Osseointegration of Dental Implants in Patients Undergoing Bisphosphonate Treatment: A Literature Review

Fawad Javed* and Khalid Almas†

Background: Bisphosphonates (BPs) are an important group of drugs used for the treatment of metabolic and oncologic pathologies involving the skeletal system. Osteonecrosis of the jaw (ONJ) is a complication observed in patients using oral or intravenous (IV) BPs. It was suggested that all patients undergoing BP therapy who are expected to receive dental implants should be informed of the possible risks of development of ONJ. The aim of this literature review is to assess the osseointegration of dental implants in patients undergoing BP therapy.

Methods: The MEDLINE–PubMed databases of The National Library of Medicine, National Institutes of Health, Bethesda, Maryland, were searched for articles addressing the focused question: Can dental implants osseointegrate and remain functionally stable in patients undergoing oral and IV BP therapy? Databases were searched from 1995 up to and including February 2010 using the following terms in different combinations: bisphosphonate, dental implant, immediate-loading, implant survival rate, intravenous, oral, osseointegration, and osteonecrosis.

Results: The initial search yielded 89 articles. Scrutiny of the titles and abstracts reduced the number of articles to 12 (seven case reports and five retrospective studies). In 10 studies, the patients were using oral BPs, and in two studies, patients were using IV BPs. Six case reports showed that the placement of implants in patients using BPs could yield a successful osseointegration and function. Four retrospective studies demonstrated that BPs did not have a negative influence on implant success. Two studies showed a negative impact of BPs on implant success.

Conclusion: Dental implants can osseointegrate and remain functionally stable in patients using BPs. J Periodontol 2010; 81:479-484.

KEY WORDS
Bisphosphonates; dental implants; oral; osseointegration; osteonecrosis.

Bisphosphonates (BPs), such as alendronate, risedronate, ibandronate, and clodronate, are an important group of drugs used for the treatment of metabolic and oncologic pathologies involving the skeletal system. The two main categories of BPs are non–nitrogen-containing and nitrogen-containing BPs.¹ Non–nitrogen-containing BPs are metabolized rapidly, whereas nitrogen-containing BPs are much more potent and are not metabolized.²,³ The mode of action of BPs depends on the chemical structure of the drugs (two phosphate groups attached to a central carbon atom that forms a three-dimensional structure); however, additional mechanisms of action exist. This molecular construct enables the molecule to attach to bone, disrupt osteoclastic function, and induce apoptosis.⁴⁻⁶ BPs may be administered by oral or intravenous (IV) routes. Oral BPs are used in the treatment of diseases such as osteoporosis and Paget’s disease, whereas IV BPs are administered to patients with breast cancer, multiple myeloma, bone metastasis, and malignant hypercalcemia. A complication observed in patients using oral or IV BPs is osteonecrosis of the jaw (ONJ), which is clinically characterized by an area of exposed bone in the maxilla, mandible, or palate that typically heals poorly or does not heal during a period of 6 to 8 weeks.⁷⁻⁹
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ONJ is markedly higher in patients receiving IV BPs. It was hypothesized that BPs concentrate in the jaws because of the associated physiology of this part of the skeleton (i.e., the greater degree of vascularization and the daily remodeling that occurs around the periodontal ligaments).

According to the American Association of Oral and Maxillofacial Surgeons, the frequency of ONJ in patients receiving IV BPs was 0.8% to 12%, and Mavrokokkii et al. reported this frequency to range between 0.88% and 1.15%. Oral BPs are less toxic and, therefore, produce far fewer cases of ONJ; these cases are less severe and more reversible. The incidence of ONJ related to oral BP use is estimated to be 0.7 per 100,000 person years of exposure. Although these studies reported a relatively low frequency of ONJ in patients using oral and IV BPs, the condition does not respond to a standard surgical treatment and is, therefore, difficult to treat. According to Marx et al., the prevention of BP-related ONJ is not completely possible, and Hewitt and Farah also recommended surgical treatment to be completed before a patient starts taking BPs.

The rehabilitation of patients with dental implants for missing teeth has become a more attractive and efficient alternative to the conventional fixed and/or removable dental appliances. The literature contains several observations on the significance of systemic disorders as contraindications to a dental endosseous implant treatment. However, there are limited studies concerning the effects of implant placement in patients taking BPs. It was suggested that all patients undergoing BP therapy who are expected to receive dental implants should be informed of the possible risks of development of ONJ and consequent implant loss beforehand, and an informed consent must be obtained prior to placement of dental implants in these individuals.

Although the risk of developing ONJ in patients using BPs was estimated to be minimal, controversy still exists concerning the placement of dental implants in patients treated with BPs. In this regard, the aim of this literature review is to investigate the osseointegration of dental-implant-based treatment in patients undergoing BP treatment.

MATERIALS AND METHODS
Rationale and Focused Question
The objective of the present literature review is to evaluate the osseointegration of dental implants in patients undergoing BP treatment. Thus, the focused question is: Can dental implants osseointegrate and remain functionally stable in patients undergoing oral and IV BP therapy?

Eligibility Criteria
For the literature to be included in this review, the following eligibility criteria were used: case reports, retrospective studies, a control group of individuals not using BPs; a reference list of potentially relevant original and review articles; an intervention involving conventional dental implants and/or the immediate loading of dental implants; and articles published only in English. Letters to the editor, historic reviews, and unpublished data were not sought.

Search Strategies
The authors (FJ and KA) searched the MEDLINE–PubMed databases of the National Library of Medicine, National Institutes of Health, Bethesda, Maryland, for appropriate articles addressing the focused question. Databases were searched for articles dating from 1995 up to and including February 2010 using the following terms in different combinations: bisphosphonate, dental implant, immediate-loading, implant survival rate, intravenous, oral, osseointegration, and osteonecrosis. Initially, the search strategy yielded 89 articles. Titles and abstracts of articles obtained using the eligibility criteria were screened by the authors and checked for agreement. The full text of the articles judged to be relevant by the title and abstract was read and independently evaluated against the eligibility criteria.

The second step was to conduct a hand search of the reference lists of original and review studies that were found to be relevant in the first step, and any disagreement between the authors was resolved via discussion. After the final selection, 12 studies fulfilled the eligibility criteria were processed for data extraction. Table 1 presents a summary of the relevant studies retrieved during the search strategy. Because only a limited number of original studies investigated the influence of BPs on dental implant treatment, the structure of the current literature review was customized to primarily summarize the pertinent information.

RESULTS
Characteristics of the Selected Publications
All 12 studies included in the present literature review were performed using human subjects and carried out at either universities or health care centers. Seven studies were case reports, and five studies had a retrospective research design. In 10 studies, the patients were using oral BPs for a duration ranging from 6 months to >10 years. In two studies, the patients were on IV BP therapy ≥2 years. In 10 studies, the patients were using nitrogen-containing BPs (including alendronate, risedronate, ibandronate, and pamidronate), whereas in two studies, the
### Table 1.

**Aim, Study Design, Subjects, Types of BP Used, Route, Duration of Use, and Main Results of Selected Studies**

<table>
<thead>
<tr>
<th>Investigators, Year</th>
<th>Aim</th>
<th>Study Design</th>
<th>Study Subject/s</th>
<th>Type of BP Used</th>
<th>Route*</th>
<th>Duration of Use†</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirih et al., 2009²⁰</td>
<td>To evaluate the prognosis of dental implant treatment in a patient with Paget’s disease.</td>
<td>Case report</td>
<td>77-year-old male</td>
<td>Etidronate</td>
<td>Oral</td>
<td>6 months</td>
<td>Placement of dental implants in patients with Paget’s disease using oral BPs can have positive outcomes.</td>
</tr>
<tr>
<td>Torres et al., 2009²¹</td>
<td>To evaluate the prognosis of dental implant therapy in a patient using BPs.</td>
<td>Case report</td>
<td>64-year-old female</td>
<td>Risedronate</td>
<td>Oral</td>
<td>7 years</td>
<td>Dental implants can be successfully installed in patients with Paget’s disease without discontinuing BP therapy.</td>
</tr>
<tr>
<td>Kasai et al., 2009²²</td>
<td>To monitor the outcome of osseointegrated implants in patients using BPs.</td>
<td>Retrospective</td>
<td>65 individuals</td>
<td>Alendronate</td>
<td>Oral</td>
<td>&gt;3 years</td>
<td>The overall implant success rate in patients using oral BPs was 86%, which was lower than the success rate (95%) in the control group.</td>
</tr>
<tr>
<td>Shirota et al., 2009²³</td>
<td>To describe a patient who developed BP-related ONJ around implants in the maxillary molar region.</td>
<td>Case report</td>
<td>54-year-old female</td>
<td>Pamidronate</td>
<td>IV</td>
<td>2 years</td>
<td>There was no recurrence of ONJ after surgery, and osseointegration of the implant was maintained.</td>
</tr>
<tr>
<td>Bell and Bell, 2008²⁴</td>
<td>To investigate the risk of dental implant failure in patients using BPs.</td>
<td>Retrospective</td>
<td>42 subjects</td>
<td>Alendronate, risedronate, and ibandronate</td>
<td>Oral</td>
<td>6 months to 11 years</td>
<td>The implant survival rate in patients using BPs was 95%, which was comparable to the normal success rate (96.5%).</td>
</tr>
<tr>
<td>Grant et al., 2008²⁵</td>
<td>To assess the outcomes of placing dental implants in patients using BPs.</td>
<td>Retrospective</td>
<td>115 subjects</td>
<td>Alendronate, risedronate, and ibandronate</td>
<td>Oral</td>
<td>3 years</td>
<td>BP therapy did not affect implant success and did not result in ONJ.</td>
</tr>
<tr>
<td>Ferrari et al., 2008²⁶</td>
<td>To investigate the outcomes of placing dental implants in a patient using BPs.</td>
<td>Case report</td>
<td>66-year-old male</td>
<td>Pamidronate</td>
<td>IV</td>
<td>&gt;2 years</td>
<td>After a 1-year follow-up, implants were functionally stable.</td>
</tr>
<tr>
<td>Fugazzotto et al., 2007²⁷</td>
<td>To evaluate the success rate of immediately loaded dental implants in patients using BPs.</td>
<td>Retrospective</td>
<td>61 subjects</td>
<td>Alendronate or risedronate</td>
<td>Oral</td>
<td>3.3 years</td>
<td>A history of BP use was not associated with the development of ONJ after the placement of immediately loaded dental implants.</td>
</tr>
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</table>
patients were using non–nitrogen-containing BPs (etidronate disodium). Nine\textsuperscript{15,21,23-29} of the 10 studies\textsuperscript{15,21-29} in which the patients were using nitrogen-containing BPs showed no negative effects of BPs on dental implants. Of the two case reports\textsuperscript{17,20} in which the patients were using non–nitrogen-containing BPs (etidronate disodium), one study\textsuperscript{17} reported a negative effect of etidronate disodium on dental implants, whereas the other study\textsuperscript{20} reported that BP therapy with etidronate disodium did not affect the implant success.

Six\textsuperscript{15,20,21,23,26,28} of the seven\textsuperscript{15,17,20,21,23,26,28} case reports showed that the placement of dental implants in patients undergoing BP therapy could yield a successful osseointegration and function. Four retrospective studies\textsuperscript{24,25,27,29} demonstrated that BPs did not have a negative influence on the success of dental implants; however, one study\textsuperscript{22} reported a lower implant survival rate in patients undergoing BP treatment compared to patients not using BPs. A study by Bell and Bell\textsuperscript{24} showed comparable implant survival rates of 95% and 96.5% between patients using BPs and controls, respectively. Brooks et al.\textsuperscript{28} installed 10 implants in a patient using BPs; nine implants osseointegrated successfully giving a success rate of 90%. The results of a case report by Wang et al.\textsuperscript{15} also showed implant healing to be uneventful with no alterations in the healing process of dental implants in a patient using BPs. Results by Fugazzotto et al.\textsuperscript{27} showed that a history of BP use was not associated with the occurrence of ONJ after placement of immediately loaded dental implants. Two studies,\textsuperscript{17,22} showed a negative impact of BPs on implant success.

**DISCUSSION**

Dental implants are a modern substitute to traditional prosthetic appliances; however, the state of the host bone (quantity and quality) and its healing capacity are significant factors that can influence the success rate and healing capacity of dental implants.\textsuperscript{14,15}

BPs are commonly used in the treatment of various osteometabolic diseases including osteoporosis, Paget’s disease, multiple myeloma, tumors that metastasize to the bone, and malignant hypercalcemia because of their properties of inhibiting bone resorption by osteoclasts. Between May 2003 and April 2004, ~22 million prescriptions for BPs were written.\textsuperscript{12} However, a worrisome correlation that has

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<tr>
<td>Brooks et al., 2007\textsuperscript{28}</td>
<td>To evaluate the success rate of dental implants in a patient using BPs.</td>
<td>Case report</td>
<td>62-year-old female</td>
<td>Risedronate</td>
<td>Oral</td>
<td>3 years</td>
<td>Nine of 10 implants osseointegrated successfully.</td>
</tr>
<tr>
<td>Wang et al., 2007\textsuperscript{15}</td>
<td>To assess the prognosis of dental implant treatment in a patient using BPs.</td>
<td>Case report</td>
<td>65-year-old female</td>
<td>Alendronate</td>
<td>Oral</td>
<td>&gt;10 years</td>
<td>Implant healing was uneventful, with no alterations in the healing process.</td>
</tr>
<tr>
<td>Jeffcoat, 2006\textsuperscript{29}</td>
<td>To present safety data in patients using BPs.</td>
<td>Retrospective</td>
<td>50 individuals</td>
<td>Alendronate</td>
<td>Oral</td>
<td>1 to 4 years</td>
<td>The implant success rate in subjects using BPs and controls was 100% and 99%, respectively. No cases of ONJ were observed.</td>
</tr>
<tr>
<td>Starck and Epker, 1995\textsuperscript{17}</td>
<td>To evaluate the prognosis of dental implants in a patient with osteoporosis using BPs.</td>
<td>Case report</td>
<td>75-year-old female</td>
<td>Etidronate</td>
<td>Oral</td>
<td>6 months</td>
<td>The patient lost the five endosseous implants after being treated with BPs.</td>
</tr>
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* Route of BP administration. \[†\] Duration of BP use.
recently emerged is the occurrence of ONJ in patients using BPs. Wang et al.\textsuperscript{15} suggested that long-term oral-BP users should be treated with caution. Similarly, Melo and Obeid\textsuperscript{30} presented a case report of a 72-year-old female with a non-healing extraction socket. The patient’s medical history revealed that she had multiple disorders including breast cancer and was using several medications including zoledronate (an IV nitrogen-containing BP).\textsuperscript{30} Surgical wound debridement was performed, and the pathology report identified that the specimen exhibited osteonecrosis.\textsuperscript{30} This case report indicated standard protocols should be adopted prior to tooth extraction in patients undergoing IV BP therapy.\textsuperscript{30} A study by Estilo et al.\textsuperscript{31} reported that the duration of BP therapy and sequential IV BP treatment were among the significant factors associated with an increased likelihood of ONJ. The incidence of BP-associated ONJ in various population subsets ranged from 9.4% to 10% among patients taking zoledronate and 4% to 14.3% among patients taking pamidronate.\textsuperscript{9,28} On the contrary, the results of a study by Jeffcoat\textsuperscript{29} suggested that BPs may not increase the incidence of ONJ. The success rates of dental implants placed in patients using BPs and controls was 100% and 99.2%, respectively.\textsuperscript{29}

Regardless of the extensive use of BPs, we identified only two studies\textsuperscript{17,22} that demonstrated a negative impact of BP use on dental implant treatment. The results of a case report by Starck and Epker\textsuperscript{17} suggested that failures of dental implants were associated with BP use. Etidronate disodium (a non–nitrogen-containing BP) was prescribed to the patient for the treatment of osteoporosis.\textsuperscript{17} However, it has been stated that etidronate is not the drug of choice for the treatment of osteoporosis.\textsuperscript{25} Although the patient in the case report\textsuperscript{17} developed a parafunctional clenching habit after the placement of dental implants (which might have also contributed to implant failure), the authors concluded that implant failures were associated with etidronate-disodium therapy. Alendronate and other BPs, such as risedronate and ibandronate, were shown to have no clinically measureable effect on bone mineralization.\textsuperscript{32} These classes of BPs may not have detrimental effects on the osseointegration and success of implants. In the present review, nine\textsuperscript{15,17,20,21,24,25,27-29} of the 10 studies\textsuperscript{15,17,20-22,24,25,27-29} where patients were using nitrogen-containing BPs showed no negative effects of BPs on dental implants.

BPs can be found in bone tissues >10 years after their administration; however it was reported that the effect of osteoclasts is diminished once new bone forms over the BP-containing bone tissue.\textsuperscript{33} Jeffcoat\textsuperscript{29} investigated the incidence of complications ∼3 years after placing dental implants in 25 patients using oral BPs and compared them to 25 age-matched controls. The implant success rate in patients using oral BPs and controls was 100% and 99.2%, respectively; in both groups, the implants were functionally stable.\textsuperscript{29} A study by Fugazzotto et al.\textsuperscript{27} showed that a history of oral BP use for a mean duration of 3.3 years was not associated with the development of ONJ after implant placement. However, the results of a study by Marx et al.\textsuperscript{34} showed a direct relationship between ONJ and the duration of oral BP use. The study\textsuperscript{34} reported that exposure to alendronate for a mean duration of 5.7 years was associated with the development of ONJ. According to a recent study,\textsuperscript{35} when IV BPs were given >21 months, the probability of ONJ was markedly low (3%) compared to other skeletal disorders (30%) observed in the study. This might be a possible explanation for the absence of ONJ and a successful implant osseointegration and function as reported by Shirota et al.\textsuperscript{23} and Ferrari et al.\textsuperscript{26} In these studies,\textsuperscript{23,26} the patients were on IV BP therapy >21 months.

**CONCLUSIONS**

The association between implant failure and BP use (either orally or intravenously) cannot be overlooked, and clinicians have to be aware of the possible risks of treating patients undergoing BP treatment. However, the results of the present literature review show that the incidence of implant failure was minimal in patients using oral and IV BPs. Therefore, we conclude that dental implants in patients taking BPs can osseointegrate and remain functionally stable.

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**REFERENCES**


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