionary letter issued by Novartis and the FDA concerning osteonecrosis of the jaw observed in cancer patients receiving treatment with i.v. bisphosphonates,⁹ raised concerns about dental treatment of patients taking oral bisphosphonates for osteopenia, osteoporosis and Paget's disease of bone. It is important to understand that based on the information currently available, the risk for developing BON is much higher for cancer patients on i.v. bisphosphonate therapy than the risk for patients on oral bisphosphonate therapy.

The risk factors for BON have not been identified, however, the bone antiresorptive potency of the drug utilized may play an important role. It is important to consider that less than 1% of the dose of a bisphosphonate taken orally is absorbed by the gastrointestinal tract, whereas, over 50% of the dose of a bisphosphonate administered intravenously is bio-available for incorporation into the bone matrix.^{10,11} This may account for the higher number of cases of BON in patients taking the i.v. formulation.

Recommendations for the prevention, diagnosis and treatment of BON in cancer patients on i.v. bisphosphonate therapy were developed by an expert panel in 2004.¹² In addition, the American Academy of Oral Medicine published a position paper on managing the care of patients with BON and the American Academy of Oral and Maxillofacial Pathology has also reviewed and addressed issues associated with BON.^{13,14} Readers should refer to these documents for recommendations on the management of cancer patients on i.v. bisphosphonate therapy and patients with BON.

Even though the risk for developing BON is very low in individuals taking oral bisphosphonates, currently, millions of patients take these drugs (total U.S. prescriptions for Fosamax between May 2003 and April 2004 was 22 million¹⁵). Because these individuals taking oral bisphosphonates often need routine dental care and no recommendations exist on the dental treatment of these patients, these recommendations were developed to assist dentists in their management. These recommendations do not address treatment of patients with BON. Readers should refer to the documents referenced above for guidance on treating patients with BON.

1.5 Osteoporosis and bisphosphonate therapy

Osteoporosis is a major cause of morbidity, functional dependence and institutionalization in older Americans. One out of every two women will sustain an osteoporosis related fracture (such as wrist, spine or hip) in their lifetime. An estimated 10 million Americans over the age of 50 have osteoporosis, while another 34 million are at risk. As the population ages, the number of hip fractures in the United States could triple by 2020.¹⁶

Bisphosphonates are analogs of inorganic pyrophosphate and are used to treat bone loss associated with osteoporosis and Paget's disease of bone. Bisphosphonates inhibit osteoclast differentiation, and induce osteoclast apoptosis¹⁷ resulting in an imbalance in the bone remodeling process. They, thereby, promote an increase in bone trabecular thickness and bone mass.¹⁷

Bisphosphonates carry the potential for oversuppression of bone turnover that may impair some of the biomechanical and reparative properties of bone. In experimental animals, alendronate has been shown to inhibit repair of normal microdamage, which in turn leads to accumulation of microdamage.¹⁸⁻²⁰ This results in a reduction in bone toughness (the ability to sustain deformity without breaking), without a reduction in bone strength. Bone biopsies of patients on risedronate show normal mineralization.^{21,22} Cases of severe suppression of bone turnover have been described in patients on alendronate.⁶ These results are in contrast to large randomized clinical trials and 7 to 10 year safety studies with risedronate and alendronate. However, it is not uncommon for rare adverse drug reactions to be uncovered during post marketing surveillance.

1.6 Clinical presentation of BON

The typical clinical presentation of BON includes pain, soft-tissue swelling and infection, loosening of teeth, drainage, and exposed bone.¹³ Symptoms may occur spontaneously in the bone; or, more commonly, at the site of previous tooth extraction. In some cases, patients seek dental care complaining of pain that may mimic a dental problem. Infection may or may not be present. The "dental" problem does not respond to routine dental therapy and there is no clinically visible osteonecrosis.

However, BON may also remain asymptomatic for weeks or months, and may only become evident after the finding of exposed bone in the jaw during routine examination. In some cases, the symptoms of BON can mimic dental or periodontal disease. Routine dental and periodontal treatment will not resolve these symptoms. In this case, if the patient is on bisphosphonate therapy, BON must be considered as a possible diagnosis, even in the absence of exposed bone. If BON is suspected, dentists are encouraged to contact the FDA's MedWatch program at www.fda.gov/MedWatch/report.htm or 800-FDA-1088.

2 Panel conclusions

Based on a literature review and on expert opinion, the panel made the following conclusions related to oral bisphosphonate therapy.

Although recommendations for the dental management of patients taking i.v. bisphosphonates have been developed,¹² no specific guidelines exist for the management of patients taking oral bisphosphonates.

The risk for developing BON appears to be very low, and is estimated to occur in approximately 0.7 per 100,000 person-years exposure to alendronate (C. Arsvær, oral communication, March 2006). Other nitrogen containing oral bisphosphonates are expected to have a similar risk profile.

BON can occur spontaneously, but is more commonly associated with dental procedures that traumatize bone, such as dental extractions.³⁻⁵

Older age (over 65 years), oral glucocorticoid use for chronic conditions, periodontitis and prolonged use of bisphosphonates have been associated with an increased risk for BON*.⁵⁻⁷

Cases of bilateral and multifocal BON have been reported in cancer patients.^{7,8}

3 Expert panel clinical recommendations for managing patients on oral bisphosphonate therapy

These panel recommendations focus on conservative surgical procedures, proper sterile technique, appropriate use of oral disinfectants and the principals of effective antibiotic therapy. There is currently no data from clinical trials evaluating dental management of patients on oral bisphosphonate therapy, and therefore, these recommendations are based on expert opinion only. Dentists are encouraged to check www.ada.org/prof/resources/topics/osteonecrosis.asp before treating patients on oral bisphosphonates as these recommendations will be updated as new information becomes available.

3.1 General recommendations

As with all dental patients, routine dental exams are recommended.

A comprehensive oral evaluation should be carried out on all patients about to begin therapy with oral bisphosphonates (or as soon as possible after beginning therapy).

Inform the patient taking oral bisphosphonates that:

- there is a very low risk (estimated at 0.7 cases per 100,000 person-years exposure) of developing BON
- there are ways to minimize the risk, but not to eliminate the already low risk
- the consensus is that good oral hygiene along with regular dental care is the best way to lower risk
- there are no diagnostic techniques to identify those at increased risk for developing BON

* See discussion on page 4.

The patient should also be informed of the dental treatment needed, alternative treatments, how any treatment relates to the risk of BON, other risks associated with various treatment options, and the risk of foregoing treatment, even temporarily. The patient should be encouraged to consult with his/her treating physician about any health risks.

BON can occur spontaneously, due to dental disease or secondary to dental therapy. Therefore, patients taking oral bisphosphonates should be instructed to contact the dentist if any problem develops in the oral cavity.

Routine dental treatment should, generally, not be modified solely on the basis of oral bisphosphonate therapy. However, patients with possible risk factors for BON use may benefit from assessment by an expert in metabolic bone diseases. These risk factors may include concomitant use of estrogen or glucocorticoids, older age (over 65 years) and prolonged use of bisphosphonates. See National Osteoporosis Foundation (www.nof.org) or American Society of Bone and Mineral Research (www.asbmr.org) directories.

Before any invasive procedure that involves manipulation of the bone or periosteum, patients should again be informed about the implications of oral bisphosphonate therapy and the risk of BON. The patient should understand that at this time the risk for developing osteonecrosis of the jaw is considered very small and that the vast majority of patients taking an oral bisphosphonate do not develop any oral complication.

When the treatment plan dictates that the medullary bone and/or periosteum is going to be involved in multiple sextants, treat one sextant or tooth first, if dentally possible. At that point, allow for a 2 month disease free follow-up covering with antimicrobials,* before other sextants are treated with similar therapy. Given success at 2 months (or longer if the area remains inflamed, irritated or erythematous) with the first sextant, treatment may accelerate to a more normal multi-sextant treatment and follow-up schedule.

Be aware that periapical pathoses, sinus tracks, purulent periodontal pockets, severe periodontitis and active abscesses already involve the medullary bone and may cause osteonecrosis by themselves. These areas should be treated immediately, because the medullary bone is already involved in the pathologic process. Some dental pathoses may not be emergent and the trial sextant approach may be applicable. The sextant by sextant approach does not apply to emergency cases even if there is involvement of multiple quadrants.

* (Note: Typically, chlorhexidine is used two times per day for two months post surgery. Based on the experience of the authors, the majority of cases of BON present within 2 months of a dental procedure. Therefore, the recommendation to wait 2 months before treating multiple sextants, when possible, is a best estimate based on current knowledge.)

Patients should have all their questions answered to the extent possible. The dentist should consider documenting the discussion of risks, benefits and treatment options with the patient (see discussion above) and obtaining the patient's written acknowledgement of that discussion and consent for the chosen course of treatment. The dentist should retain in his/her file the acknowledgement and consent for the treatment.

Once general recommendations are discussed with the patient taking an oral bisphosphonate, there may be specific clinical questions regarding specialty treatment, as follows.

3.2 Management of periodontal diseases

Despite the untoward effects of bisphosphonate therapy, the periodontal literature has suggested that these drugs may be beneficial in modulating host response for management of periodontal diseases.^{23,24} As such, patients with destructive periodontal diseases who are on oral bisphosphonate therapy should receive appropriate forms of non-surgical therapy which should be combined with a prolonged phase of initial therapy for observation. If the disease does not resolve, surgical treatment should be aimed primarily at obtaining access to root surfaces with modest bone recontouring being considered when necessary. Without further data, guided bone regeneration or guided tissue regeneration should be judiciously considered, in view of the fact that bisphosphonates have been shown to decrease the vascularity of tissues,²⁵ which may have a negative affect on grafted sites.

Patients without periodontal disease should receive accepted mechanical and pharmaceutical methods to prevent periodontal disease, and should be monitored on a regular basis as determined by the patient's dentist.

3.3 Implant placement and maintenance

In recent years, rehabilitation of patients with dental implants for edentulous areas or when tooth prognosis was considered hopeless, has been a successful method to manage patients. At this time, there is limited data regarding the effects of implant placement in patients taking bisphosphonates. Therefore, treatment plans in patients taking bisphosphonates should be carefully considered since implant placement requires the preparation of the osteotomy site. The patient may be at increased risk for BON when extensive implant placement or guided bone regeneration to augment the deficient alveolar ridge prior to implant placement is necessary. Prior to implant placement, the dentist and the patient should discuss the risks, benefits and treatment alternatives, which may include but are not limited to periodontal, endodontic or non-implant prosthetic treatments. As discussed above, this discussion should be documented and the patient's written acknowledgement of that discussion and consent for the chosen course of treatment the patient's consent should be obtained.

Maintenance of implants should follow accepted mechanical and pharmaceutical methods to prevent peri-implantitis, with regular monitoring of the patient.

Appropriate forms of non-surgical therapy combined with a prolonged phase of initial therapy should be considered for patients with peri-implantitis. If the disease does not resolve, surgical revision of soft tissues around the implant(s) may be appropriate; and, when necessary, modest bone recontouring may be considered.

3.4 Oral and maxillofacial surgery

When dental and/or periodontal diseases treatment has failed, surgical intervention may be the only alternative. Patients on oral bisphosphonates who are undergoing invasive surgical procedures should be informed of the risk, although small, of developing BON. Alternative treatment plans consisting of endodontics instead of extraction, bridges and partial dentures versus implant reconstruction should be discussed with the patient. (Please see the discussions above regarding discussion and documentation of risks, benefits and alternative treatments.)

If extractions or bone surgery are necessary, conservative surgical technique with primary tissue closure should be considered, when possible. In addition, immediately prior to and following surgical procedures involving bone, the patient should gently rinse with a chlorhexidine containing rinse. Typically, chlorhexidine is used two times per day for two months post surgery. This can be extended based on how the patient is healing.

Prophylactic antibiotics may be utilized during the healing/wound closure phase, for procedures that involve extensive manipulation of the bone (e.g. extractions, periodontal recontouring, sinus lifts etc.) but is not mandatory nor even recommended. Use of prophylactic antibiotics depends on the clinician's level of concern relative to the individual patient and their specific situation including concomitant risk factors (i.e. prolonged use of oral bisphosphonates, older age, concomitant use of estrogen or glucocorticoids^{*}). In some situations, prophylactic antibiotics may be instituted a day or two prior to the procedure.

The antibiotics listed below may appropriately be used if the patient has unexpected pain, purulence or active sequestration following the procedure. It must be reiterated that no controlled studies in patients with BON are available to support any of the above recommendations and that they are derived from expert opinion based on oral infections of bone in other dental situations.

* See discussion on page 4.

Patient Type	Suggested Drug	Oral Regimen
Patients not allergic to penicillin	Amoxicillin	500 mg 3X per day 14 days
	May be combined with* Metronidazole	250 mg 3X per day 14 days
Patients allergic to penicillin	Clindamycin	300 mg 3X per day 14 days
	Or Azithromycin	250 mg 1X per day 10 days

*Amoxicillin may be combined with Metronidazole for maximum coverage of periodontal microflora

3.5 Endodontics

Endodontic treatment takes preference over surgical manipulation, if a tooth is salvageable. Routine endodontic technique should be used. Manipulation beyond the apex is not recommended.

Para-endodontic surgical procedures should be guided by the same recommendation as for any oral and maxillofacial surgical procedure described above.

3.6 Restorative dentistry and prosthodontics

All routine restorative procedures can be carried out. There is no evidence that mal-occlusion or masticatory forces increase the risk for BON.

4 Recommendation for research

Based on the current literature on BON pathophysiology and based on the lack of knowledge on the risk factors for the development of BON, the panel recommends that research be conducted on the following topics:

4.1 Basic research

Basic research should aim to discover the molecular mechanisms that lead to the formation of BON, and the role of bisphosphonates in the alteration of bone remodeling and its effect on BON. Research on the pharmacogenetics that place patients at risk for BON may be helpful for the detection of patients at increased risk.

4.2 Clinical research

Active pharmacovigilance of patients currently on bisphosphonates as BON is a relatively rare complication and randomized clinical trials may not have the power or the necessary duration to detect rare adverse drug reactions.

Outcomes of routine dental therapy in patients taking oral bisphosphonates.

Outcomes of placing dental implants in patients taking oral bisphosphonates.

Studies relevant to managing patients with BON.

Development of a national registry to allow systematic study of cases of BON and the effect of co-morbidities and concurrent therapies.

Collaboration with bone specialists in order to establish whether BON is a localized or systemic condition. Bone biopsy and histomorphometric assessment will provide insights into the underlying bone pathology.

Assessment of the effect of discontinuation of bisphosphonate therapy and its relevance to healing.

5 References

1. [Marx RE](#). Pamidronate (Aredia) and zoledronic acid (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003;61:1115-7.
2. [Migliorati CA](#). Bisphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol* 2003;21:4253-4.
3. [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.
4. [Migliorati CA](#), [Schubert MM](#), [Peterson DE](#), [Seneda LM](#). Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy. *Cancer* 2005 Jul 1;104(1):83-93.
5. [Marx RE](#), [Sawatari Y](#), [Fortin M](#), [Broumand V](#). Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg* 2005;63:1567-75.
6. [Odvina CV](#), [Zerwekh JE](#), [Rao DS](#), [Maalouf N](#), [Gottschalk FA](#), [Pak CY](#). Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab* 2005;90:1294-301.
7. [Bagan JV](#), [Jimenez Y](#), [Murillo J](#), [Hernandez S](#), [Poveda R](#), [Sanchis JM](#), [Diaz JM](#), [Scully C](#). Jaw osteonecrosis associated with bisphosphonates: Multiple exposed areas and its relationship to teeth extractions. Study of 20 cases. *Oral Oncol* 2006;42:327-9.
8. [Markiewicz MR](#), [Margarone JE](#), [Campbell JH](#), [Aguirre A](#). Bisphosphonate-associated osteonecrosis of the jaws: A review of current knowledge. *JADA* 2005;136:1669-74.

9. U.S. Food and Drug Administration. MedWatch 2005 Safety Alerts. (<http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#zometa2>, accessed March 27, 2006).
10. [Ezra A, Golomb G](#). Administration routes and delivery systems of bisphosphonates for the treatment of bone resorption. *Adv Drug Deliv Rev*. 2000;42:175-95.
11. [Berenson JR, Rosen L, Vescio R, Lau HS, Woo M, Sioufi A, Kowalski MO, Knight RD, Seaman JJ](#). Pharmacokinetics of pamidronate disodium in patients with cancer with normal or impaired renal function. *J Clin Pharmacol*. 1997;37:285-90.
12. [Ruggiero S, Gralow J, Marx RE, Hoff AO, Schubert MM, Huryn JM, Toth B, Damato K, Valero V](#). Practical Guidelines for the Prevention, Diagnosis, and Treatment of Osteonecrosis of the Jaw in Patients With Cancer. *J Oncol Prac* 2006;2:7-14.
13. [Migliorati CA, Casiglia J, Epstein J, Jacobsen PL, Siegel MA, Woo S-K](#). Managing the care of patients with bisphosphonate-associated osteonecrosis. *JADA* 2005;136:1658-68.
14. [Woo SB, Hellstein JW, Kalmar J](#). Bisphosphonates and Osteonecrosis of the Jaws. *Ann Intern Med* 2006;144:753-61.
15. Sachs HC. One Year Post Exclusivity Adverse Event Review: Alendronate. Center for Drug Evaluation and Research, Food and Drug Administration. http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4067s1_07_Sachs%20%20Final.pdf (Accessed February 27, 2006)
16. U.S. Department of Health and Human Services. Bone Health and Osteoporosis: A Report of the Surgeon General (2004) <http://www.surgeongeneral.gov/library/bonehealth/content.html> (accessed March 27, 2006).
17. [Sato M, Grasser W, Endo N, Akins R, Simmons H, Thompson DD, Golub E, Rodan GA](#). Bisphosphonate action: alendronate localization in rat bone and effects on osteoblast ultrastructure. *J Clin Invest* 1991;88:2095-105.
18. [Li J, Mashiba T, and Burr DB](#). Bisphosphonate treatment suppresses not only stochastic remodeling but also targeted repair of microdamage. *Calcif Tissue Int* 2001;69:281-6.
19. [Mashiba T, Turner CH, Hirano T, Forwood MR, Johnston CC, Burr DB](#). Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles. *Bone* 2001;28:524-31.
20. [Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB](#). Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces biomechanical properties in the dog rib. *J Bone and Miner Res* 2000;15:613-20.
21. [Eriksen EF, Melsen F, Sod E, Barton I, Chines A](#). Effects of long term risedronate on bone quality and bone turnover in women with postmenopausal osteoporosis. *Bone* 2002;31(5):620-5.

22. [Ste-Marie LG, Sod E, Johnson T, Chines A](#). Five years treatment with risedronate and its effects on bone safety in women with postmenopausal osteoporosis. *Calcif Tissue Int* 2004;75:469-476.
23. [Rocha ML, Malacara JM, Sanchez-Marin FJ, Vazquez de la Torre CJ, Fajardo ME](#). Effects of alendronate on periodontal disease in postmenopausal women: a randomized placebo-controlled trial. *J Periodontol* 75:1579-1585, 2004.
24. [Lane N, Armitage GC, Loomer P, Hsieh S, Majumdar S, Wang HY, Jeffcoat M, Munoz T](#). Bisphosphonate therapy improves the outcome of conventional periodontal treatment: results of a 12-month, randomized, placebo-controlled study. *J Periodontol*. 76:1113-1122, 2005.
25. [Fournier P, Boissier S, Filleur S, Guglielmi J, Cabon F, Colombel M, Clezardin P](#). Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. *Cancer Res* 2002;62:6558-44.