

Immediate Implant Placement in a Patient With Osteoporosis Undergoing Bisphosphonate Therapy: 1-Year Preliminary Prospective Study

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The purposes of this preliminary study are to assess the risk of developing bisphosphonate-related osteonecrosis of the jaw (BRONJ) in a patient with osteoporosis using zoledronic acid and to report the results of a 1-year prospective clinical study regarding 5 immediately inserted implants in the anterior mandible. For this comparative prospective study, 24 female patients, aged ≥ 54 years, were chosen, all with partially edentulous mandibles. Group A consisted of 12 patients with osteoporosis taking zoledronic acid receiving a once-yearly intravenous infusion of zoledronic acid (5 mg). Control group B consisted of 12 other patients without osteoporosis and not taking drugs. In both groups, the remaining teeth were extracted before 120 implants, 3.7-mm wide and 16-mm long, were immediately installed in the interforaminal region of the mandibles. The 1-year implant survival rate was 100%. No apparent necrotic bone was observed among patients receiving zoledronic acid (group A) after implant surgery. Immediate implant osseointegration can be successful in a patient with osteoporosis using bisphosphonates, suggesting the safety of implantology as a treatment modality.

Key Words: osteoporosis, bisphosphonate-related osteonecrosis of the jaw, immediate implant placement, mandible

INTRODUCTION

Osteoporosis is a skeletal disorder characterized by low bone mass and the micro-deterioration of bony tissue. Bisphosphonate (BP)-related osteonecrosis of the jaw (BRONJ) is recognized as a serious complication among patients receiving BP therapy. It has become evident that BPs used intravenously (IV), particularly zoledronic acid, could lead to painful refractory bone exposure in the jaws. This phenomenon is defined as BRONJ, which presents with oral signs and symptoms of painful, exposed, and necrotic bone, primarily of the mandible and, to a lesser extent, the maxilla.

In 2003–2004, oral and maxillofacial surgeons were the first clinicians to recognize and report cases of nonhealing exposed bone in the maxillofacial region in patients treated with IV BPs.¹

Intravenous BPs are primarily used in the effective treatment and management of cancer-related conditions, such as hypercalcemia of malignancy; skeletally related events associated with bony metastases in the context of solid tumors, such as breast, prostate, and lung cancer; and management of lytic lesions in the setting of multiple myeloma.^{2–4}

Intravenous BP exposure in the setting of managing malignancy remains the major risk factor for BRONJ. Various case series, case-control studies, and cohort studies have estimated the cumulative incidence of BRONJ to range from 0.8%–12%.^{5–7}

Zoledronic acid (Reclast, Novartis AG, Basel, Switzerland) administered once per year for the treatment of osteoporosis was approved by the US Food and Drug Administration in August 2007.⁸ A single, large, prospective placebo-controlled study established the efficacy of zoledronic acid for this indication through 3 years of treatment.⁹

The risk of developing BRONJ in patients who do not have cancer appears to be low, with the highest prevalence estimate at approximately 0.10% in a large sample of patients.¹⁰ Nevertheless, the low prevalence of BRONJ in osteoporosis patients poses a significant challenge for future clinical trials aimed at establishing accurate incidence data.¹¹

The ultimate goals of an immediate loading protocol are to reduce the number of surgical interventions and to decrease the time frame between surgery and prosthetic delivery without sacrificing implant success rates.

The purposes of this preliminary study are to assess the risk of developing BRONJ in a patient with osteoporosis using zoledronic acid and to report the results of a 1-year prospective clinical study regarding 5 immediately inserted implants in the interforaminal region of the mandible.

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TABLE		
Summary of gender, age, therapy, and the results of the preliminary study		
	Group A	Group B (Control)
Sample characteristics		
Gender	Female	Female
Age, y	54+	54+
Sample size	12	12
Anamnesis		
Osteoporosis	Yes	No
Bisphosphonate therapy	Yes	No
General	Nonsmokers, no chemotherapy, no radiotherapy, no glucocorticosteroid therapy	
Therapy		
Implant system	Lasak Impladent STI-BIO	
Number	60	60
Implant diameter, mm	3.7	3.7
Implant length, mm	16	16
Surface	BIO	BIO
Antibiotic therapy	Yes	Yes
Healing period, wk	6	6
Results		
Survival rate of implants*	100%	100%

*Evaluated by Buser's criteria.¹²

MATERIALS AND METHODS

This comparative prospective study enrolled 24 female patients aged 54 years or older, all with edentulous maxillae and partially edentulous mandibles with terminal chronic periodontitis.

Group A consisted of 12 female patients with osteoporosis receiving annual infusions of 5 mg of zoledronic acid (Aclasta, Novartis Europharm Ltd, Frimley, UK). Patients received treatment during a time frame ranging from 2 to 3 years.

All patients had confirmed osteoporotic disease (t-scan <2.5). All patients treated with BP had to be given a full explanation of the risks of necrosis and the possibility of implant loss over the long term before continued use of BP. Informed consent was obtained before placing the dental implants.

Group B, the control group, consisted of 12 other female patients without osteoporosis or BP use. All patients were confirmed to be without osteoporotic disease based on t-scan methods.

All patients were nonsmokers with noncontributory medical histories. None of the patients had received chemotherapy or radiation. None of the patients were taking concomitant glucocorticosteroid therapy.

Clinically significant BRONJ has been defined as a condition in which all of the following 3 characteristics are present⁹:

1. current or previous treatment with BP,
2. exposed bone in the maxillofacial region that has persisted for more than 8 weeks, and
3. no history of radiation therapy to the jaws.

It is important to understand that patients at risk for BRONJ or with established BRONJ can also present with other common clinical conditions not to be confused with BRONJ.

In both groups, all remaining teeth were extracted before a total of 120 implants, 3.7-mm wide and 16-mm long (STI BIO, Impladent, Lasak, Prague, Czech Republic), were immediately

inserted in the anterior mandibles. The implant fixtures were sealed with cover screws, and the postimplant surgery wound was primarily treated with an absorbable suture.

During the treatment, all patients received systemic antibiotic therapy of 1 g amoxicillin + clavulanic acid twice daily for 6 days, starting 24 hours prior to surgery.

The second-stage surgery involving healing abutments was performed after 6 weeks. The implants were functionally loaded after 8 weeks involving final fixed screw-retained prostheses with bilateral cantilevers.

Radiographic evaluation of marginal bone-level changes was performed after 1 year of definitive functional loading. Implant survival was evaluated using the Buser's criteria as follows¹²:

1. absence of persistent subjective complaints such as a pain, foreign body sensation, and/or dysesthesia;
2. absence of peri-implant infection with suppuration;
3. absence of mobility; and
4. absence of continuous radiolucency around the implant.

RESULTS

The implant survival rate was defined as the percentage of implants that were still present at follow-up. No implant mobility was detected at the time of the second-stage surgery. The 1-year implant survival rate was 100% (Table).

After 1 year of functional loading, the mean marginal bone loss in group A was similar to the loss in the control group B. However, there were no statistically significant differences between the groups. Crestal bone loss around the immediately inserted implants in the osteoporosis patients was similar to the loss reported for standard protocols involving the insertion and loading of implants.

A specific implant system was chosen for this study involving patient risk because of its high success rate and its biosurface.

DISCUSSION

This study involved a group of medically compromised patients with osteoporosis undergoing treatment via parenterally administered zoledronic acid and with chronic periodontitis. This combination occurs frequently in the age group of patients studied here. Therefore, it is important in the interest of both the patients and their providers to monitor the course of BP treatment in such compromised patients, specifically regarding the short- and long-term results of therapy.

Osteoporosis is very common, particularly in postmenopausal women; it is characterized by decreases in bone mass and strength. Osteoporosis also affects the jawbone and is considered a potential contraindication in the placement of dental implants. Experimental models have shown that osteoporosis affects the process of osseointegration, which can be reversed by treatment. However, studies in subjects with osteoporosis have shown no differences regarding implant survival when compared with healthy individuals. Therefore, osteoporosis cannot be considered a contraindication for implant placement. Oral BPs are the most commonly used pharmacologic agents in the treatment of osteoporosis.¹³

In our work, we started with the knowledge that proper surgical implantation has the same chance of successful osseointegration as in bone unaffected by osteoporosis, which was the first exit thesis of our study and treatment modality.¹⁴

Osseointegration, which is measured by the percentage of contact between the surface of the implant and bone, can be affected not only by the characteristics of the implant and surgical procedure but also by patient-dependent variables that can affect the quantity and quality of bone. To achieve implant osseointegration, it is necessary to secure the implants' adequate primary stability. We took this requirement into account during treatment, exercising great caution. Other published studies have supported the fact that implant osseointegration in osteoporotic bone is comparable to implantation in healthy bone.

Shibili et al¹⁵ performed a comparative histological analysis of implants with load removed from patients with and without osteoporosis. The percentages of bone-implant contact did not differ between the 2 groups. The histomorphometric results were also not different between the groups once osseointegration was established. These data suggest that osteoporosis cannot be considered a contraindication against implant placement in patients with osteoporosis. Reduction of both bone density and mineral content in peripheral bones has been associated with high resorption and atrophy of edentulous jaws, although no relationship has been established with increased loss of implants.¹⁶

For good osseointegration, good primary stability of the implant in the bone is a critical factor, which depends on a number of factors. One is the density of bone receiving implantation. An objective preoperative evaluation is neither easy nor straightforward. Nevertheless, quantitative computerized tomography may be informative to the implantologist.¹⁷

A study evaluated osseointegration in postmenopausal women aged between 48 and 70 years, and of these women, 19 had a densitometric diagnosis of osteoporosis and 20 others had a normal diagnosis. In total, 82 mandibular implants were placed (39 in the osteoporosis group and 43 in the control group) before osseointegration was analyzed after 9 months. Panoramic X rays revealed no significant differences between the osteoporosis patient group and the control group. In addition, histological analysis of jaw biopsies revealed no differences in bone formation and bone resorption between the 2 groups. The failure rate of 1.2% (only 1 implant lost) was compatible with the literature and was not attributed to osteoporosis.¹⁸

Another retrospective study with a follow-up of 3 years 4 months assessed 70 implants placed in patients diagnosed with osteoporosis at the lumbar level of the spine and hip. This study reported a success rate of 97% for the maxilla and 97.3% for jaw.¹⁹ The results of the reviewed studies show that it is feasible to place implants in subjects with osteoporosis, with success rates similar to those obtained in healthy subjects, even in cases involving poor bone quality during placement.

Approximately a decade ago, BPs were introduced as an alternative to hormone replacement therapies for osteoporosis and in the treatment of osteolytic tumors. More recently, it has become evident that intravenous BPs, particularly pamidronate (Aredia; Novartis Pharmaceuticals Corp, East Hanover, NJ) and zoledronate (Zometa; Novartis Pharmaceuticals Corp, Frimlay, UK), could lead to painful refractory bone exposure (sometimes termed *osteonecrosis* or *osteonecrosis*) in the jaws. Patients with osteonecrosis of the jaw (ONJ) usually present after dental treatment, with oral signs and symptoms of painful, exposed, and necrotic bone, primarily of the mandible and, to a lesser extent, the maxilla. Although the precipitating event that produces this complication may be spontaneous, there is little doubt that oral surgery and endosseous implants can be responsible. Exodontia is the main precipitant. The present postulated mechanism of ONJ is that the prolonged use of BPs may suppress bone turnover to the point that the repair function of physiologic bone microdamage is abolished. Such a mechanism could presumably interfere with the healing process after implant placement. While to our knowledge, there is no evidence that bone disorders are a contraindication to implants, there is evidence that BP therapy is a contraindication. Extractions should be avoided wherever possible, and it is best to avoid all elective oral surgery in patients on BPs, including endosseous implant placement. In addition, treatment should be performed well before commencing a BP regimen. If surgery on a patient taking BPs is essential, the patient must be counseled about the risks.²⁰

Lee et al²¹ assessed whether serum cross-linked C-telopeptide of type I collagen could be a valid test for preoperative risk of ONJ following oral surgery involving bone. The authors concluded that it was not a valid parameter.

Bisphosphonates are a group of drugs used to treat various bone diseases, such as osteoporosis, multiple myeloma, metastatic bone tumor (primarily breast and prostate cancer), Paget's disease, and malignant hypercalcemia.

Our patients were treated parenterally with zoledronic acid. However, their regimen of a 5-mg infusion once a year was different from standard protocols.

Bisphosphonate compounds have high affinity for bony tissue, especially in areas that are remodeling. The compounds accumulate for long periods of time in the mineral matrix of bone. Depending on the duration of treatment and BP-specific requirements, BP compounds can remain in the bone for many years. In the process of bone resorption, BPs are released and can be incorporated into newly formed bone.

In the treatment of osteoporosis, oral (used most frequently) or IV BPs are the modalities of choice because their mechanisms of action are effective in both increasing bone mineral density and reducing the risk of fractures.²²

In the past decade, a new complication has been described to be associated with treatment of BP-related ONJ, which consists of the appearance of foci of exposed bone necrosis in the maxilla or mandible. Osteonecrosis of the jaw presents with a slow or lack of healing after 6–8 weeks. The causal relationship between BPs and ONJ is still under investigation, although there is a clear correlation with the systemic administration of aminobisphosphonates.²³

As such, clinicians must exercise caution when dealing with patients undergoing BP therapy. Osteonecrosis of the jaw occurs most commonly in patients receiving parenteral BPs over extended periods, mostly for cancer metastases.

In a review published in 2006 assessing 368 cases of ONJ, 4.1% involved patients who received BP for the treatment of osteoporosis, while 91.6% involved patients treated for multiple myeloma or breast or prostate cancer.²⁴ As stated in the literature, more than 90% of the cases occur in patients receiving intravenous BP (pamidronate and zoledronic acid) for the treatment of multiple myeloma and metastatic breast or prostate cancer, whereas cases are rare involving patients receiving oral BPs for the treatment of osteoporosis. A recent revision in 2007 also reported the low risk of ONJ in patients receiving oral BP therapy (1/10 000–1/100 000).²⁵

In a review of 468 implants placed in 115 patients treated with oral BP, there was no evidence of ONJ, with only 2 implants showing failure. Thus, the success rate is comparable to the rate for patients not treated with BP. Implant placement and osseointegration during the first 3 years of treatment with oral BP, without the presence of other diseases or medications, can be conducted in a safe manner.²⁶ Another retrospective study of implant placement in 61 patients treated with oral BP over an average period of 3.3 years showed no cases of ONJ during follow-up (12–24 months), with a success rate of 100% according to the Albrektsson criteria.²⁷

Marx²⁸ presented a series of patients with BP-related ONJ; 3 of these cases were related to dental implants. In addition, studies by Starck et al,²⁹ Jeffcoat,³⁰ and Wang et al³¹ are the only other reported clinical cases relating peri-implant ONJ with BPs. Marx²⁸ and Starck et al²⁹ also observed complications such as radiolucent images, exposed and pale alveolar maxillary processes, fetid smell, pain, inflammation, infection, candidiasis, fistulas, bone abductions, and secondary osteomyelitis, among others.

Peri-implantitis in implants that are already healing and functional could provoke the emergence of ONJ in patients

receiving peroral BP, which is otherwise a rare complication. Therefore, it is extremely important to follow these patients regularly and thoroughly to minimize risk as much as possible, thereby avoiding serious complications.³²

Osteonecrosis of the jaw and its associated processes can involve serious infections with Actinomycetes. It is always very important to impress upon patients the importance of careful hygiene of the oral cavity, which has the potential to reduce the pathogenic bacterial load.³³ In 2009, Madrid and Sanz²¹ analyzed 1 prospective study and 3 retrospective series involving 217 patients and found implant placement to be a safe procedure in patients taking oral BPs for <5 years. No occurrence of BRONJ was reported in these studies. Moreover, the intake of oral BPs did not influence short-term (1–4 years) implant survival rates.

In 2010, Bedogni et al⁵ described a 63-year-old patient who, at the time of implantation, had undergone 6 years of oral alendronate. The patient began to have problems after 2 years of successful implant treatment and prosthetic load: He was swollen and began experiencing pain and bleeding around the implants. This situation was managed with local treatment and systemic antibiotics. However, upon an examination in the next year, exposed necrotic bone was found in the vicinity of 1 of the implants. The patient had actually discontinued BP therapy after implant placement. In our study, no patients displayed any complications of ONJ.

Yildiz et al,³⁴ in their research on rabbits, showed that parenteral zoledronic acid could improve osseointegration of titanium implants placed into bone in estrogen-deficient states. According to our results, it appears that this strategy can also work for humans.

Qi et al³⁵ also reported similar results with rabbits regarding implant osseointegration, even into autologous iliac bone grafts. Unlike Yildiz et al,³⁴ Qi et al³⁵ used local administration of zoledronic acid in the context of implant osseointegration. The authors showed that this modality, in contrast to total IV administration, had a positive effect on the samples.

Giro et al³⁶ examined the impact of estrogen therapy and alendronate treatment on bone loss around osseointegrated implants in postmenopausal human patients. They found that both treatment modalities had long-term positive impacts on the stability of bone around dental implants.

In 2007, the American Association of Oral and Maxillofacial Surgeons¹¹ offered performance guidelines for patients treated with BP. If BPs are administered IV in cancer patients, the placement of dental implants is contraindicated. If BPs are taken orally, 3 possibilities exist, as follows: (1) if the patient has been treated for fewer than 3 years and has no clinical risks, dental implants can be placed without altering conventional surgical treatment; (2) if the patient has been treated for fewer than 3 years and is treated jointly with corticosteroids, BPs must be removed 3 months before and not administered again until the bone has completely healed; and (3) if the patient has taken BPs for more than 3 years, it is possible to place dental implants if BPs are removed 3 months before surgery and not administered again until the bone has completely healed. All patients treated with BPs must be given a full explanation of the risks of ONJ and the possibility of implant loss over the long

term for continuing to take BP. Informed consent must also be obtained before placing dental implants.^{11,29}

Improved patient compliance with treatment is one of the clear objectives of implant therapy. A large percentage of treatment failure may involve patient neglect and long medication doses. However, beginning a treatment involving parenteral infusion of BP (zoledronic acid) once a year is a result of this effort.

It is important to have treatment with efficiency that is comparable to current intensified peroral treatment of osteoporosis, and it is important that the treatment has few adverse effects. Unlike dental implants that are contraindicated in patients receiving BPs for cancer, implant therapy can be very promising for patients with osteoporosis who receive disproportionately lower total doses.

Patient comfort with implant treatment can be increased when implants are immediately loaded with functional prostheses. By respecting certain clinical and prosthetic principles, immediate loading can minimize the toothless period in patients and can increase their postoperative comfort.³⁷ The scientific literature has discussed this treatment modality in patients with osteoporosis treated with BPs.³⁸

CONCLUSION

Because of the lack of complete knowledge on BRONJ pathogenesis, it is difficult to establish a protocol for dental implant rehabilitation in patients receiving BP therapies.³⁹ The risk of developing BRONJ cannot be eliminated, although it can be minimized. Currently, no validated diagnostic technique is available to determine which patients are at increased risk of developing this necrosis. Discontinuing BP therapy may not eliminate the risk of developing necrosis. Within the limitations of this study, the implant survival rate was similar to the rates in other studies that reported on immediately inserted implants in the anterior mandible. This study has demonstrated that immediate implant osseointegration can be successful in a patient with osteoporosis. As such, we recommend implantology as a safe treatment modality. With our patients, we cautiously recommend this option because of specific cases. We assume that the proper identification of suitable candidates would result in the success of this therapeutic modality. However, the assessment of long-term results warrants future studies.

ABBREVIATIONS

BP: bisphosphonate

BRONJ: bisphosphonate-related osteonecrosis of the jaw

IV: intravenously

ONJ: osteonecrosis of the jaw

REFERENCES

1. Marx RE. Pamodronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg.* 2003;61:1115–1118.
2. Hillner BE, Ingle JN, Chelbowski RT, et al. American Society of

Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol.* 2003;21:4042–4057.

3. Rosen LS, Gordon D, Tchekmedyan NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with non-small cell lung carcinoma and other solid tumors: a randomized, phase III, double-blind placebo-controlled trial. *Cancer.* 2004;100:2613–2621.

4. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst.* 2002;94:1458–1468.

5. Bedogni A, Bettini G, Totola A, et al. Oral bisphosphonate-associated osteonecrosis of the jaw after implant surgery: a case report and literature review. *J Oral Maxillofac Surg.* 2010;7:1662–1666.

6. Dimopoulos MA, Kastiris E, Anagnostopoulos A, et al. Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. *Haematologica.* 2006;91:968–971.

7. Durie BGM, Katz M, Crowley J. Osteonecrosis of the jaws and bisphosphonates [Letter]. *N Engl J Med.* 2005;353:99.

8. US Food and Drug Administration. Center for Drug Evaluation and Research. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=SearchDrugDetails>. Accessed November 11, 2008.

9. Delmas PD, Meunier PJ. The management of Paget's disease of bone. *N Engl J Med.* 1997;336:558–566.

10. American Association of Oral and Maxillofacial Surgeons. Position paper on bisphosphonate-related osteonecrosis of the jaw—2009 update. Approved by the Board of Trustees January 2009. http://www.aaoms.org/docs/position_papers/bronj_update.pdf.

11. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg.* 2007;65:369–376.

12. Buser D, Weber HP, Bragger U, et al. Tissue integration of one-stage ITI implants: 3-year results of a longitudinal study with Hollow Cylinder and Hollow-Screw implants. *Int J Oral Maxillofac Implants.* 1991;6:405–412.

13. Mellado-Valero A, Ferrer-García JC, Calvo-Catalá J, Labaig-Rueda C. Implant treatment in patients with osteoporosis. *Med Oral Patol Oral Cir Bucal.* 2010;15:52–57.

14. 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.

15. Shibli JA, Aguiar KC, Melo L, et al. Histological comparison between implants retrieved from patients with and without osteoporosis. *Int J Oral Maxillofac Surg.* 2008;37:321–327.

16. Slagter KW, Raghoobar GM, Vissink A. Osteoporosis and edentulous jaws. *Int J Prosthodont.* 2008;21:19–26.

17. Hirofumi K, Schulz EE, Kakura K, et al. Human mandibular trabecular bone density correlation with mechanical strength: implications for implant dentistry. *Implant Dent.* 2011;4:323–326.

18. Amorim MA, Takayama L, Jorgetti V, Pereira RM. Comparative study of axial and femoral bone mineral density and parameters of mandibular bone quality in patients receiving dental implants. *Osteoporos Int.* 2007;18:703–709.

19. Friberg B, Ekstubb A, Mellström D, Sennerby L. Brånemark implants and osteoporosis: a clinical exploratory study. *Clin Implant Dent Relat Res.* 2001;3:50–56.

20. Scully C, Madrid C, Bagan J. Dental endosseous implants in patients on bisphosphonate therapy. *Implant Dent.* 2006;3:212–218.

21. Madrid C, Sanz M. What impact do systemically administered bisphosphonates have on oral implant therapy? A systematic review. *Clin Oral Implants Res.* 2009;(suppl 4):87–95.

22. Pazianas M, Miller P, Blumentals WA, Bernal M, Kothawala P. A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates: prevalence, risk factors, and clinical characteristics. *Clin Ther.* 2007;29:1548–1558.

23. Gómez Font R, Martínez García ML, Olmos Martínez JM. Osteonecrosis of the jaws due to bisphosphonate treatments: update. *Med Oral Patol Oral Cir Bucal.* 2008;13:318–324.

24. Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws [published correction appears in *Ann Intern Med.* 2006;145:235]. *Ann Intern Med.* 2006;144:753–761.

25. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated

osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2007;22:1479–1491.

26. Grant BT, Amenedo C, Freeman K, et al. Outcomes of placing dental implants in patients taking oral bisphosphonates: a review of 115 cases. *J Oral Maxillofac Surg.* 2008;66:223–230.

27. Fugazzotto PA, Lightfoot WS, Jaffin R, et al. Implant placement with or without simultaneous tooth extraction in patients taking oral bisphosphonates: postoperative healing, early follow-up, and the incidence of complications in two private practices. *J Periodontol.* 2007;78:1664–1669.

28. Marx RE. *Oral and Intravenous Bisphosphonate-Induced Osteonecrosis of the Jaws: History, Etiology, Prevention, and Treatment.* 1st ed. Hanover Park, Ill: Quintessence; 2007.

29. Starck WJ, Epker BN. Failure of osseointegrated dental implants after diphosphonate therapy for osteoporosis: a case report. *Int J Oral Maxillofac Implants.* 1995;10:74–78.

30. Jeffcoat MK. Safety of oral bisphosphonates: controlled studies on alveolar bone. *Int J Oral Maxillofac Implants.* 2006;21:349–353.

31. Wang HL, Weber D, McCauley LK. Effect of long-term oral bisphosphonates on implant wound healing: literature review and a case report. *J Periodontol.* 2007;78:584–594.

32. Yuan K, Chen KC, Chan YJ, et al. Dental implant failure associated with bacterial infection and long-term bisphosphonate usage: a case report. *Implant Dent.* 2012;1:3–7.

33. Lee CYS, Pien F, Suzuki JB. Identification and treatment of bisphosphonate-associated actinomycotic osteonecrosis of the jaws. *Implant Dent.* 2011;5:331–336.

34. Yildiz A, Esen E, Kürkçü M, et al. Effect of zoledronic acid on osseointegration of titanium implants: an experimental study in an ovariectomized rabbit model. *J Oral Maxillofac Surg.* 2010;3:515–523.

35. Qi M, Hu J, Li J, et al. Effect of zoledronate acid treatment on osseointegration and fixation of implants in autologous iliac bone grafts in ovariectomized rabbits. *Bone.* 2012;1:119–127.

36. Giro G, Coelho PG, Pereira RM, et al. The effect of oestrogen and alendronate therapies on postmenopausal bone loss around osseointegrated titanium implants. *Clin Oral Implants Res.* 2011;3:259–264.

37. Ormianer Z, Garg AK, Palti A. Immediate loading of implant overdentures using modified loading protocol. *Implant Dent.* 2006;1:35–40.

38. Degidi M, Piattelli A. Immediately loaded bar-connected implants with an anodized surface inserted in the anterior mandible in a patient treated with diphosphonates for osteoporosis: a case report with a 12-month follow-up. *Clin Implant Dent Relat Res.* 2003;4:269–272.

39. Sverzut CE, Sverzut AT, de Matos FP, et al. Mandibular bisphosphonate-related osteonecrosis after dental implant rehabilitation: a case report. *Implant Dent.* 2012;21:449–453.