Dental management of patients receiving oral bisphosphonate therapy

Expert panel recommendations

American Dental Association Council on Scientific Affairss

ABSTRACT

Background. In light of the uncertainty surrounding the incidence of bisphosphonate-associated osteonecrosis of the jaw (BON) and concomitant risk factors, dentists have questioned how to manage the care of patients receiving oral bisphosphonate therapy. Expert panelists were selected by the American Dental Association Council on Scientific Affairs on the basis of their expertise in the relevant subject matter and on their respective dental or medical specialties, and the panel was tasked with developing guidance for dentists treating these patients.

Methods. There are no data from clinical trials evaluating dental management of the care of patients receiving oral bisphosphonate therapy and, therefore, these recommendations are based on a thorough review of the available literature relating to bisphosphonate use and osteonecrosis of the jaw. After reviewing the literature, the panel developed these recommendations based on their expert opinion.

Results. These panel recommendations focus on conservative surgical procedures, proper sterile technique, appropriate use of oral disinfectants and the principles of effective antibiotic therapy.

Conclusions. 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.

Key Words. Bisphosphonates; osteonecrosis; osteochemonecrosis; bone pathology; bisphosphonate-associated osteonecrosis (BON); jaw.
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Background. Reports of osteonecrosis (also called "osteochemonecrosis" and "bisphosphonate-associated osteonecrosis") of the jaw associated with the use of the bisphosphonates zoledronic acid (Zometa, Novartis, East Hanover, N.J.) and pamidronate (Aredia, Novartis), began to surface in 2003.[1,2] Zoledronic acid and pamidronate are intravenous (IV) 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 (BON) of the jaw 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 also had been reported in individuals taking orally administered nitrogen-containing bisphosphonates, used for the treatment of osteoporosis.[3-5] The total number of

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reported cases of possible BON in people taking alendronate (Fosamax, Merck & Co., Whitehouse Station, N.J.) is approximately 170 worldwide, according to Merck & Co. (C. Arsever, oral communication, March 2006); approximately 12 in people taking risedronate (Actonel), according to Procter & Gamble Pharmaceuticals, Cincinnati (M. Schorr, oral communication, March 2006); and approximately one in a person taking ibandronate (Boniva, Roche Pharmaceuticals, Basel, Switzerland), 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 between osteonecrosis of the jaw and bisphosphonate use has not been established. Table 1 lists all oral and IV bisphosphonates on the market in the United States.

TABLE 1

Bisphosphonates on the market in the United States.

BRAND NAME	MANUFACTURER	GENERIC NAME
Orally Administered		
Actonel	Procter & Gamble Pharmaceuticals, Cincinnati/sanofi-aventis Group, New York	Risedronate
Boniva	Roche Pharmaceuticals, Basel, Switzerland/ GlaxoSmithKline, Philadelphia	Ibandronate
Didronel	Procter & Gamble Pharmaceuticals	Etidronate
Fosamax	Merck & Co., Whitehouse Station, N.J.	Alendronate
Fosamax Plus D	Merck & Co.	Alendronate
Skelid	sanofi-aventis Group	Tiludronate
Intravenously Administered		
Aredia	Novartis, East Hanover, N.J.	Pamidronate
Bonefos	Schering AG, Montville, N.J.	Clodronate
Zometa	Novartis	Zoledronic acid

The limited data on reported cases have not allowed for identification of other risk factors for developing this complication. Extrapolating from cases described in oncology patients receiving IV bisphosphonate therapy, it might be possible that using oral glucocorticoids for chronic conditions[5,6] and estrogen[6] may increase the risk of developing BON. In cancer patients receiving IV 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 the risk.[7,8] The most common dental comorbidity in these patients reportedly is 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 the care of patients receiving oral bisphosphonate therapy. The American Dental Association Council on Scientific Affairs assembled an expert panel to develop guidance for dentists treating these patients.

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. To address these gaps in the evidence, topics for future research are included in this document.

Expert panel. Panelists were selected on the basis of 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.

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Rationale for development of expert panel recommendations on managing patients receiving oral bisphosphonate therapy. A precautionary letter issued by Novartis and the FDA concerning osteonecrosis of the jaw observed in cancer patients receiving treatment with IV 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 of developing BON is much higher for cancer patients receiving IV bisphosphonate therapy than it is for patients receiving 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 percent of the dose of a bisphosphonate taken orally is absorbed by the gastrointestinal tract, whereas more than 50 percent of the dose of a bisphosphonate administered intravenously is bioavailable for incorporation into the bone matrix.[10,11] This may account for the higher number of cases of BON in patients taking the IV formulation.

Recommendations for the prevention, diagnosis and treatment of BON in cancer patients receiving IV bisphosphonate therapy were developed by an expert panel assembled by Novartis in 2004.[12] In addition, the American Academy of Oral Medicine[13] published a position paper on managing the care of patients with BON and the American Academy of Oral and Maxillofacial Pathology also reviewed and addressed issues associated with BON.[14] Readers should refer to these documents for recommendations on the management of cancer patients receiving IV bisphosphonate therapy and patients with BON.

Even though the risk of developing BON is very low in individuals taking oral bisphosphonates, millions of patients take these drugs (total U.S. prescriptions for Fosamax between May 2003 and April 2004 were 22 million[15]). Because these individuals taking oral bisphosphonates often need routine dental care and no recommendations exist regarding 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.

Osteoporosis and bisphosphonate therapy. Osteoporosis is a major cause of morbidity, functional dependence and institutionalization in older Americans. One of every two women will sustain an osteoporosis-related fracture (in locations such as the wrist, the spine or the hip) in her lifetime. More than 10 million Americans older than 50 years 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 apoptosis,[17] resulting in an imbalance in the bone-remodeling process. They, thereby, promote an increase in bone trabecular thickness and bone mass.[17]

Bisphosphonates may carry a potential for severe suppression of bone turnover that may impair some of bone's biomechanical and reparative properties. 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 from patients receiving risedronate for three and five years and alendronate for two and three years show normal mineralization.[21-23] However, cases of severe suppression of bone turnover in patients receiving alendronate have been described in an uncontrolled study.[6] These results are in contrast to those of large randomized clinical trials and of seven- to 10-year safety studies with risedronate and alendronate. However, rare adverse drug reactions may be uncovered during postmarketing surveillance.

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 a 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 also may remain asymptomatic

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for weeks or months, and may become evident only after the finding of exposed bone in the jaw during a 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 receiving 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 1-800-FDA-1088.

PANEL CONCLUSIONS

On the basis of a literature review and of expert opinion, the panel made the following conclusions related to oral bisphosphonate therapy.

Although recommendations for the dental management of patients taking IV bisphosphonates have been developed,[12,13] no specific guidelines exist for the management of patients taking oral bisphosphonates.

The risk of 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. Arsver, 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 (greater than 65 years), oral glucocorticoid use for chronic conditions, periodontitis and prolonged use of bisphosphonates have been associated with an increased risk of developing BON (see discussion on pages 1144-5).[5-7]

Cases of bilateral and multifocal BON have been reported in cancer patients.[7,8]

Tori and other bony exostoses may increase the risk of developing BON.

EXPERT PANEL CLINICAL RECOMMENDATIONS FOR MANAGING PATIENTS RECEIVING ORAL BISPHOSPHONATE THERAPY

These panel recommendations focus on conservative surgical procedures, proper sterile technique, appropriate use of oral disinfectants and the principles of effective antibiotic therapy. There are no data from clinical trials evaluating dental management of patients receiving 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 who are taking oral bisphosphonates, as these recommendations will be updated as new information becomes available.

General recommendations. As with all dental patients, routine dental examinations are recommended.

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

The dentist should 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 of developing BON.

The patient also should 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 or her treating physician about any health risks.

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

Routine dental treatment generally should not be modified solely on the basis of oral bisphosphonate therapy. However, patients with possible risk factors for BON 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. For more information, readers may consult the National Osteoporosis Foundation ("www.nof.org") or the American Society for Bone and Mineral Research ("www.asbmr.org").

Before undergoing any invasive procedure that involves manipulation of the bone or periosteum, patients should again be informed about the

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implications of oral bisphosphonate therapy and the risk of BON. The patient should understand that at this time, the risk of 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 complications.

When the treatment plan dictates that the medullary bone and/or periosteum is going to be involved in multiple sextants, the dentist should treat one sextant or tooth first, if dentally possible. At that point, the dentist should allow for a two-month disease-free follow-up, treating the patient with antimicrobials, before other sextants are treated with similar therapy. (Note: Typically, chlorhexidine is used two times per day for two months after surgery. On the basis of the experience of the expert panelists, the majority of cases of BON arise within two months of a dental procedure. Therefore, the recommendation to wait two months before treating multiple sextants, when possible, is a best estimate based on current knowledge.) Given success at two months (or longer if the area remains inflamed, irritated or erythematous) with the first sextant, treatment may accelerate to a more normal multisextant treatment and follow-up schedule.

Be aware that periapical pathoses, sinus tracts, 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 already is involved in the pathologic process. Some dental pathoses may not be evident 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.

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 acknowledgment of that discussion and consent for the chosen course of treatment. The dentist should retain in his or her file the acknowledgment 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.

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.[24,25] As such, patients with destructive periodontal diseases who are receiving oral bisphosphonate therapy should receive appropriate forms of nonsurgical 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,[26] which may have a negative effect on grafted sites.

Patients without periodontal disease should receive accepted mechanical and pharmaceutical methods to prevent periodontal disease, and they should be monitored on a regular basis as determined by their dentists.

Implant placement and maintenance. In recent years, rehabilitation of patients with dental implants for edentulous areas or for whom tooth prognosis was considered hopeless has been successful. At this time, there are limited data regarding the effects of implant placement in patients taking bisphosphonates. Therefore, treatment plans for patients taking bisphosphonates should be considered carefully, since implant placement requires the preparation of the osteotomy site. The patient may be at increased risk of developing BON when extensive implant placement or guided bone regeneration to augment the deficient alveolar ridge before implant placement is necessary. Before 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 nonimplant prosthetic treatments. As discussed above, this discussion should be documented and the patient's written acknowledgment of that discussion and consent for the chosen course of treatment 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 nonsurgical therapy com-

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TABLE 2

Antibiotics that may be used to treat unexpected pain, purulence or active sequestration after a dental procedure.

PATIENT TYPE	SUGGESTED DRUG	ORAL REGIMEN
Patients Not Allergic to Penicillin	Amoxicillin	500 milligrams three times per day for 14 days
	may be combined with*	
	Metronidazole	250 mg three times per day for 14 days
Patients Allergic to Penicillin	Clindamycin	300 mg three times per day for 14 days
	or	
	Azithromycin	250 mg one time per day for 10 days

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

bined 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.

Oral and maxillofacial surgery. When dental and/or periodontal disease treatment has failed, surgical intervention may be the only alternative. Patients taking oral bisphosphonates who are undergoing invasive surgical procedures should be informed of the risk, albeit small, of developing BON. Alternative treatment plans consisting of endodontics instead of extraction and bridges and partial dentures versus implant reconstruction should be discussed with the patient. (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 before and after surgical procedures involving bone, the patient should rinse gently with a chlorhexidine-containing rinse. Typically, chlorhexidine is used two times per day for two months after surgery. This can be extended on the basis of 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 (for instance, extractions, periodontal recontouring, sinus lifts) but are not mandatory or even recommended. Use of prophylactic antibiotics depends on the clinician's level of concern relative to the individual patient and his or her specific situation, including concomitant risk factors (that is, prolonged use of oral bisphosphonates, older age, concomitant use of estrogen or glucocorticoids [see the discussion on pages 1144-5]). In some situations, prophylactic antibiotics may be instituted a day or two before the procedure.

The antibiotics listed in Table 2 may be used appropriately 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 the recommendations are derived from expert opinion based on treatment of oral infections of bone in other dental situations.

Endodontics. Endodontic treatment is preferable to 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 is used for any oral and maxillofacial surgical procedure described above.

Restorative dentistry and prosthodontics. All routine restorative procedures can be carried out. There is no evidence that malocclusion or masticatory forces increase the risk of developing BON.

All prosthodontic appliances in patients taking an oral bisphosphonate should be adjusted for fit as needed.

RECOMMENDATIONS FOR RESEARCH

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

Basic research. Basic research should aim

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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 of developing BON may be helpful for the detection of patients at increased risk.

Clinical research. Research in the following clinical areas is needed:

- active pharmacovigilance regarding patients currently taking bisphosphonates, as BON is a relatively rare adverse event 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 the care of patients with BON;
- development of a national registry to allow systematic study of cases of BON and the effect of comorbidities 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. ■

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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;104(1):83-93.
5. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonerosis/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 Metabolism 2005;90:1294-301.
7. Bagan JV, Jimenez Y, Murillo J, et al. 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. Available at: "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, et al. 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, et al. 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. Available at: "www.fda.gov/ohrms/dockets/ac/04/slides/2004-4067s1_07_Sachs percent202 percent20Final.pdf". Accessed Feb. 27, 2006.
16. U.S. Department of Health and Human Services. Bone health and osteoporosis: A report of the surgeon general—2004. Available at: "www.surgeongeneral.gov/library/bonehealth/content.html". Accessed March 27, 2006.
17. Sato M, Grasser W, Endo N, et al. Bisphosphonate action: alendronate localization in rat bone and effects on osteoblast ultrastructure. J Clin Invest 1991;88:2095-105.
18. Li J, Mashiba T, 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 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;75:469-76.
23. Roschger P, Rinnerthaler S, Yates J, Rodan A, Fratzl P, Klaushofer K. Alendronate increases degree and uniformity of mineralization in cancellous bone and decreases the porosity in cortical bone of osteoporotic women. Bone 2001;29:185-91.
24. 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 2004;75:1579-85.
25. Lane N, Armitage GC, Loomer P, et al. Bisphosphonate therapy improves the outcome of conventional periodontal treatment: results of a 12-month, randomized, placebo-controlled study. J Periodontol 2005;76:1113-22.
26. Fournier P, Boissier S, Filleur S, et al. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. Cancer Res 2002;62:6538-44.

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