Influence of Bisphosphonates on Alveolar Bone Loss Around Osseointegrated Implants

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The relationship between bisphosphonates (BP) and dental implant failure has not been fully elucidated. The purpose of this retrospective radiographic study was to examine whether patients who take BP are at greater risk of implant failure than patients not using those agents. Treatment records of 362 consecutively treated patients receiving endosseous dental implants were reviewed. The patient population consisted of 227 women and 135 men with a mean age of 56 years (range: 17–87 years), treated in the University at Buffalo Postgraduate Clinic from 1997–2008. Demographic information collected included age, gender, smoking status, as well as systemic conditions and medication use. Implant characteristics reviewed included system, date of placement, date of follow-up radiographs, surgical complications, number of exposed threads, and implant failure. The relationship between BP and implant failure was analyzed using generalized estimating equation (GEE) analysis. Twenty-six patients using BP received a total of 51 dental implants. Three implants failed, yielding success rates of 94.11% and 88.46% for the implant-based and subject-based analyses, respectively. Using the GEE statistical method we found a statistically significant ($P < .001$; OR $= 3.25$) association between the use of BP and implant thread exposure. None of the other variables studied were statistically associated with implant failure or thread exposure. In conclusion, patients taking BP may be at higher risk for implant thread exposure.

Key Words: bisphosphonates, dental implants, alveolar bone loss

**INTRODUCTION**

The literature is replete with data supporting the long-term success rate of dental implants. Patient selection and clinical technique both contribute to outcomes, with many authors reporting survival rates in the 98%–99% range. Absolute contraindications to dental implants may include recent myocardial infarction or cerebrovascular accident, valvular prosthesis surgery, immunosuppression, hematologic issues, active treatment of malignancy, drug abuse, psychiatric illness, and intravenous bisphosphonate use. Relative contraindications may include adolescence, aging, osteoporosis, smoking, diabetes, positive interleukin-1 genotype, human immunodeficiency virus positivity, cardiovascular disease, and hypothyroidism.

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Osteoporosis is a skeletal disorder characterized by reduction of the bone mass per unit of volume. This condition is characterized by an increased susceptibility to bone fracture. Osteoporosis can be classified as either primary or secondary. Primary osteoporosis can affect both genders at all ages. It more frequently occurs after menopause in women or during late age in men. Secondary osteoporosis results from the use of medications, or from other conditions or diseases. It is preventable through different modalities, including adequate calcium and vitamin D intake, physical activity, hormone replacement therapy, selective estrogen receptor modulators, and bisphosphonates.

Bisphosphonates (BP) inhibit osteoclast action and thereby bone resorption. It can be administered via oral or intravenous routes. Oral bisphosphonates are commonly used in the treatment of osteoporosis, Paget’s disease, and osteogenesis imperfecta. On the other hand, intravenous bisphosphonates are used primarily for the treatment of osteolytic tumors, hypercalcemia of malignancy, multiple myeloma, bone metastases from solid tumors, and for treatment of other tumors.

BP have demonstrated promising results in treating osteoporosis. Randomized placebo-controlled trials of different bisphosphonates revealed that they generally increase bone mineral density and reduce the risk of vertebral fracture by 30%–50%. However, there are case reports of osteonecrosis of the jaw (ONJ) in osteoporotic patients treated with such agents in conjunction with (primarily) surgical dental treatment.

Several studies have described an association between osteoporosis and the onset or progression of periodontal diseases. Although osteoporosis may be associated with the loss of the alveolar crest height and tooth loss, there are conflicting data regarding the relationship between osteoporosis and clinical attachment level. Systemic factors may affect implant success rate by increasing the host’s susceptibility to other diseases, interfering with wound healing, and altering host response. Medications used to treat those conditions also might have an effect on the clinical outcome of treatment with dental implants. Although numerous studies have investigated the relationship between systemic diseases and implant success rates, the influence of those conditions remain incompletely characterized.

Several reports have demonstrated successful implant placement in patients taking BP. The relationship between osteoporosis and dental implant failure also has been investigated by many authors. Collectively, those studies observed high implant success rates, without apparent contraindication, in osteoporotic patients. However, the relationship between BP and implant outcome has not been thoroughly investigated.

The purpose of this radiographic retrospective study was to examine whether patients who take BPs are at greater risk of implant failure than patients not taking these agents.

**Materials and Methods**

**Patient population**

Treatment records of 362 consecutively treated patients receiving endosseous dental implants were reviewed. Exclusion criteria involved lack of follow-up radiographs. The study was approved by the Institutional Review Board, University at Buffalo, State University of New York at Buffalo. The patient population consisted of 227 women and 135 men with a mean age of 56 years (range: 17–87 years), treated by postgraduate residents in the University at Buffalo Postgraduate Clinics from 1997 to 2008. To qualify as a candidate for dental implant therapy, patients were required to have...
adequate oral hygiene (O’Leary plaque index <15%), absence of local inflammation (absence of bleeding upon probing and gingival index <1), pocket depths ≤3 mm, and absence of oral mucosal diseases.

**Surgical protocol**

The surgical procedures were explained and reviewed with the patient, and informed consent was obtained. Briefly, antimicrobial prophylaxis was performed using 1 g/d of amoxicillin, beginning 1 day prior to the procedure, for a total of 10 days. For penicillin-allergic patients, 600 mg/d of clindamycin was substituted. In addition, an anti-inflammatory agent, dexamethasone (Decadron, Merck, Whitehouse Station, NJ), was initiated 1 day prior to the surgery for a total of 6 days (3 mg on the first day, 6 mg on the second, 6 mg on the third, 4.5 mg on the fourth, 3 mg on the fifth, and 3 mg on the sixth day). Lidocaine infiltration was used for local anesthesia. In general, a midcrestal incision was performed, followed by elevation of a mucoperiosteal flap to access the osteotomy site. If necessary, terminal vertical releasing incisions were performed for access purposes. A surgical template was used for all placement procedures, and fixtures generally were placed to the level of the osseous crest. Implant sites were prepared according to standard procedures described by the manufacturer, relative to each type of implant used. Tissues were replaced using 3-0 or 4-0 black silk or polyglactin 910 (Vicryl, Ethicon Inc, a Johnson & Johnson Company, Somerville, NJ) sutures. Postoperatively, patients rinsed with 0.5 oz of 0.12% chlorhexidine gluconate 4 times a day for 2 weeks. Sutures were removed 1 week after surgery.

**Prosthodontic rehabilitation**

All implants were subjected to delayed loading following surgical placement, generally 3–5 months. Prosthetic rehabilitation of the implants was performed by residents in either the University of Buffalo Postgraduate Prosthodontics or Advanced Education General Dentistry clinics. The treatment modality ranged from single crown replacement, bridge supported by implants, or overdentures.

**Treatment record review**

Systematic record review was performed for each patient who qualified for the study. Demographic information collected included age, gender, and smoking status. The presence of systemic conditions and medication usage was recorded.

Any implant site preparation, including particulate bone grafting, sinus elevation, and block bone grafting was also noted. Additional characteristics recorded included number of implants placed, implant system, date of implant placement, date of follow-up radiographs, any surgical complications, presence of implant thread exposure, and implant success or failure. The criteria for implant success were clinical osseointegration of implants without radiolucency and bone loss less than 0.2 mm annually after the first year of service. Implant failure criteria were implant mobility and the implant no longer present.

Implant service time was determined by calculating the time between implant placement and the most recent follow-up radiograph. Radiographic data (ie, implant presence and extent of implant thread exposure) were collected from panoramic and/or periapical radiographs.

**Statistical analysis**

The generalized estimating equations (GEE) method was utilized for data analysis. Statistical analyses were performed using SPSS software (SPSS version 16.0.1 for Windows, SPSS, Chicago, Ill). The statistical analyses were performed using an implant-based unit.

The GEE approach of Zeger and Liang was used to facilitate data analysis due to
data collection in a longitudinal design. This method uses a generalized linear model to estimate regression parameters (relative to conventional least squares regression). This method allows specification of a working correlation matrix accounting for the form of within-subject correlation of responses on dependent variables of a variety of different distributions, including normal, binomial, and Poisson. The significance level established for all analyses was 5% ($P < .05$).

**RESULTS**

In the original population of 362 patients, 62 were excluded from the study due to incomplete data (generally, patients who moved out of town, sought follow-up care with private dentists, or declined radiographs at reevaluation appointments). A total of 661 implants were placed in the remaining 300 patients (111 Straumann [ITI, Straumann, Waltham, Mass], 389 Branemark [Branemark, Nobel Biocare, Yorba Linda, Calif], 158 Zimmer [Zimmer, Carlsbad, Calif], 3 American Dental Implant [ADI, American Dental Implant Corporation, New Castle, Pa]). Collectively, 19 implants failed, resulting in an implant-based success rate of 97.1%. Two failed implants were anterior and 17 implants were posterior. We have also summarized the implant-based parameters in Table 1.

Twenty-six patients (25 women and 1 man) using BP received 51 implants. Among these patients, 3 were current smokers at the time of placement and subsequent follow-up appointments. Three fixtures failed (2 Branemark and 1 ADI implant) resulting in success rates of 94.11% and 88.46% for the implant-based and subject-based analyses, respectively. None of the variables demonstrated statistically significant association with implant failure (Table 2). No cases of osteonecrosis of the jaw were observed. The average postsurgical follow-up was 26 months, ranging from 2 months to 78 months (Table 3). BP duration and dosage are noted in Table 3.

Interestingly, we found statistically significant associations between implant thread exposure and use of BP ($P = .001$; 3.25 odds ratio), with 13 implants exhibiting thread exposure among the 51 implants placed (Table 2). Thread exposure varied from 1 to 8 threads (Table 3).

Three implants failed in 3 different patients. The first patient was a 72-year-old female patient. She received a 4.3 $\times$ 10 mm Noble Biocare dental implant at the area of number 30. She was using alendronate (Fosamax, Merck), 70 mg once a week for an unknown period of time. As noted on examination 7 weeks after placement, the implant failed to osseointegrate for no apparent reason. The implant was replaced after 9 months and was successful for a 1-year observation period.

The second patient was a 75-year-old woman. She received a 2.4-mm ADI implant at area number 22. She was using ibandronate sodium (Boniva, Roche Pharmaceutical, Nutley, NJ), 150 mg once a month for an unknown period of time. As noted on examination 8 weeks after placement, the implant failed to osseointegrate for no apparent reason. The implant was replaced after 4 months with no complication.

The third patient was a 75-year-old woman. She received an immediate implant after extraction of tooth number 13. She was using alendronate for 4 years. The site was prepared with a series of blunt osteotomes,
without using osteotomy burs. Initial stability was not achieved at the time of implant insertion. Sutures were removed after 2 weeks and the healing was uneventful. Four weeks after placing the implant, the patient complained of swelling at her right ankle, a severe headache, and no oral complications. Clinical examination revealed the implant failed to osseointegrate. The implant was removed and the patient declined further implant placement. Although all the failures occurred in patients taking BP, the small number of failures precluded the establishment of a statistically significant relationship.

**DISCUSSION**

This retrospective study was performed to determine the relationship between BP and implant failure. Our data suggested that there was no statistically significant relationship between BP and implant failure. The overall implant success rate was 94%, which is consistent with other reports. However, our results did reveal a relationship between BP and alveolar bone loss around the osseointegrated implants.

Although recent animal studies have shown that BP may be useful in minimizing bone loss around integrated implants, those fixtures were placed in rat tibia. Consequently, those findings may not be directly comparable to our results since bacterial flora and occlusal forces are absent and may not be directly applicable to humans.

BP may function differently depending on their chemical structure. Non-nitrogen BP such as tiludronic acid (Tiludronate), etidronate disodium (Didronel), and clodronate disodium (Bonefos) are metabolized by osteoclasts and yield cytotoxic analogs of adenosine triphosphate. The accumulation of those analogs leads to osteoclast apoptosis and decreased resorption. On the other hand, nitrogen containing BP are metabolized by osteoclasts and disrupt the mevalonate pathway, leading to inhibition of posttranslational protein modifications. This will affect the osteoclasts’ ability to form a ruffled border and thus interfere with bone resorption.

The majority of implant failure cases and BP-osteonecrosis that have been reported in the literature are related to nitrogen-containing BP, with the exception of one case report. In the latter case, Starck and Epker reported the failure of 5 implants placed in a female patient. They hypothesized that the failure was due to initiation of etidronate (Didronel, Proctor & Gamble Pharmaceutical, Cincinnati, Ohio) (a non-nitrogen containing BP) 6 months after implant placement. The author advised that implant placement should be avoided in patients taking BP. Starck and Epker recommendations were subsequently questioned by Grant et al because non-nitrogen BP are generally 1000 times less potent than alendronate and because the patient in the case cited above developed a parafunctional habit that might have contributed to implant

### Table 2

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### Table 3
Bisphosphonate (BP) duration and dosage, implant location, implant system, follow-up period, and number of exposed threads*

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<th>Patient</th>
<th>BP Duration Prior to Implant Placement</th>
<th>BP Dosage</th>
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<th>Implant System</th>
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*N/A indicates not applicable; NB, Nobel Biocare; ITI, ITI Straumann; ADI, American Dental Implant.
failure. Subsequent reports further explored the relationship between BP and implant failure\(^{80-83,87}\) (Table 4).

Jeffcoat\(^{83}\) matched 102 dental implants placed in 25 patients taking BP with 108 dental implants placed in 25 healthy patients. The patients took BP for an average period of 3 ± 0.1 years. A 100% success rate was reported for the 3-year period of the study for the BP group, in comparison to 99.2% for the control group.

Fugazzotto et al\(^{80}\) in a 2-year study reported a 100% success rate following placement of 169 dental implants in 61 patients who were taking BP for an average period of 3.3 years. Forty-three implants were placed in 26 patients immediately after tooth extraction. All of the implants were considered successful without complication except for one patient. This patient received an immediate implant and exhibited exposed bone that healed uneventfully.

In a retrospective study, Bell and Bell\(^{82}\) reported a 95% success rate following placement of 101 implants in 41 patients taking BP. Five implants failed; however, those were assumed to be a result of placing the implants in the posterior maxilla and positive smoking status.

In 2008 Grant et al\(^{81}\) used a questionnaire to assess 1319 female patients who had received dental implants. Of the 458 respondents, 115 patients were taking BP. Clinical examination of 72 patients receiving 468 implants was performed. However, it was unclear if the 468 implants were placed in the 115 patients who responded to the questionnaire or the 72 patients who were examined. Two implants failed to osseointegrate, giving a 99.6% success rate.

Kasai et al\(^{87}\) compared 35 dental implants placed in 11 patients taking BP for more than 3 years with 161 dental implants placed in 40 patients not taking BP. Five implants failed, giving a success rate of 85.7% (in comparison with 95.7% for the control group). Three implants were placed in the anterior maxilla and 2 implants in the posterior mandible. The implants failed to osseointegrate with no signs of ONJ.

In a recent case report,\(^{88}\) the authors followed up 6 dental implants that were placed in a female patient with Paget’s disease. The patient was treated with BP for 7 years prior to placement. The 6 implants were loaded and had functioned successfully for 4 years with unremarkable marginal bone resorption (ie, 0.5 mm) and without soft tissue complication. No signs of ONJ were reported.

Despite the high success rates of implants placed in patients taking BP, complications have been reported. In a review of the literature, Wang et al\(^{89}\) reported a case of a 65-year-old patient taking BP for 10 years (alendronate). Three weeks after receiving 5 dental implants, BP was discontinued and Teriparatide (intravenous) synthetic parathyroid hormone was initiated. After 6 weeks the patient presented with swelling and radiolucency around 2 implants. She was treated with regenerative methods (ossseous graft and collagen membrane), an antimicrobial rinse, and systemic antibiotics. A follow up after 15 months showed a bone fill and disappearance of the pathologic radiolucency. However, the relationship of parathyroid hormone to the observed signs was unclear.

Bell and Bell\(^{82}\) reported a patient who experienced 2 mm of vertical loss around an implant. She had stopped using BP a year before her follow-up appointment but 2 years after implant placement. We have also observed one patient with a similar history. The patient’s 1-year follow-up radiograph did not demonstrate any bone loss. She stopped using BP at the same time as the follow-up appointment. One year later, 2-mm bone loss was observed around the implant.

In the present study, 13 implants exhibited radiographic thread exposure among
the 51 implants placed in BP patients. Thread exposure varied from 1 to 8 threads. It had been speculated that exposed threads might act as a risk factor for implant success by causing traumatic ulceration of the soft tissues.\(^9^0\) This trauma might be more significant if there is insufficient attached gingiva or if there are muscle attachments. Exposed threads also can harbor plaque and decrease the effectiveness of home care, which may lead to chronic inflammation and increased bone loss around implants.\(^1,9^0\)

Bisphosphonates can cause apoptosis of osteoblasts and osteoclasts cells as well as inhibit angiogenesis.\(^9^1\)—\(^9^4\) Those processes may lead to increased amounts of avascular and acellular bone that may be less tolerant to oral bacterial insult and lead to increased peri-implant bone loss. Such bone loss also might be due to the relative avascularity and acellularity of crestal bone, since it is the furthest from the blood supply. Alternatively, it is possible that suppression of bone turnover by BP might be associated with microdamage accumulation, which reduces the mechanical properties of bone, enhancing the effect of occlusal forces and leading to increased bone resorption.\(^9^5\)

There are several limitations to the present study. The major limitation in the study is the absence of a control group with osteoporotic patients not taking BP who received an implant. Unfortunately, obtaining a group with these criteria, especially in a retrospective study, is very difficult if not impossible. Other limitations include lack of clinical examinations to assess possible factors that might affect implant success such as oral hygiene, gingival inflammation, parafunctional habits, and amount of attached gingiva. In addition, standardized radiographs were not used, and implants were placed by different operators. Consequently, further retrospective and prospec-

<table>
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<th>Number of Patients</th>
<th>Number of Implants</th>
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<th>ONJ</th>
<th>Success Rate, %</th>
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<td>Fugazzotto et al(^8^0)</td>
<td>61</td>
<td>169</td>
<td>0</td>
<td>No</td>
<td>100</td>
</tr>
<tr>
<td>Bell and Bell(^8^2)</td>
<td>41</td>
<td>101</td>
<td>5</td>
<td>No</td>
<td>95</td>
</tr>
<tr>
<td>Grant et al(^8^1)</td>
<td>115 Patients reported taking BP; 72 patients were examined</td>
<td>468</td>
<td>2</td>
<td>Estimated 2.6% or less (based on 1-sided confidence interval for 0 events and n = 115)</td>
<td>99.6</td>
</tr>
<tr>
<td>Kasai et al(^8^7)</td>
<td>11</td>
<td>35</td>
<td>5</td>
<td>No</td>
<td>85.7</td>
</tr>
</tbody>
</table>

\(^*\)ONJ indicates osteonecrosis of the jaw; PD, pocket depth; BOP, bleeding on probing.
tive studies are indicated to further explore the relationship between BP and bone loss around implants.

CONCLUSION

Although we did not find a relationship between BP and implant failure, our data suggested that patients taking BP may be at greater risk of peri-implant bone loss. Further studies are indicated to determine the clinical significance of these findings.

ABBREVIATIONS

BP: bisphosphonates
GEE: generalized estimating equation
ONJ: osteonecrosis of the jaw

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REFERENCES

Influence of Bisphosphonates on Bone Loss Around Implants

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