

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

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TABLE 1
General health status of patients*

	BP	Non-BP
Age (yr)		
61-70	8	10
>70	3	4
Mean	69.6 ± 5.2	67.3 ± 4.2
Bisphosphonate taking		
1-3yr	5	N/A
>3yr	6	N/A
Diabetes mellitus	0	0
Smoking	0	0

*BP indicates patients receiving bisphosphonate therapy; Non-BP, patients not receiving BP therapy.

divided into two groups: (1) the BP group (mean age 69.6 ± 5.2 years), which consisted of 11 women who had taken BPs for ≥1 year; and (2) the non-BP group (mean age 67.3 ± 4.2 years), which consisted of 14 women who had been prescribed either selective estrogen receptor modulator (SERM) or parathyroid hormone (PTH) at the discretion of their physician. Among the 14 patients in the non-BP group, 8 patients were prescribed SERM and the remaining 6 were prescribed PTH. The patients' general health statuses are summarized in Table 1. This study was approved by the Ethics Committee of Kanagawa Dental University and included only patients who provided written consent (approval number 792).

Measurement methods

The measurement methods described in our previous study were used again here² and are outlined below.

1. Advanced imaging was performed using a 64 slice multi-detector 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 (Figure 1).
3. The images captured in the soft tissue mode that were scanned parallel to the mandibular plane and included the mental foramen were selected from among the acquired images.
4. A threshold value of 500 HU was used to distinguish the cortical 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 × 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.

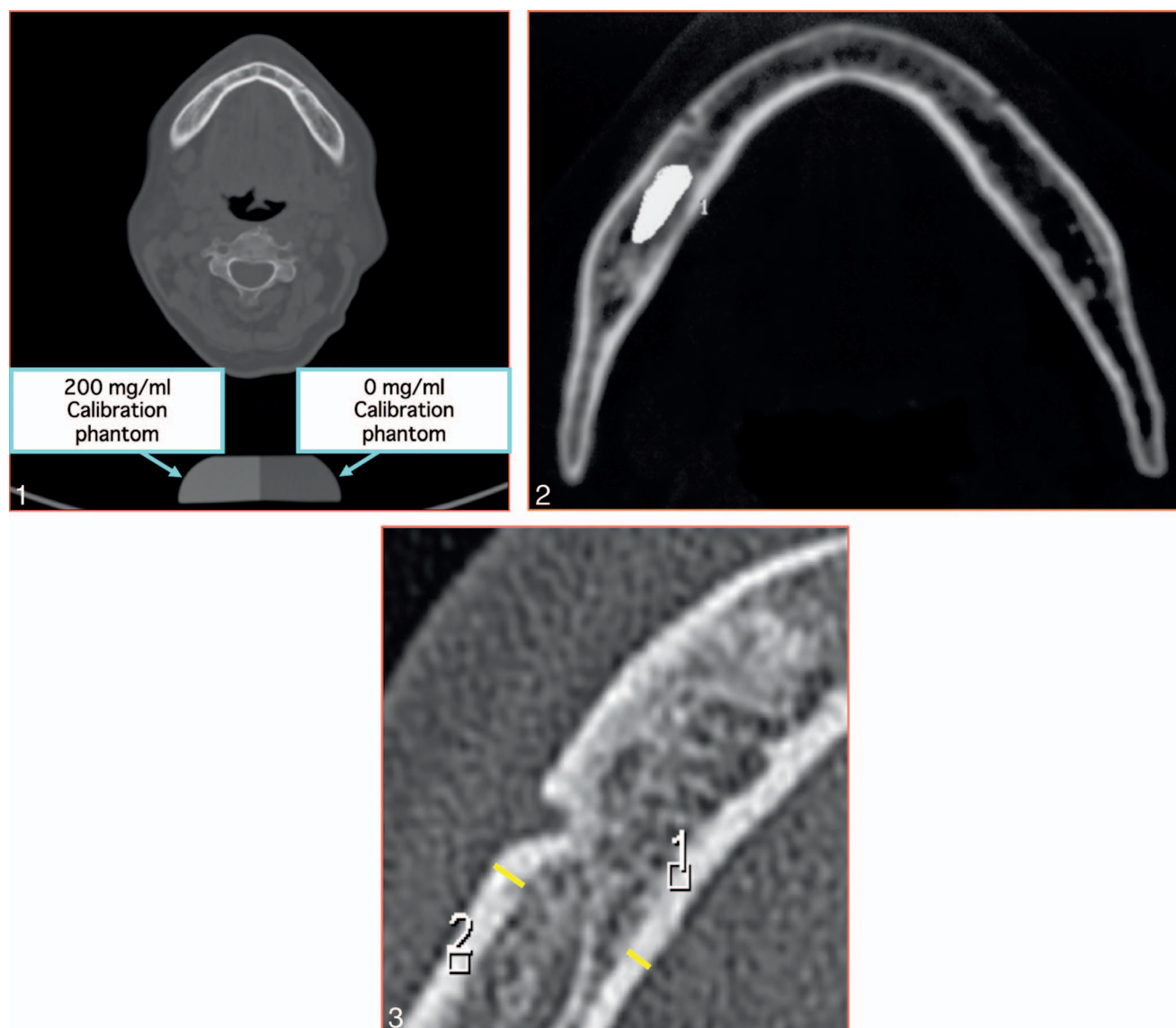
RESULTS

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



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†

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

* $P < .05$.

†BP indicates patients receiving bisphosphonate therapy; BMD-C, bone mineral density of cortical bone; BMD-T, bone mineral density of trabecular bone.

TABLE 3

This table shows the mean values and standard deviations of the bone mineral density in the cortical and trabecular bone, as well as the thickness of the cortical bone in both the BP and non-BP groups. There was a statistically significant difference in the cortical BMD between the groups ($P < .001$)†

	BMD-C (mg/mL)	BMD-T (mg/mL)	Cortical Thickness (mm)
BP	1449 ± 140*	83 ± 55	2.5 ± 0.8
Non-BP	1035 ± 99	101 ± 80	2.0 ± 0.7

* $P < .001$.

†BP indicates patients receiving bisphosphonate therapy; non-BP, patients not receiving BP therapy; BMD-C, bone mineral density of cortical bone; BMD-T, bone mineral density of trabecular bone.

difference was found between the cancellous BMDs of the 2 groups.

There was no significant difference in cortical bone thicknesses between the groups. The results are summarized in Table 3.

Association of duration of BP use with BMDs and cortical bone thicknesses

No correlations were found between the duration of BP use and the cortical or cancellous BMDs. However, a longer duration of BP use tended to contribute to increased cortical bone thickness ($P < .01$). Graphs of this data are displayed in Figures 4 through 6.

Discussion

The results of this study suggest that BP use is associated with cortical BMD and thickness. Mashiba et al⁶ studied cortical BMD in beagle dogs and reported significantly increased cortical BMDs in the edentulous mandibular region of the BP group, which is similar to our findings.

Furthermore, Mashiba et al⁶ investigated the effect of BP therapy on cortical bone mass and reported that there was no increase in cortical bone mass histologically, despite an increased cortical BMD. The investigators suggested that the increased mineralization—but not the increased bone mass—contributed to the increase in cortical BMD. Carvas et al⁷ also reported a significant increase in cortical bone thickness and mass in the tibia of osteoporotic rabbits following zoledronic acid administration. In this study, cortical bone thickness was found to increase with extended BP use, which is consistent with the results of a study by Torres et al⁸ utilizing intravenous BP. Collectively, these findings suggest that BPs increase not only cortical BMD but also cortical bone thickness.

With regards to implant failure rate, Zahid et al⁹ conducted a retrospective study to evaluate whether patients who took BPs were at greater risk of implant failure. In that study, 26 patients taking BPs received a total of 51 dental implants. Three implants failed, yielding success rates of 94.11% and 88.46% for the implant-based and patient-

based analyses, respectively. A significant ($P = .001$; OR = 3.25) association was found between the use of BPs and implant thread exposure.⁹ In 2012, Yip et al³ reported a decreased implant survival rate (66.7%) in patients receiving oral BPs. The investigators in that study found a higher correlation between oral BP use and implant failure in the maxilla than in the mandible. A retrospective study by Memon et al⁴ evaluated 153 implants in 100 patients receiving oral BPs to determine the early implant failure rate. The investigators reported a higher early implant failure rate (6.5%) in patients receiving BPs than in those not receiving BPs, but the difference was not significant. De-Freitas et al⁵ also conducted a systematic review of the association between BP treatment and dental implants. They reported a significantly higher implant failure rate (8.5%) in patients receiving BP than in the control patients (1.6%). In the present study, 11 patients who were treated with BPs received a total of 27 implants. Although none of the patients developed ONJ, 3 implants (7.7%) in 3 patients (17.6%) failed to achieve osseointegration and were lost before functional loading. Additional analyses of the patients who experienced early implant failure revealed that their cortical BMDs were ≥ 1 SD different than the average density of the BP group. This can be explained by the enhanced mineralization of the cortical bone in the edentulous posterior mandible. In addition, the BP-induced inhibition of osteoclast function also decreased the implant-bone contact rate, which further hindered osseointegration.

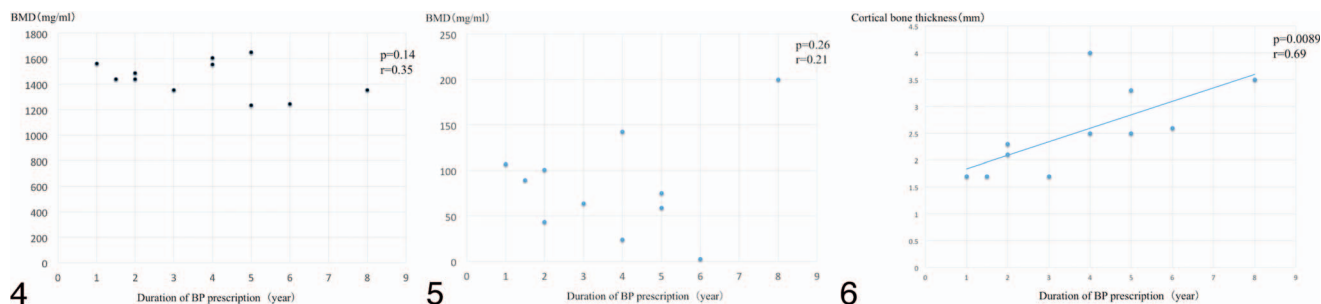
Therefore, before initiating implant treatment in patients receiving oral BPs, clinicians should be mindful of the bone density in the ROI and the risks of overheating and reduced remodeling due to bone sclerosis. A preoperative explanation of the risks of ONJ and aggravation of osseointegration should 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



FIGURES 4–6. **FIGURE 4.** Correlation between cortical bone mineral density and duration of bisphosphonate use. **FIGURE 5.** Correlation between trabecular bone mineral density and duration of bisphosphonate use. **FIGURE 6.** Correlation between cortical bone thickness and duration of bisphosphonate use.

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.

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