Case Report

Effect of Long-Term Oral Bisphosphonates on Implant Wound Healing: Literature Review and a Case Report

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Background: *Bisphosphonates suppress osteoclast activity, and their intravenous use has been reported in hundreds of cases to be associated with osteonecrosis in the jaw. Little is known of the risks associated with long-term use of oral bisphosphonates despite their use for >10 years by an oral mode of delivery for the treatment of osteopenia, osteoporosis, and Paget's disease of bone. The purpose of this report is to review the literature associated with bisphosphonate use that could impact bone healing and to report a case of bone necrosis in a patient on long-term oral bisphosphonates.*

Methods: *A Medline search was carried out to find relevant articles from both medical and dental literature between 1960 and 2006. A patient, who had been taking an oral bisphosphonate for >10 years, developed unexplained clinical signs of bone necrosis after routine dental implant placement. This case was followed, documented, and the treatment of the osteonecrosis described.*

Results: *A summary of how bisphosphonates may play a role in wound healing is presented. The compromised healing noted in a patient, who was under long-term oral bisphosphonate use, was successfully treated with systemic antibiotics, local microbial mouthrinse, and aggressive defect management (detoxification and mixture of bone graft and tetracycline).*

Conclusions: *This case suggests that patients under long-term oral bisphosphonate use should be treated with caution. Well-controlled, prospective clinical trials on the effect of oral bisphosphonates on bone are warranted to determine which patients may be at risk for such complications.* J Periodontol 2007; 78:584-594.

KEY WORDS

Bisphosphonate; dental implants; Fosamax; osteonecrosis; wound healing.

Bisphosphonates are synthetic biochemical modifiers of bone resorption. This class of drugs has proved to be highly effective in the treatment of osteoporosis, Paget's disease, and skeletal complications of bone metastases. Initial work with bisphosphonates can be traced back to the pioneering work of Fleisch et al.[1] Even before evidence of biologic activity in vivo, bisphosphonates were used for many industrial applications because of their ability to prevent calcium carbonate precipitation. The early work that formed the basis for bisphosphonate development stemmed from findings that inorganic pyrophosphate from serum and urine was able to inhibit the precipitation of calcium in vitro.[2] Further work found that pyrophosphates were able to prevent calcium phosphate dissolution in vitro, and in vivo applications proved valuable in the prevention of ectopic calcifications, but there was little effect on bone formation or resorption.[3] Francis et al.[4] and Fleisch et al.[5] proceeded to explore various chemical formulations of pyrophosphates to discover an analogue with potent effects on mineralization and resorption.

The action of bisphosphonates depends on the drug's chemical structure. The two main categories of bisphosphonates are the non-nitrogen and nitrogen-containing bisphosphonates.[6] Both forms of bisphosphonates are taken up into mineralized structures and released during resorption. On release, bisphosphonates are internalized by osteoclasts. The non-nitrogen bisphosphonates are metabolized by osteoclasts into cytotoxic analogues of adenosine triphosphate.[7] These analogues build up and lead to osteoclast apoptosis or cell death. In addition, nitrogen-containing bisphosphonates are taken up by osteoclasts during resorption and disrupt the mevalonate pathway.[6,8-10]

The mevalonate pathway was identified by Katsuki and Bloch[11] and Lynen[12] as the pathway that leads to the synthesis of cholesterol. Three molecules of cytosolic acetyl succinyl-coenzyme (CoA), transported from mitochondria, condense to form 3-hydroxy-3-methylglutaryl CoA (HMG CoA). HMG-CoA reductase

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reduces HMG-CoA into mevalonate, the first committed step in cholesterol synthesis.[13] Cholesterol-lowering drugs, statins, act directly on this step and disrupt the reduction of HMG-CoA into mevalonate.[14] Devoid of any interference, mevalonate proceeds through phosphorylations and decarboxylation to become isopentenyl pyrophosphate. Isopentenyl pyrophosphate condenses with its isomer, dimethylallyl pyrophosphate, to form geranyl pyrophosphate. Geranyl pyrophosphate further condenses with another isopentenyl pyrophosphate by the enzymatic action of farnesyl diphosphonate synthase to form farnesyl pyrophosphate. Nitrogen-containing bisphosphonates inhibit this step in the mevalonate pathway.[15] Inhibition of the mevalonate pathway prevents many post-translational modifications, including those needed to adequately promote intracellular vesicular transport.[16] Without proper transport, osteoclasts are unable to form a ruffled border, which is essential for bone resorption.[17]

The inhibition of the mevalonate pathway at the level of farnesyl pyrophosphate formation produces similar effects as non–nitrogen-containing bisphosphonates, in particular the formation of apoptotic metabolites.[15] Inhibition at the level of the farnesyl pyrophosphate formation results in a build-up of isopentenyl diphosphonate. Isopentenyl diphosphonate can be metabolized into Appi, an intracellular adenosine triphosphate analogue.[18] Appi has been shown to produce apoptosis similar to that of the clodronate metabolite, adenosine 5′-(β, γ-dichloromethylene) triphosphate (AppCCl2p).[19,20]

The chemical composition of the bisphosphonate determines the drug's potency. All bisphosphonates contain two carbon-phosphate bonds (C-P), comprised primarily of a central core of P-C-P. The addition of an amine group to the end of a side chain increases the drug's potency.[3] Table 1 presents a list of bisphosphonates and their route of administration. A large proportion of the drug is rapidly taken up by the skeleton after administration. Fifty percent of the drug is excreted by the kidneys without any metabolism, and the remainder is sequestered in the bone. The half-life of bisphosphonates ranges from months to years, with reports suggesting that bisphosphonates can still be found in bone over a decade after their administration. However, once new bone is deposited over bisphosphonate-containing layers, the effect on osteoclasts is diminished.[10]

Early bisphosphonates, such as etidronate and clodronate, have a narrow therapeutic window; large doses were required to achieve the desired resorption inhibition.[21] Etidronate and clodronate must be infused over a lengthy period of time with careful monitoring of serum creatinine; yet, even with careful monitoring, both have been associated with acute renal failure.[22] The development of nitrogen-containing bisphosphonates allowed for the delivery of bisphosphonates that conveyed nearly 10- to 100-fold increases in potency compared to etidronate and clodronate,[23] but did not require the same quantity of drug or lengthy infusion times. The more potent bisphosphonates have become a more convenient and highly effective treatment option.

Table 1.

Current Commercially Available Bisphosphonates

Generic Name	Brand Name	Nitrogen	Delivery Route
Zoledronic acid*	Zometa	+	IV
Pamidronate†	Aredia	+	IV
Etidronate‡	Didronel	–	IV
Clodronate§	Bonefos	–	IV/oral
Ibandronate‖	Bondronat or Boniva	+	IV/oral
Tiludronate¶	Skelid	–	Oral
Risedronate#	Actonel	+	Oral
Alendronate**	Fosamax	+	Oral

* Zometa, Novartis Pharmaceuticals, New York, NY.
† Aredia, Novartis Pharmaceuticals.
‡ Didronel, Procter & Gamble Pharmaceutical, Cincinnati, OH.
§ Bonefos, Aventis Pharmaceuticals, Bridgewater, NJ.
‖ Boniva, Roche Pharmaceutical, Nutley, NJ.
¶ Skelid, Sanofi Pharmaceuticals, New York, NY.
# Actonel, Procter & Gamble Pharmaceutical.
** Fosamax, Merck, Whitehouse Station, NJ.

Bisphosphonates are administered either by intravenous (IV) infusion or oral administration. Either route of delivery has been shown to be effective clinically, but both have their associated risks.[21] Bisphosphonate delivery by IV infusion has been associated with adverse renal function, but this has been seen primarily with higher infusion rates and increased dosages.[24,25] The oral administration of bisphosphonates has not been found to be as deleterious to renal function, it but has been associated with adverse gastrointestinal events, such as esophagitis, mucositis, and nausea.[26] The biggest concern with oral administration is the rate of non-compliance and the subsequent decrease in clinical effectiveness of the drug.[27,28] Therefore, IV bisphosphonate delivery has been used extensively for the treatment of such conditions as breast, prostate, and lung cancer; plasma cell dyscrasias; and other malignant bone diseases, all of which require strict drug therapy compliance.[21,29]

Recently, retrospective reports have been published that demonstrate an association between

bisphosphonate therapy and osteonecrosis of the mandible and maxillae. In 2003, Marx[30] published an article concerning avascular necrosis of the jaws associated with 36 patients taking IV bisphosphonates. Twenty-four of these patients were on IV pamidronate, six had started with pamidronate and were currently taking zoledronate, and the final six were taking only zoledronate. Twenty-eight of these patients had received tooth extractions, whereas the other eight spontaneously developed lesions. Treatment consisted of systemic antibiotics and chlorhexidine 0.12% mouthrinse with debridement as necessary. A more recent report[31] from this group included 119 patients; most but not all were on IV bisphosphonates and a few were under treatment for osteoporosis. The incidence of periodontal disease in the overall population was high (84%), nearly 38% of bone exposures were post–tooth extraction, and a small percentage (3.4%) was associated with dental implant placement. This group[31] was effective in obtaining pain control in most patients using antibiotics and a chlorhexidine mouthrinse but reported that the exposed bone often remains. Migliorati[32] reported avascular bone necrosis in five patients taking pamidronate or zoledronic acid. Three of the cases involved the mylohyoid plate and two involved previous extraction sites. Both hyperbaric oxygen and surgical treatment proved to be ineffective. Periodic treatment of debridement, bone trimming, or antibacterial measures were required. Ruggiero et al.[33] reported 63 cases of "osteonecrosis of the jaws." These patients were also taking pamidronate or zoledronic acid, but were not limited to only these IV bisphosphonates; a few of the patients were taking alendronate, an oral bisphosphonate. Treatment of these patients involved far more advanced surgical interventions, from sequestrectomy to partial or total maxillectomy or mandibulectomy. A retrospective analysis of 22 patients with multiple myeloma and IV bisphosphonates use found a history of tooth extraction and age at diagnosis of the multiple myeloma to be significantly associated with the occurrence of osteonecrosis of the jaw.[34] In another recent article, Hellstein and Marek[35] reported 20 cases of bisphosphonate-associated osteonecrosis. Histology was performed for one of the cases. The histology revealed minimal presence of Howship's lacunae, congested venules, and bacterial infiltrate within the deep trabeculae. Histologic analyses have also revealed microbiota of the *Actinomyces* species to be highly associated with areas of osteonecrosis in the jaw of patients.[36] Two recent reviews[37,38] have begun to assimilate findings from the rapidly accumulating case reports of bisphosphonate-associated osteonecrosis of the jaws, but there continues to be a lack of knowledge regarding the impact of bisphosphonate on normal healing in the oral cavity.

Oral alendronate‡ is a drug marketed for the treatment of osteoporosis (10 mg/day or 70 mg/week) and Paget's disease (40 mg/day for 6 months). The mechanism of action involves a process called prenylation, which directs the formation of the osteoclast-ruffled border. This process is the covalent modification with lipids of guanosine triphosphatase (GTPase) signaling proteins. The modification allows the attachment of proteins to the cell membrane, creating the ruffled border. Bisphosphonates bound to bone are released and taken up by osteoclasts during bone resorption. The bisphosphonates taken up into the cell are thought to block the signals that organize the ruffled border. The exact mechanism is still not understood.[39] Another nitrogen-containing bisphosphonate, ibandronate,§ has recently been released on the market offering a once-monthly oral dosing regimen. Studies have found equivalent effectiveness of once-monthly dosing (single 150-mg dose) of ibandronate compared to daily (2.5-mg dose) ibandronate dosing.[40] This new dosing regimen has helped to increase patient acceptance and compliance with pharmaceutical therapy.[41] Ibandronate has been shown to offer similar binding to bone and interactions with hydroxyapatite as alendronate.[42,43] In summary, alendronate slows bone turnover, which allows secondary mineralization to progress, increasing the tissue mineral content. Alendronate therapy results in an increase in tissue mineral content (mineral level divided by tissue volume), not bone mass (tissue volume divided by the total volume). As secondary mineralization continues, there is an overall hypermineralization, which may be more brittle and contribute to reduced fracture toughness. In addition, the suppression of bone turnover inhibits the ability to repair bone microdamage, which leads to an accumulation of microdamage. Alendronate suppression of bone turnover produces a 2% to 7% increase in bone microdamage accumulation resulting in a 20% reduction in bone toughness. There is no change in bone strength, only in toughness, which is the ability to withstand deformation without breaking.[44]

To date, there has been little in the literature regarding the influence of the use of oral bisphosphonate on bone healing. These drugs have now been in use for >10 years, and the numbers of patients who have used them or continue to use them are increasing. This report reviews the implant-based therapy of a long-term oral bisphosphonate user. In particular, treatment modalities that were implemented successfully to overcome unexpected complications in healing post–implant placement are presented.

‡ Fosamax, Merck, Whitehouse Station, NJ.
§ Boniva, Roche Pharmaceutical, Nutley, NJ.

CASE REPORT

The patient, a 65-year-old white woman, presented to the faculty clinic on November 30, 2004, at the University of Michigan School of Dentistry (DFA) for implant evaluation. The patient's medical history was positive for osteoporosis and arthritis; she also reported a history of right hip fracture at age 55. The patient's list of medications included a calcium supplement[‖] and oral alendronate, which she later reported taking orally for over 10 years. She had previously been taking conjugated estrogens[¶] but discontinued. She had a history of smoking but quit >20 years prior. Hematologic (complete blood count) and urine analysis did not reveal any abnormalities other than elevated cholesterol (216 mg/dl, expected is <200 mg/dl) and low-density lipoproteins (134 mg/dl, expected is <100 mg/dl). Her bone mineral density by dual x-ray absorptiometry over the previous 10 years ranged from T scores of –1.6 to –1.9 for the vertebrae and –1.8 to –3.5 at the femur.

The patient's chief complaint on presentation to the university dental clinic was that of a fractured bridge on the lower left, which she reported having occurred during a recent biopsy procedure. A thorough clinical examination was performed, leading to the following diagnosis: generalized mild chronic periodontitis, gingival recession, apical periodontitis on tooth #29, mandibular partial edentulism with associated functional deficit, and maxillary complete edentulism.

The treatment plan consisted of extraction of tooth #29 and implants to replace teeth #18 through #20, #29, and #30 for the correction of the mandibular functional deficit associated with partial edentulism. Tooth #29 was extracted by the referring general dentist, and the patient presented to DFA 2.5 months after initial consultation. The healing of the extraction socket from tooth #29 appeared radiographically and clinically to have progressed without any complications. Alginate impressions were taken, and surgical guides were fabricated to aid implant placement.

The patient presented 1 month after the mandibular impression was taken for implant surgery. Five implants[#] were placed into the patient's mandible, three on the left side replacing teeth #18 through #20 and two implants on the right side replacing teeth #29 and #30 (Figs. 1 through 4). The implant placement proceeded without incident. The site was sutured to achieve primary closure. Postoperative prescriptions consisted of azithromycin,[**] 500 mg every day for 3 days, which was started the day of surgery; 7.5 mg hydrocodone/500 mg acetaminophen,[††] 1 tablet every 4 to 6 hours as needed for pain; and ibuprofen,[‡‡] 400 to 600 mg as needed every 4 to 6 hours. The patient was telephoned later that same day and reported no complications.

Ten days after surgery, the patient returned for suture removal and postoperative examination. Healing

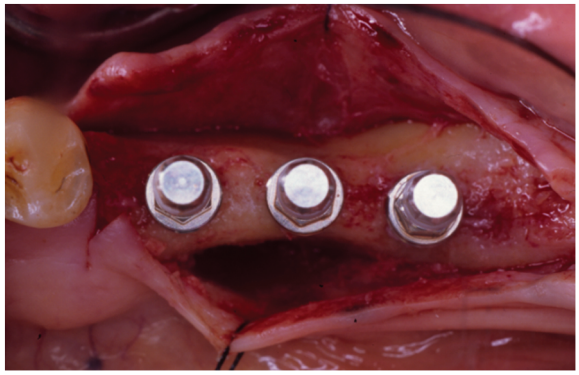

Figure 1.
Occlusal view. Implants placed according to the surgical guides in the area of teeth #18 through #20.

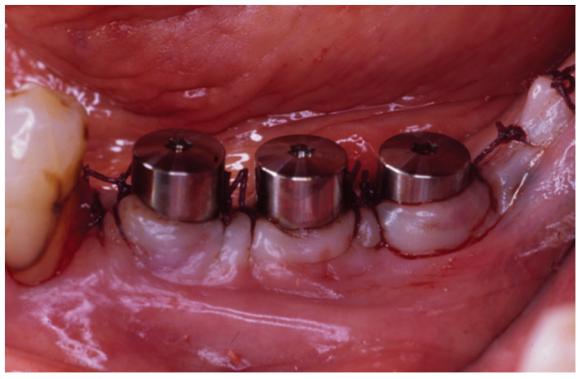

Figure 2.
Buccal view. Flap closure after bone graft.

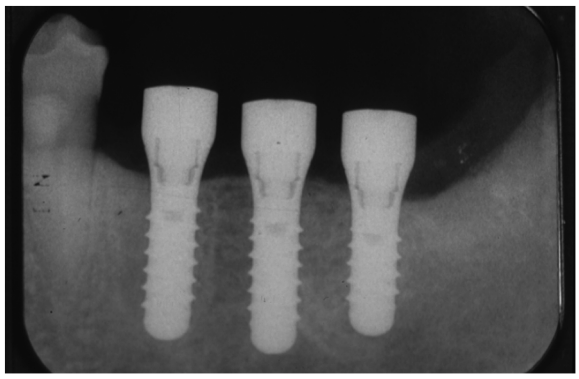

Figure 3.
Radiograph shows good radiodensity surrounding three implants placed (location: teeth #18 through #20). The x-ray was taken right after implant placement.

‖ Caltrate D, Wyeth Pharmaceuticals, Madison, NJ.
¶ Premarin, Wyeth Pharmaceuticals.
# ITI Standard Plus, Straumann USA, Andover, MA.
** Zithromax, Pfizer, New York, NY.
†† Vicodin ES, Knoll Pharmaceuticals, Mount Olive, NJ.
‡‡ Advil, Wyeth Pharmaceuticals.

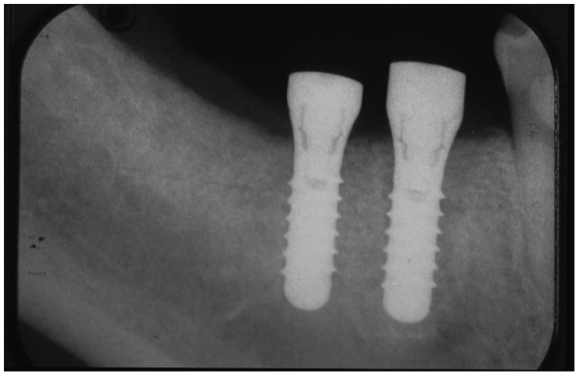

Figure 4.
Radiograph shows good radiodensity surrounding two implants placed (location: teeth #29 and #30). The x-ray was taken right after implant placement.

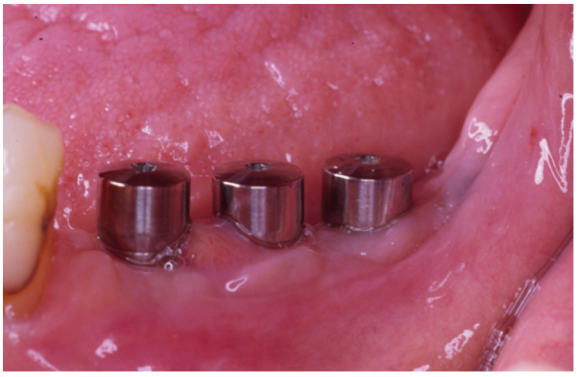

Figure 5.
Six weeks postoperative. Clinical buccal view showed teeth #19 and #20 had swelling buccally as well as between implants. Pus exacerbation was evident on probing on both sites.

appeared to be progressing rather uneventfully, and the patient was scheduled for an additional postoperative visit 4 weeks later. The patient returned to the DFA 6 weeks after implant surgery with a fluctuant swelling located in the buccal mucosa near implants #19 and #20 (Fig. 5). A small needle puncture was performed and revealed suppuration. A periapical x-ray was taken of the area. The x-ray revealed radiolucency around the apex of implants #19 and #20 (Fig. 6). The site was locally anesthetized, and incision and drainage of the fluctuant mass were performed. The site was irrigated with normal saline, and the patient was placed on azithromycin, 500 mg every day for 3 days. The patient was scheduled for surgery to evaluate and correct any osseous defects surrounding the implants.

Roughly 1 week after incision and drainage, the patient returned to DFA for surgical evaluation of the area of implants #18 through #20. The patient reported a change in her osteoporosis medication from oral alendronate to teriparatide[§§] nearly 3 weeks before. Two periapical films were taken before surgery. Radiolucencies were still evident around the apex of implants #19 and #20. The additional periapical film of the right side revealed a periapical radiolucency at the apex of implant #29. Clinically, both implant sites appeared to have healed sufficiently, and there were no signs of suppuration. The decision was made to surgically evaluate the implants on the lower left. On flap reflection, two intrabony defects were found (Fig. 7). One defect was located near the apex of implant #18, and the other was found mesial to implant #19. The areas were thoroughly degranulated, and the bone was curetted and detoxified with tetracycline (pH = 2 to 3). The bony defects were repaired with mineralized human cancellous bone[||||] mixed with tetracycline solution (500 mg in 5 cc sterile water) and

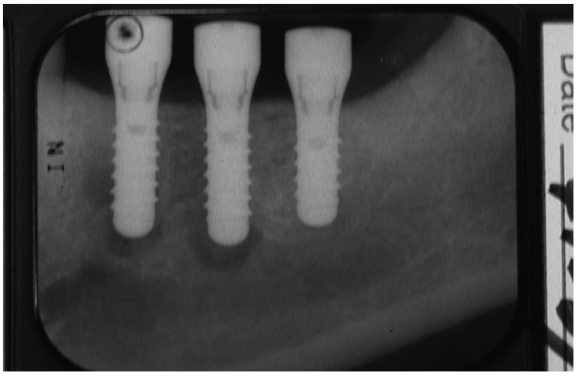

Figure 6.
Six weeks postoperative. Radiograph shows radiolucency surrounding implants #19 and #20.

covered with a collagen membrane[¶¶] (Figs. 8 and 9). The flaps were replaced and sutured to achieve primary closure (Fig. 10). The patient received thorough oral hygiene instructions and was placed on cephalexin,[##] 500 mg four times a day for 14 days, and a chlorhexidine*** rinse.

The patient returned 10 days later for a scheduled postoperative appointment. Sutures were removed and the surgical site was evaluated clinically. Healing was progressing with minimum complications. A small piece of necrotic lingual bone was noted between implants #19 and #20 but was not a source of discomfort to the patient. This piece of necrotic bone was gently removed with a cotton forceps (Fig. 11). The area was then irrigated with chlorhexidine 0.12%. The patient was instructed to rinse the

§§ Forteo, Eli Lilly, Indianapolis, IN.
|||| Puros, Zimmer Dental, Carlsbad, CA.
¶¶ Biomend, Zimmer Dental.
Keflex, Eli Lilly, Indianapolis, IN.
*** Peridex, Zila Pharmaceuticals, Phoenix, AZ.

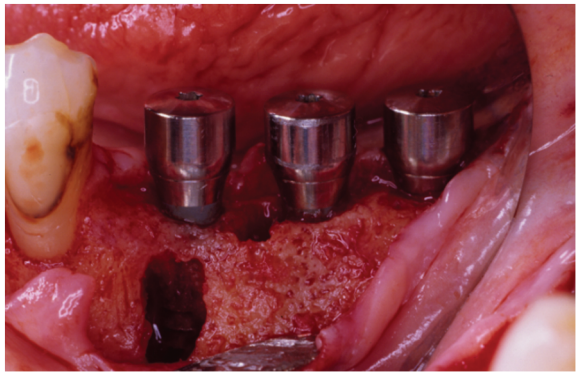

Figure 7.
Seven weeks postoperative. Area was reflected and granulomatous tissues were removed. A huge defect was noted on the buccal aspect of implant #18. Furthermore, a deep (12 mm) pocket without bone was also noted between implants #19 and # 20.

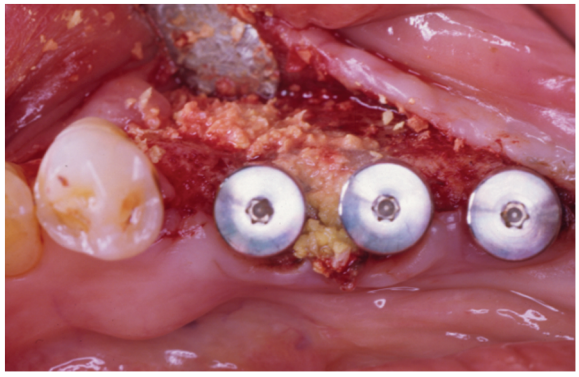

Figure 8.
After degranulation, area was detoxified with tetracycline solution and then grafted with 4:1 ratio mixture of human mineralized cancellous bone and tetracycline.

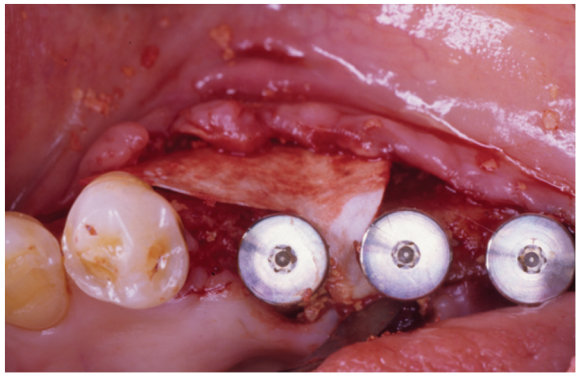

Figure 9.
The grafted site was then covered with collagen membrane to facilitate proper healing.

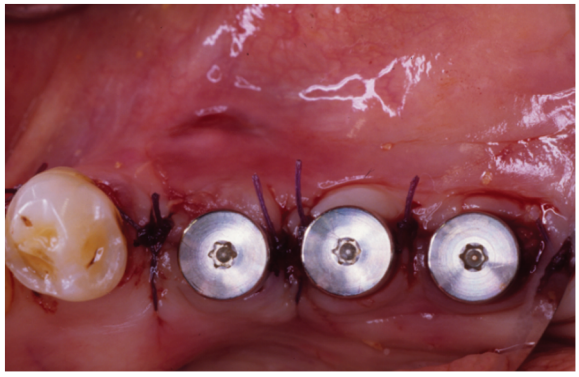

Figure 10.
Occlusal view. Flap closure.

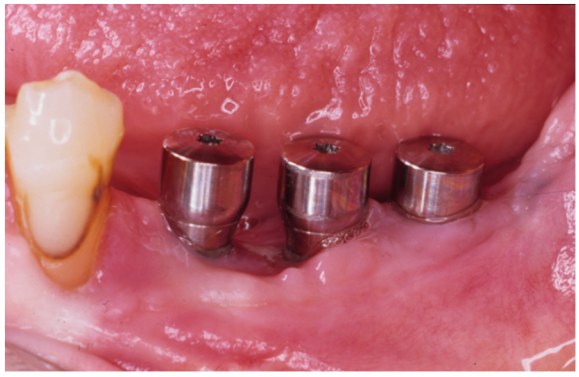

Figure 11.
Two weeks post-corrective surgery. A piece of necrotic bone was noted between implants #19 and #20. It was gently removed using a cotton forceps. Clinical picture shown after necrotic bone was removed.

area with chlorhexidine 0.12% at home to keep the area clean. The patient was given a prescription for azithromycin, 500 mg every day for 3 days, to begin immediately after completing the cephalexin.

Two weeks later the patient returned for a scheduled postoperative visit. Oral examination of the surgical site revealed complete uneventful healing. The patient reported that a small piece of bone sequestered out after the last visit. Two periapical films revealed an increased density of the previous radiolucent areas (Fig. 12). The patient returned 4 weeks later for another scheduled visit (Fig. 13). Clinically, the surgical area appeared to be completely healed. Two additional periapical films were taken, revealing continued healing of the previous radiolucencies.

The patient returned to DFA 6 months after the initial implant placement (Figs. 14 and 15). Two periapical films were taken revealing a continued healing of the apical radiolucencies around implants #19, #20, and #29 (Fig. 16). At 1 year, 3 months after temporary prosthesis in function, radiograph demonstrated bone fill and disappearance of radiolucency (Fig. 17).

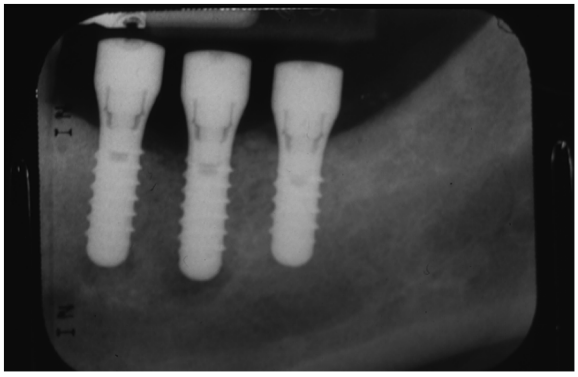

Figure 12.
Three months post-corrective surgery. Radiograph shows improved bone radiodensity around implants #19 and #20.

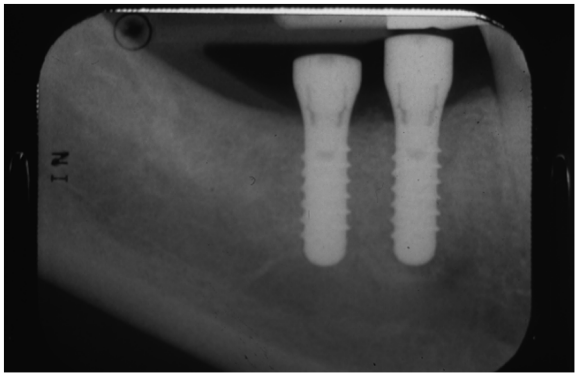

Figure 13.
Four months postsurgery. Radiograph shows improved bone radiodensity around implants #29 and #30.

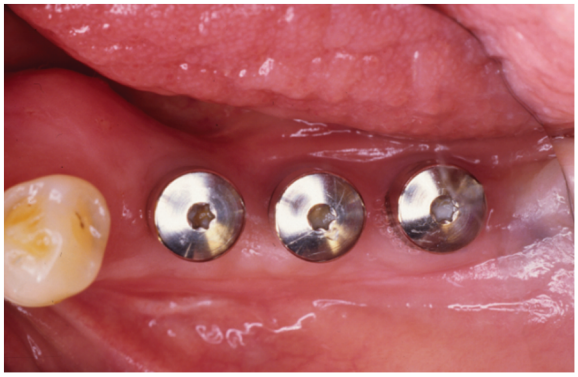

Figure 14.
Six months post-corrective surgery. Clinical examination revealed uneventful healing, and the abutments were torqued to 35 Ncm as recommended by the manufacturer. No movement of implants was found, suggesting the osseointegration was achieved in all implants.

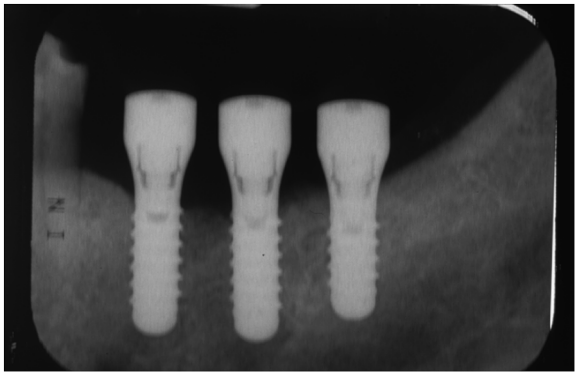

Figure 15.
Six months post-corrective surgery. Radiograph shows improved bone radiodensity around implants #19 and #20.

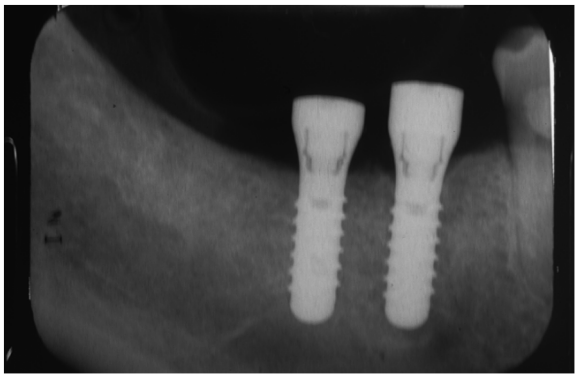

Figure 16.
Seven months postoperative surgery. Radiograph shows improved bone radiodensity around implants #29 and #30.

Clinical evaluation showed no evidence of any altered healing, and the sites were deemed ready to progress to the final prosthetic restoration.

DISCUSSION

The prevalence of osteoporosis rises with age; epidemiologic studies indicate that bone loss arises after the fourth or fifth decade in both men and women.[45] Postmenopausal women are at particular risk for bone loss. The National Osteoporosis Risk Assessment[46] investigation reported 40% of 200,160 healthy postmenopausal women had peripheral bone mineral density denoting osteopenia, and 7% had scores that correlated with osteoporosis.

A major concern regarding patients with osteoporosis requiring implant placement is the possibility that the disease modifies the quality of bone or its regenerative capacity to an extent that osseointegration is compromised. In human histologic studies,[47] osteoporotic bone exhibits reduced mechanical strength, altered trabecular architecture, decreased mineral

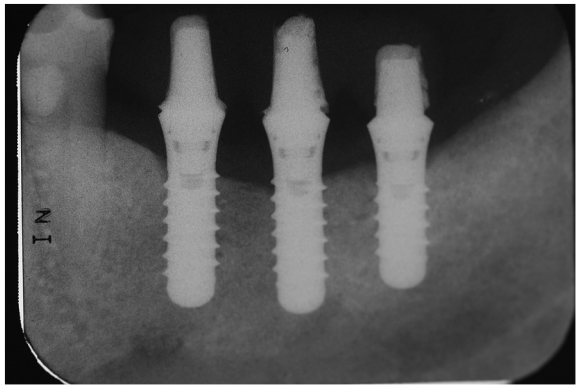

Figure 17.
Twelve months post-corrective surgery. A temporary implant-supported bridge was placed. Periapical radiograph shows continuing improvement of bone radiodensity around implants #19 and #20.

content, increased crystallinity, and increased carbonate:phosphate ratios. The exact clinical significance of these properties remains unclear. An examination of dental clinical studies on this osteoporosis reveals little effect of this disease on implant success, at least in the lower jaw. Friberg et al.[48] placed 70 implants in the jaws of 14 patients with osteoporosis. This group achieved ≥97% success in both maxilla and mandible after 3-year follow-up. These studies suggested that osteoporosis, by itself, does not affect implant success.

Minsk and Polson[49] analyzed a total of 450 maxillary and mandibular implants placed in 116 postmenopausal women aged >50 years and achieved an overall success of 92%; all failures occurred around the time of abutment connection. A retrospective analysis by August et al.[50] determined that mandibular implant failure rates did not vary between premenopausal and postmenopausal women; in contrast, postmenopausal subjects had significantly more maxillary implants fail than their premenopausal counterparts. Although these studies did not mention the patient's osteoporosis status, this study implies that postmenopause patients have a higher risk for implant failure. One reason that contributes to this high failure rate, as stated by authors,[50] is that many of these patients had developed osteoporosis.

To prevent future bone fracture, many patients are taking bisphosphonates. Recent interest has focused on patients taking IV bisphosphonates and the risk of developing osteonecrosis.[31,35,51-56] However, there is limited information about how long-term usage of oral bisphosphonates may pose a challenge to overall bone healing, in particular, during implant therapy. The use of bisphosphonates is extensive and there are now patients who have been on oral bisphosphonates for >10 years. This case report illustrates a patient who developed a significant bone defect with necrosis after proper implant placement. Although a cause and effect relationship cannot be established, the long-term use of oral bisphosphonates should be considered a potential contributing factor. This raises an important consideration while treating patients who are under long-term care with oral bisphosphonates. Clearly, well-controlled studies are needed to link or deny any potential association.

The bony defect was successfully treated with a combination of systemic antibiotics, antimicrobial mouthrinse, and proper local defect management. The local defect management included thorough debridement of defects, detoxification with tetracycline solution, mixed bone graft with tetracycline (4:1 ratio), and coverage with a collagen membrane. However, it is important to address that the usage of membrane in this case may not serve its purpose because it increases the chance of exposing the flap,[57] which may result in exposing bone to oral cavity. This may explain why there was necrotic bone noted after this treatment.

Another factor that should be considered in the patient's response to treatment is the medication change from the bisphosphonate to teriparatide. The patient's physician switched the patient from oral alendronate to teriparatide. Teriparatide, unlike bisphosphonates or estrogen, is a synthetic parathyroid hormone (PTH). Teriparatide contains recombinant human PTH (1-34), which has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human PTH. Teriparatide is given once daily by injection and usually is taken for a period of 18 months. The drug is prescribed for osteoporotic men and postmenopausal women at risk for fracture and is the only pharmaceutical agent on the market that is anabolic (versus antiresorptive) for bone. PTH is an endocrine factor that plays a prominent role in regulating bone turnover. PTH is produced by the parathyroid glands in response to a reduction in serum calcium. The mechanism of PTH, although not completely understood, is by both catabolic and anabolic influences on bone.[58-63] The action of PTH on bone resorption is thought to be by an indirect action on osteoblasts. Osteoclast recruitment, differentiation, and activation are regulated primarily through the interaction of receptor activator of nuclear factor-kappa B ligand (RANKL) with its receptor RANK. The interaction of RANKL on osteoblasts with RANK on preosteoclasts leads to an increase in mature, active osteoclasts. A decoy receptor, osteoprotegerin (OPG), can bind to RANKL and block osteoclast differentiation and activity. PTH alters the ratio of OPG:RANKL.[64,65] The continuous delivery of PTH produces an increase in RANKL mRNA and decreases the mRNA transcription of OPG.[66] In contrast, the

intermittent delivery of PTH leads to an early decrease of RANKL mRNA and increase of OPG mRNA, and over time, both level off.[67] The continuous presence of PTH by infusion results in bone loss, whereas the pulsatile delivery of PTH stimulates an increase in bone formation.[68] Interestingly, a recent report suggests that the risk of osteonecrosis with bisphosphonate use could be associated with a preexisting metabolic condition of elevated serum PTH levels and the subsequent development of hypocalcemia.[69] Bisphosphonates have been reported to induce hyperparathyroidism and hypocalcemia.[70,71] Elevated PTH levels at the same time that the resorption-mediated repair is inhibited may compromise the mineralization repair of bone in a healing site. It is unclear how the use of teriparatide impacts this, but patients on oral alendronate do not have sustained elevated PTH levels, nor do they typically have hypocalcemia, so it is unlikely that its use would compromise the repair status and, in contrast, its anabolic mode of action may be beneficial.

CONCLUSIONS

It is important for clinicians to be aware of the potential risk of treating patients who are under bisphosphonate treatment, either orally or by IV infusion. As stated on the American Academy of Periodontology website regarding bisphosphonates: "However, in light of the precaution, periodontists are advised to determine whether a patient is receiving IV bisphosphonate therapy. If so, invasive dental procedures should be avoided unless absolutely necessary. Conversely, if a periodontist becomes aware that a patient is going to be treated with IV bisphosphonates, any needed invasive dentistry should, if possible, be performed before the initiation of such treatment."[72] Although this does not include the oral usage of bisphosphonate, this case report suggests that the practitioners should be aware of the potential risk of long-term oral usage of bisphosphonates, because it may possess some risk in certain patient populations. Future studies in this area are certainly encouraged.

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REFERENCES

1. Fleisch H, Russell RG, Bisaz S, Casey P, Muhlbayer R. The influence of pyrophosphate analogues (diphosphonates) on the precipitation and dissolution of calcium phosphate in vitro and in vivo. *Calcif Tissue Res* 1968; (Suppl.):10-10a.
2. Fleisch H, Russell RG, Straumann F. Effect of pyrophosphate on hydroxyapatite and its implications on calcium hemostasis. *Nature* 1966;212:901-903.
3. Fleisch H. Development of bisphosphonates. *Breast Cancer Res* 2002;4:30-34.
4. Francis MD, Russell RG, Fleisch H. Disphosphonates inhibit formation of calcium phosphate crystals in vitro and pathologic calcifications in vivo. *Science* 1969;165: 1264-1266.
5. Fleisch H, Russell RG, Francis MD. Disphosphonates inhibit hydroxyapatite dissolution in vitro and bone resorption in tissue culture and in vivo. *Science* 1969; 165:1262-1264.
6. Green J. Bisphosphonates: Preclinical review. *Oncologist* 2004;9(Suppl. 4):3-13.
7. Benford HL, Frith JC, Auriola S, Monkkonen J, Rogers MJ. Farnesol and geranylgerniol prevent activation of caspases by aminobisphosphonates: Biochemical evidence for two distinct pharmacological classes of bisphosphonate drugs. *Mol Pharmacol* 1999;56: 131-140.
8. Bergstrom JD, Bostedor RG, Masarachia PJ, Reszka AA, Rodan G. Alendronate is a specific, nanomolar inhibitor of farnesyl diphosphate synthase. *Arch Biochem Biophys* 2000;373:231-241.
9. Lehenkari PP, Kellinsalmi M, Napankangas JP, et al. Further insight into mechanism of action of clodronate: Inhibition of mitochondrial ADP/ATP translocase by a nonhydrolyzable, adenine-containing metabolite. *Mol Pharmacol* 2002;61:1255-1262.
10. McClung MR. Bisphosphonates. *Endocrinol Metab Clin North Am* 2003;32:253-271.
11. Katsuki H, Bloch K. Studies on the biosynthesis of ergosterols in yeast: Formation of methylated intermediates. *J Biol Chem* 1967;242:222-227.
12. Lynen F. Biosynthetic pathways from acetate to natural products. *Pure Appl Chem* 1967;14:137-167.
13. Moran LA, Scrimgeour KG, Horton HR, Ochs RS, Rawn JD. *Biochemistry*, 2nd ed. Upper Saddle River, NJ: Prentice Hall; 1994:852.
14. Watanabe Y, Shiomi M, Tsujita Y, et al. Preventive effect of pravastatin sodium, a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, on coronary atherosclerosis and xanthoma in WHHL rabbits. *Biochim Biophys Acta* 1988;960:294-302.
15. Gober HJ, Kistowska M, Angman L, et al. Human T cell receptor gamma delta cells recognize endogenous mevalonate metabolites in tumor cells. *J Exp Med* 2003; 197:163-168.
16. Luckman SP, Coxon FP, Ebetino FH, Russell RG, Rogers MJ. Heterocycle-containing bisphosphonates cause apoptosis and inhibit bone resorption by preventing protein prenylation: Evidence from structure-activity relationships in J774 macrophages. *J Bone Miner Res* 1998;13:1668-1678.
17. Alakangas A, Selander K, Mulari M, et al. Alendronate disturbs vesicular trafficking in osteoclasts. *Calcif Tissue Int* 2002;70:40-47.
18. Dunford JE, Thompson K, Coxon FP, et al. Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. *J Pharmacol Exp Ther* 2001;296:235-242.
19. Monkkonen H, Lehenkari PP, Kellinsalmi M, et al. A new mechanism of action for bisphosphonates: Appi dedicated cytotoxicity of N-BPs. In: *Bone Workshops, Davos 2004. Abstracts from the Workshop: Frontiers of*

Skeletal Biology and Workshop: What is New in Bisphosphonates? Davos, Switzerland, March 20-26, 2004. Bone 2004;34(Suppl. 1):S66.
20. Selander KS, Monkkonen J, Karhukorpi EK, Harkonen P, Hannuniemi R, Vannanen K. Characteristics of clodronate-induced apoptosis in osteoclasts and macrophages. *Mol Pharmacol* 1996;50:1127-1138.
21. Conte P, Guarneri V. Safety of intravenous and oral bisphosphonates and compliance with dosing regimens. *Oncologist* 2004;9(Suppl. 4):28-37.
22. Bounameaux HM, Schifferi J, Montani JP, Jung A, Chatelanat F. Renal failure associated with intravenous disphosphonates. *Lancet* 1983;1:471.
23. Shinoda H, Adamek G, Felix R, Fleisch H, Schenk R, Hagan P. Structure relationships of various bisphosphonates. *Calcif Tissue Int* 1983;35:87-99.
24. Markowitz GS, Apple GB, Fine PL, et al. Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. *J Am Soc Nephrol* 2001;12:1164-1172.
25. Rosen LS, Gordon D, Tchekmedyian S, et al. Zolendric acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: A phase III, double-blind, randomized trial. The Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003;21:3150-3157.
26. Atula S, Powles T, Paterson A, McCloskey E, Nevalainen J, Kanis J. Extended safety profile of oral clodronate after long-term use in primary breast cancer patients. *Drug Saf* 2003;26:661-671.
27. Tanko LB, McClung M, Schimmer RC, Mahoney P, Christiansen C. The efficacy of 48-week oral ibandronate treatment in postmenopausal osteoporosis when taken 30 versus 60 minutes before breakfast. *Bone* 2003;32:421-426.
28. Clowes JA, Peel NF, Eastell R. The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: A randomized controlled trial. *J Clin Endocrinol Metab* 2004;89:1117-1123.
29. Thakkar SG, Isada C, Smith J, et al. Jaw complications associated with bisphosphonate use in patients with plasma cell dyscrasias. *Med Oncol* 2006;23:51-56.
30. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic. *J Oral Maxillofac Surg* 2003;61:1115-1117.
31. 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;63:1567-1575.
32. Migliorati CA. Bisphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol* 2003;21:4253-4254.
33. 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;62:527-534.
34. Badros A, Weikel D, Salama A, et al. Osteonecrosis of the jaw in multiple myeloma patients: Clinical features and risk factors. *J Clin Oncol* 2006;24:945-952.
35. Hellstein JW, Marek CL. Bisphosphonate osteochemonecrosis (bis-phossy jaw): Is this phossy jaw of the 21st century? *J Oral Maxillofac Surg* 2005;63:682-689.
36. Hansen T, Kunkel M, Weber A, James Kirkpatrick C. Osteonecrosis of the jaws in patients treated with bisphosphonates: Histomorphologic analysis in comparison with infected osteoradionecrosis. *J Oral Pathol Med* 2006;35:155-160.
37. Woo SB, Hellstein JW, Kalmar JR. Narrative review: Bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006;144:753-761.
38. Migliorati CA, Siegel MA, Elting LS. Bisphosphonate-associated osteonecrosis: A long-term complication of bisphosphonate treatment. *Lancet Oncol* 2006;7:508-514.
39. Strewler GJ. Decimal point–osteoporosis therapy at the 10-year mark. *N Engl J Med* 2004;350:1172-1174.
40. Dando TM, Noble S. Once-monthly ibandronate. *Treat Endocrinol* 2005;4:381-387.
41. Emkey R, Koltun W, Beusterien K, et al. Patient preference for once-monthly ibandronate versus once-weekly alendronate in a randomized, open-label, cross-over trial: The Boniva Alendronate Trial in Osteoporosis (BALTO). *Curr Med Res Opin* 2005;21:1895-1903.
42. Leu CT, Luegmayr E, Freedman LP, Rodan GA, Reszka AA. Relative binding affinities of bisphosphonates for human bone and relationship to antiresorptive efficacy. *Bone* 2006;38:628-636.
43. Nancollas GH, Tang R, Phipps RJ, et al. Novel insights into actions of bisphosphonates on bone: Differences in interactions with hydroxyapatite. *Bone* 2006;38:617-627.
44. 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;90:1294-1301.
45. Dao TT, Anderson JD, Zarb GA. Is osteoporosis a risk factor for osseointegration of dental implants? *Int J Oral Maxillofac Implants* 1993;8:137-144.
46. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: Results from the National Osteoporosis Risk Assessment. *JAMA* 2001;286:2815-2822.
47. Gadeleta SJ, Boskey AL, Paschalis E, et al. A physical, chemical, and mechanical study of lumbar vertebrae from normal, ovariectomized, and nandrolone decanoate-treated cynomolgus monkeys (*Macaca fascicularis*). *Bone* 2000;27:541-550.
48. Friberg B, Ekestubbe A, Mellstrom D, Sennerby L. Brånemark implants and osteoporosis: A clinical exploratory study. *Clin Implant Dent Relat Res* 2001;3:50-56.
49. Minsk L, Polson AM. Dental implant outcomes in postmenopausal women undergoing hormone replacement. *Compend Contin Educ Dent* 1998;19:859-862.
50. August M, Chung K, Chang Y, Glowacki J. Influence of estrogen status on endosseous implant osseointegration. *J Oral Maxillofac Surg* 2001;59:1285-1289.
51. Bamias A, Kastritis E, Bamia C, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: Incidence and risk factors. *J Clin Oncol* 2005;23:8580-8587.
52. Ficarra G, Beninati F, Rubino I, et al. Osteonecrosis of the jaws in periodontal patients with a history of bisphosphonates treatment. *J Clin Periodontol* 2005;32:1123-1128.
53. Shlomi B, Levy Y, Kleinman S. Avascular necrosis of the jaw bone after bisphosphonate therapy (in Hebrew). *Harefuah* 2005;144:536-539, 599-600.
54. Migliorati CA, Schubert MM, Peterson DE, Seneda LM. Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone. *Cancer* 2005;104:83-93.

55. Lackner H, Benesch M, Moser A, et al. Aseptic osteonecrosis in children and adolescents treated for hemato-oncologic diseases: A 13-year longitudinal observational study. *J Pediatr Hematol Oncol* 2005;27:259-263.
56. Gralow J. Evolving role of bisphosphonates in women undergoing treatment for localized and advanced breast cancer. *Clin Breast Cancer* 2005;5(Suppl. 2):S54-S62.
57. Park S-H, Lee K-W, Oh T-J, Misch CE, Shotwell JL, Wang H-L. Effect of absorbable membranes on sandwich bone augmentation. *Clin Oral Implants Res*; in press.
58. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344:1434-1441.
59. Seeman E, Delmas PD. Reconstructing the skeleton with intermittent parathyroid hormone. *Trends Endocrinol Metab* 2001;12:281-283.
60. Dempster DW, Cosman F, Kurland ES, et al. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: A paired biopsy study. *J Bone Miner Res* 2001;16:1846-1853.
61. Lindsay R, Nieves J, Henneman E, Shen V, Cosman F. Subcutaneous administration of the amino-terminal fragment of human parathyroid hormone-(1-34): Kinetics and biochemical response in estrogenized osteoporotic patients. *J Clin Endocrinol Metab* 1993;77:1535-1539.
62. Lindsay R, Nieves J, Formica C, et al. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. *Lancet* 1997;350:550-555.
63. Hock JM, Gera I. Effects of continuous and intermittent administration and inhibition of resorption on the anabolic response of bone to parathyroid hormone. *J Bone Miner Res* 1992;7:65-72.
64. Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell* 1998;93:165-176.
65. Yasuda H, Shima N, Nakagawa N, et al. Osteoclast differentiation factor is a ligand for osteoprotegerin/osteoclastogenesis-inhibitory factor and is identical to TRANCE/RANKL. *Proc Natl Acad Sci U S A* 1998;95:3597-3602.
66. Ma YL, Cain RL, Halladay DL, et al. Catabolic effects of continuous human PTH (1-38) in vivo is associated with sustained stimulation of RANKL and inhibition of osteoprotegerin and gene-associated bone formation. *Endocrinology* 2001;142:4047-4054.
67. Locklin RM, Khosla S, Turner RT, Riggs BL. Mediators of the biphasic responses of bone to intermittent and continuously administered parathyroid hormone. *J Cell Biochem* 2003;89:180-190.
68. Tam CS, Heersche JN, Murray TM, Parsons JA. Parathyroid hormone stimulates the bone apposition rate independently of its resorptive action: Differential effects of intermittent and continuous administration. *Endocrinology* 1982;110:506-512.
69. Ardine M, Generali D, Donadio M, et al. Could the long-term persistence of low serum calcium levels and high serum parathyroid hormone levels during bisphosphonate treatment predispose metastatic breast cancer patients to undergo osteonecrosis of the jaw? *Ann Oncol* 2006;17:1336-1337.
70. Vinholes J, Guo CY, Purohit OP, Eastell R, Coleman RE. Metabolic effects of pamidronate in patients with metastatic bone disease. *Br J Cancer* 1996;73:1089-1095.
71. Berruti A, Dogliotti L, Tucci M, Tarabuzzi R, Fontana D, Angeli A. Metabolic bone disease induced by prostate cancer: Rationale for the use of bisphosphonates. *J Urol* 2001;166:2023-2031.
72. American Academy of Periodontology. AAP statement on bisphosphonates. Available at: http://www.perio.org/resources-products/bisphosphonates.htm. Accessed May 25, 2006.

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