Influence of Bisphosphonates on Implant Failure Rates and Characteristics of Postmenopausal Woman Mandibular Jawbone

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Rehabilitation of oral function using dental implants is clinically effective and highly predictable. Both bone quantity and quality at the implant site affect the success of the procedure. However, the effect of bisphosphonate (BP) use on mandibular bone quality has not been well documented. The purpose of this retrospective cohort study was to evaluate the bone mineral density (BMD) and cortical thickness of the mandible, as well as the influence of BP use on early implant failure. Twenty-five female patients (>60 years of age) were selected from among 93 candidates with partially edentulous posterior mandibles. Eleven patients had received BP therapy using alendronate (BP group), and 14 patients had received alternate therapy (non-BP group). Cortical and trabecular BMD was measured using quantitative computed tomography. Cortical thickness was measured using computed tomography. The BMDs and cortical thicknesses of the two groups were compared. The results were as follows: (1) Cortical BMD was significantly higher in the BP group, (2) trabecular BMD was not affected by BP use, and (3) Cortical thickness was affected by the duration of BP use. These results indicate that BP use affects the quality and quantity of the cortical bone in the partially edentulous posterior mandible of patients with osteoporosis, which should be considered prior to treatment with dental implants in patients taking BPs.

Key Words: bone quality, cortical bone, bisphosphonate, bone mineral density, dental implant, early implant failure

INTRODUCTION

Patients receiving bisphosphonate (BP) therapy are known to be at risk for developing osteonecrosis of the jaw (bisphosphonate-related osteonecrosis of the jaw), but the mechanism of action has not been fully elucidated.1 In a previous study, we evaluated the jaw bones using quantitative computed tomography (QCT) and reported that the bone mineral density (BMD) of the edentulous mandible decreased with the onset of menopause, similar to the other bones in the body.2 In addition, the proportion of cancellous bone in the mandible was found to increase while that of the cortical bone decreased following menopause.2 Therefore, these physiologic and histologic alterations caused by BP use would be expected to negatively affect implant stability even if no osteonecrosis of the jaw (ONJ) occurred. Because most of the studies analyzing the effects of BPs have focused on ONJ, there is little research evaluating the influence of BPs on cortical and trabecular BMD in the mandible. The influence of BPs on implant failure rates remains controversial.3–5 In this study, we evaluated both clinically and radiologically the effect of oral BPs on jaw bones and implant failure rates in female patients with osteoporosis.

MATERIALS AND METHODS

Patient population

Twenty-five female patients were included in this study. The inclusion criteria were as follows: female, at least 60 years of age, previously diagnosed with osteoporosis, possessing a unilateral or bilateral partially edentulous posterior mandible treated with dental implants between January 2010 and March 2013. Osteoporosis is defined as having a BMD of no more than 70% of the young adult mean (YAM) or, alternatively, of less than the standard deviation (SD) of −2.5. Excluded from this study were patients with a steroid prescription, metabolic bone disease other than osteoporosis, type 2 diabetes mellitus, a smoking habit, poor dental hygiene, or severe periodontal disease. Prior to the placement of dental implants, the absence of periodontal disease was confirmed with an O’Leary plaque index <15%, the absence of local inflammation (no bleeding with probing and gingival index <1), probing pocket depths ≤3 mm, and the absence of mucosal disease. The patients were...
Advanced imaging was performed using a 64 slice multidetector row CT scanner (Somatom Sensation 64, Siemens, Munich, Germany) set at 120 kV and 125 mA, with a slice thickness of 1 mm. The patient’s mandible was positioned perpendicular to the table as a reference plane.

During the CT scans, a phantom containing calibration cells of 2 equivalent concentrations of calcium hydroxyapatite (0 and 200 mg/mL) was simultaneously scanned to quantify the BMDs per unit area (mg/mL) for both regions. The CT values obtained from the mandible were then compared with those of the calibration phantom to calculate the BMDs per unit area (mg/mL) for both regions.

The measurement methods described in our previous study were used again here and are outlined below.

1. Advanced imaging was performed using a 64 slice multidetector row CT scanner (Somatom Sensation 64, Siemens, Munich, Germany) set at 120 kV and 125 mA, with a slice thickness of 1 mm. The patient’s mandible was positioned perpendicular to the table as a reference plane.
2. During the CT scans, a phantom containing calibration cells of 2 equivalent concentrations of calcium hydroxyapatite (0 and 200 mg/mL) was simultaneously scanned to quantify the BMDs per unit area (mg/mL) for both regions. The CT values obtained from the mandible were then compared with those of the calibration phantom to calculate the BMDs per unit area (mg/mL) for both regions.
3. The images captured in the soft tissue mode that were acquired 3 times and were averaged to obtain mean CT values and the values obtained with the calibration phantom were converted based on their linear relationship with the X-ray attenuation coefficients to determine the BMD (in milligrams per milliliter). Additionally, in the same image slices of the edentulous posterior mandible (bone mode), the widths of the trabecular and cortical bone regions, for both the buccal and lingual aspects of the cortex, were determined using the distance measurement software provided with the CT scanner. The ROIs for each cancellous and cortical bone segment are illustrated in Figures 2 and 3. The CT values obtained from the mandible were then compared with those of the calibration phantom to calculate the BMDs per unit area (mg/mL) for both regions.
4. A threshold value of 500 HU was used to distinguish the cancellous bone from the cancellous bone. Then, a region of interest (ROI) was selected in the edentulous posterior mandible to determine the mean CT values for the cancellous and cortical bone. The regions with CT values of <500 HU were regarded as trabecular bone regions. Images with localized sclerosis within the trabecular bone region were excluded from analysis. The areas adjacent to the interface between the cortical and trabecular bone were also excluded from the ROI to eliminate the partial volume effect. Measurements within the ROI (3 x 3 mm) were acquired 3 times and were averaged to obtain mean CT values for individual trabecular bone regions. These mean CT values and the values obtained with the calibration phantom were converted based on their linear relationship with the X-ray attenuation coefficients to determine the BMD (in milligrams per milliliter). Additionally, in the same image slices of the edentulous posterior mandible (bone mode), the widths of the trabecular and cortical bone regions, for both the buccal and lingual aspects of the cortex, were determined using the distance measurement software provided with the CT scanner. The ROIs for each cancellous and cortical bone segment are illustrated in Figures 2 and 3. The CT values obtained from the mandible were then compared with those of the calibration phantom to calculate the BMDs per unit area (mg/mL) for both regions.
5. The buccal and lingual cortical bone thicknesses (mm) in the edentulous posterior mandible were also measured in the same image slices and then averaged.

**Evaluation and statistical analyses**

The following comparisons were made, and the associations were explored, based on the measured bone thicknesses in the CT images and the calculated BMDs.

1. Comparison of BMDs between the BP and non-BP groups.
2. Comparison of cortical bone thicknesses between the BP and non-BP groups.
3. Association of the duration of BP use with the BMDs and cortical bone thicknesses.

The Mann-Whitney U test was used to compare the differences between the two groups. Spearman’s rank correlation coefficient was used to evaluate the correlation between the duration of BP use and the BMDs and cortical bone thicknesses. Differences in implant failure rates were calculated using the chi-squared test at both the patient and implant levels. All statistical analyses were performed using SPSS Statistics 21 (IBM Japan Ltd, Tokyo, Japan), with P values <.05 considered significant.

**RESULTS**

No patient developed ONJ in either group. In the BP group, 11 patients (25 total implants) were followed for an average of 3.2 ± 1.3 years. Three implants (11.1%) were found to have failed in 3 different patients (25%) within 1 year. In the non-BP group, all implants survived in all 14 patients (28 total implants) over an average follow-up period of 5.2 ± 1.2 years. However, the difference in implant failure rates between the 2 groups was not statistically significant at either the patient (P = .071) or implant (P = .098) level.

In BP-treated patients with early implant failure, the type and duration of BP therapy, cortical and cancellous BMDs, and cortical bone thicknesses were further analyzed. These patients were found to have a BMD ≥1 SD different than the average BMD of the BP group (P = .013; Table 2).

**Comparison of BMDs and cortical bone thicknesses**

The cortical BMDs of the BP group were significantly higher (P < .001) than those of the non-BP group, but no significant

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>General health status of patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP</strong></td>
<td><strong>Non-BP</strong></td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td></td>
</tr>
<tr>
<td>61–70</td>
<td>8</td>
</tr>
<tr>
<td>&gt;70</td>
<td>3</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td><strong>69.6 ± 5.2</strong></td>
</tr>
<tr>
<td><strong>Bisphosphonate taking</strong></td>
<td></td>
</tr>
<tr>
<td>1–3yr</td>
<td>5</td>
</tr>
<tr>
<td>&gt;3yr</td>
<td>6</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>0</td>
</tr>
</tbody>
</table>

*BP indicates patients receiving bisphosphonate therapy; Non-BP, patients not receiving BP therapy.
FIGURES 1–3. **FIGURE 1.** Simultaneous scanning of calibration phantom. Scanning of the bone density calibration phantom with two compartments containing 0 and 200 mg/mL of calcium hydroxyapatite equivalent, respectively, was performed simultaneously with CT scanning of the patients. **FIGURE 2.** Region of interest for measuring bone mineral density in the trabecular bone (white marked area). **FIGURE 3.** Region of interest for measuring the cortical bone mineral density and thickness (yellow line).

**TABLE 2**

This table shows the details of each of the three patients who lost implants during the observation period. The bottom line shows the mean value for each clinical parameter for all patients in the BP group.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Site</th>
<th>Duration of BP Use (yr)</th>
<th>BMD-C (mm/mL)</th>
<th>BMD-T (mg/mL)</th>
<th>Cortical Thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>30</td>
<td>1</td>
<td>1563</td>
<td>107</td>
<td>1.7</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>21</td>
<td>4</td>
<td>1607</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>30</td>
<td>5</td>
<td>1653</td>
<td>76</td>
<td>2.5</td>
</tr>
<tr>
<td>Mean</td>
<td>70</td>
<td></td>
<td>3.3</td>
<td>1608*</td>
<td>69</td>
<td>2.7</td>
</tr>
<tr>
<td>Mean of all patients in BP group</td>
<td>69.6</td>
<td></td>
<td>3.8 ± 2.1</td>
<td>1449 ± 140</td>
<td>83 ± 55</td>
<td>2.5 ± 0.8</td>
</tr>
</tbody>
</table>

*P < .05.

1BP indicates patients receiving bisphosphonate therapy; BMD-C, bone mineral density of cortical bone; BMD-T, bone mineral density of trabecular bone.
BMD-T, bone mineral density of trabecular bone.  
not receiving BP therapy; BMD-C, bone mineral density of cortical bone;  
Torres et al 8 utilizing intravenous BP. Collectively, these  
BP use, which is consistent with the results of a study by  
cortical bone thickness was found to increase with extended  
following zoledronic acid administration. In this study,  
which is similar to our findings.  
BMDs in the edentulous mandibular region of the BP group,  
in beagle dogs and reported significantly increased cortical  
increased mineralization—but not the increased bone  
increased cortical BMD. The investigators suggested that the  
no increase in cortical bone mass histologically, despite an  
therapy on cortical bone mass and reported that there was  
recommendations related to occlusion such as the number of remaining  
receiving oral BPs, clinicians should be mindful of the bone  
mineralization in the cortical bone in the edentulous  
contact rate, which further hindered osseointegration.  
 Therefore, before initiating implant treatment in patients  
oral BPs, clinicians should be mindful of the bone density in the ROI and the risks of overheating and reduced remodeling due to bone sclerosis. A preoperative explanation of the risks of ONJ and aggravation of osseointegration should be provided and alteration of the BP prescription should be considered. Regarding the limitations of this study, the population size is relatively small. It is also possible that the medications such as SERM and PHT taken by patients in the non-BP group might affect the characteristics of the cortical and trabecular bone. Moreover, other clinical parameters related to occlusion such as the number of remaining teeth and parafunctional habits of the patients were not taken into account. These issues should be addressed in future studies.  
**CONCLUSION**  
We reached the following conclusions:  
1. Oral BP drugs increase the cortical BMD in the edentulous mandible.  
2. Oral BP drugs affected the cancellous BMD to a lesser extent than the cortical BMD in the edentulous mandible.  
3. Prolonged BP use tended to increase the cortical bone thickness.  

Finally, these results indicate that BPs affect the quality and quantity of the cortical bone in the partially edentulous posterior mandible of patients with osteoporosis, which should
be considered prior to treatment with dental implants in patients taking BPs.

**ABBREVIATIONS**

BMD: bone mineral density  
BP: bisphosphonate  
CT: computerized tomography  
ONJ: osteonecrosis of the jaw  
PTH: parathyroid hormone  
QCT: quantitative computed tomography  
ROI: region of interest  
SD: standard deviation  
SERM: selective estrogen receptor modulator  
YAM: young adult mean

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**NOTE**

The authors declare that they have no conflicts of interest.

**REFERENCES**