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Enhancement of peri-implant bone formation via parathyroid hormone administration in a rat model at risk for medication-related osteonecrosis of the jaw

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ABSTRACT

Purpose: Dental implant-associated medication-related osteonecrosis of the jaw has been frequently reported in patients administered bisphosphonates (BPs) to prevent osteoporosis. The aim of this study was to investigate the effect of intermittent administration of parathyroid hormone (PTH) on peri-implant bone in the maxillae of ovariectomized rats systemically administered BPs.
Methods: Thirty 8-week-old female Sprague-Dawley rats were randomly divided into 3 groups. The OVX-ZP group included ovariectomized rats administered 60 μg/kg of zoledronate once a week for 6 weeks and 30 μg/kg PTH after implant installation. The OVX-Z group included ovariectomized rats administered 60 μg/kg of zoledronate once a week for 6 weeks and saline after implant installation, and the control group included rats that underwent a sham operation and were then administered saline. Rats were sacrificed 4 weeks after implant placement for histomorphometric and micro-computed tomography (CT) analyses.
Results: The average bone area percentage was greater in the OVX-ZP group than in the OVX-Z group (53.4%±4.0% vs. 28.9%±9.5%, P=0.01). The bone-to-implant contact ratio was 50.8%±1.4% in the OVX-ZP group and 16.9%±2.4% in the OVX-Z group (P=0.012). The average bone volume ratio as shown on micro-CT was 31.3%±19.8% in the OVX-ZP group and 19.4%±9.3% in the OVX-Z group (P=0.045). The OVX-ZP and OVX-Z groups displayed similar trabecular thickness (0.06±0.004 mm vs. 0.06±0.002 mm) (P>0.05) and trabecular separation (0.21±0.02 mm vs. 0.29±0.13 mm) (P>0.05). However, the number of trabeculae in the OVX-ZP group was significantly higher than that in the OVX-Z group (4.3±1.33/mm^3 vs. 2.2±0.19/mm^3) (P=0.024).
Conclusions: The present findings indicate that intermittently-administered PTH can promote peri-implant bone formation and suggest that PTH administration may aid in effective treatment for medication-related osteonecrosis of the jaw after dental implantation.

Keywords: Bisphosphonate-associated osteonecrosis of the jaw; Dental implants; Osteoporosis; Parathyroid hormone; Zoledronic acid

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Bisphosphonates (BPs) have been widely prescribed for the prevention and treatment of osteoporosis, osteopenia, Paget disease, and other metastatic malignant diseases [1]. When deposited into the bone, they are potent inhibitors of the differentiation and function of osteoclasts and ultimately induce osteoclastic apoptosis [2]; as such, they decrease bone remodeling [2]. The association between long-term use of BPs and medication-related osteonecrosis of the jaw (MRONJ) was first reported in 2003 [3]. Researchers have since developed different theories to attempt to explain the pathophysiology of MRONJ [4,5]. After the definition and staging of MRONJ were presented in detail by the American Association of Oral and Maxillofacial Surgeons (AAOMS) [5], successful treatment outcomes for all stages of MRONJ after surgical [6-8] and nonsurgical treatments [9,10] have been reported. However, MRONJ still adversely affects quality of life because it results in substantial morbidity.

Dental implants can be valuable for the recovery of masticatory function of patients experiencing tooth loss. MRONJ associated with dental implants has been frequently reported in patients receiving BPs for the prevention of osteoporosis, and treatment with BPs is considered to be a potential local risk factor for MRONJ [11-13]. Although the frequency of MRONJ has been reported to be relatively low [14], dental implantation in patients receiving BP treatment remains a subject of debate [14-16].

Recent studies have suggested that parathyroid hormone (PTH) could be used to effectively treat MRONJ [17-19] and lesions developed after dental implantation [20]. At low doses, intermittent administration of PTH can promote the maturation of circulating osteoblast precursors and the differentiation of lining cells into osteoblasts [21]. In addition, it can increase bone turnover by stimulating new bone generation as part of bone metabolism [21-23]. Its anabolic actions may counter the inhibitory functions of BPs, which are known to interfere with bone remodeling [22,24].

Few studies have systemically administered BPs in animal models to induce MRONJ [17-19]. Some clinical reports have described the successful use of PTH for the management of MRONJ [20,24,25]. To the best of our knowledge, experimental evidence from osteoporotic animal models treated with BPs prior to dental implantation in the maxilla has not yet been reported. Therefore, we established an osteoporotic animal model via ovariecomy (OVX) and inserted an implant into the maxilla of each animal. In this study, we hypothesized that PTH could exert a stimulatory effect on the remodeling of peri-implant bone previously exposed to BPs, thereby reversing the deteriorating influence of BPs on bone. To investigate the effect of intermittently-administered PTH on the bone response around the implant, we performed histomorphometric analyses and micro-computed tomographic (micro-CT) examinations.

MATERIALS AND METHODS

Animals

Thirty 8-week-old female Sprague-Dawley rats (weight, 250–300 g) were purchased (Nara Biotech, Pyeongtaek, Korea). All animal handling and surgical procedures were in compliance with guidelines for the care and use of laboratory animals published by the Institutional Animal Care and Use Committee of Bucheon St. Mary's Hospital (BSM 14-004) and the Animal Research: Reporting of *In Vivo* Experiments checklist. Animals were kept at a

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controlled temperature (25°C±1°C) with humidity of 55% and lighting conditions of a 12-/12-hour light/dark cycle, with unrestricted access to food and water.

Experimental design

Rats were randomly assigned to 1 of 3 groups. The OVX-ZP group (n=10) contained ovariectomized rats that were administered zoledronate (Sigma-Aldrich, St. Louis, MO, USA) and PTH (rhPTH 1-34; GenScript, Piscataway, NJ, USA) using vehicle (0.1 M Tris-HCl, pH 7.5, and 2% rat serum albumin). The OVX-Z group (n=10) included ovariectomized rats that were administered zoledronate and vehicle only. The control group (n=10) consisted of rats that underwent a sham operation followed by administration of the same volume of normal saline instead of zoledronate and PTH. One week after acclimatization, rats from the OVX-ZP and OVX-Z groups underwent bilateral OVX to induce osteoporosis. Control animals received the sham operation only. Procedures were performed under 3% isoflurane (JW Pharmaceutical Co., Seoul, Korea) inhalation anesthesia. The experimental design is presented in Figure 1.

Tooth extraction and administration of zoledronate

Eight weeks following OVX, the maxillary left first molar was extracted without injuring the alveolar bone to reproduce the edentulous ridge. This procedure was performed under general anesthesia with 30 mg/kg of zolazepam-tiletamine (Zoletil®, Virbac, Carros, France) and 10 mg/kg of xylazine hydrochloride (Rompun®, Bayer, Leverkusen, Germany) administered by intramuscular injection. A 4-week healing period was allowed for the extraction wound to become completely covered by mucosa. Then 60 μg/kg of zoledronate dissolved in 0.9% sodium chloride solution was intraperitoneally administered once a week for 6 weeks to the rats in the OVX-ZP and OVX-ZA groups to induce a BP-loaded osseous condition of the jawbone. The same volume of saline was provided to the rats in the sham-operated control group. The amount of zoledronate was adjusted as described in a previous study [26].

Implant placement and administration of PTH

After 6 weeks of zoledronate administration, general anesthesia was administered again, a recipient site was prepared with a pilot drill (diameter, 1.0 mm) at the site of the previous extraction, and a titanium screw implant (diameter, 1.2 mm; length, 3 mm) (commercial-grade Ti; Leibinger-Stryker, Freiburg, Germany) was placed (Figure 2). Copious irrigation with normal saline was used to minimize heat production during implant installation. For

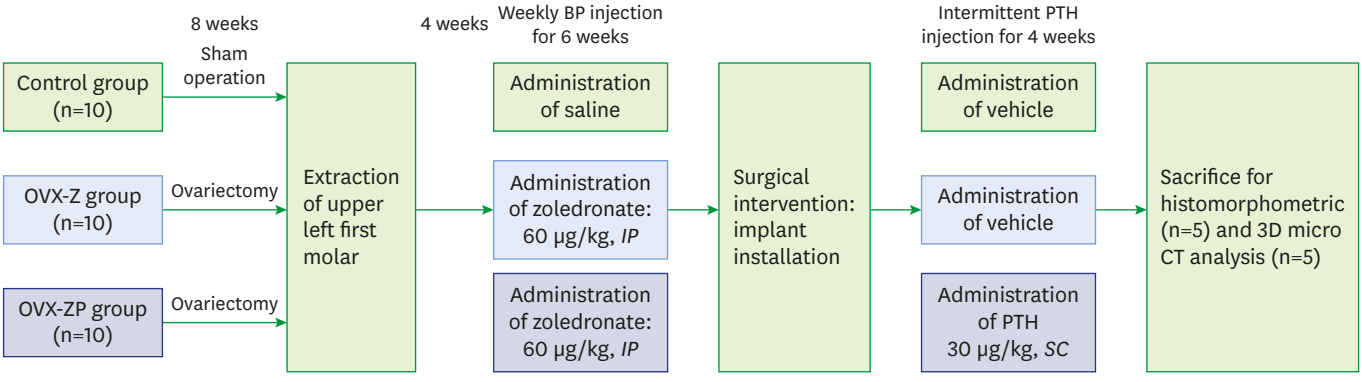

Figure 1. Flow chart showing the experimental design. Group were randomly divided into 3 groups: ovariectomized, zoledronate- and parathyroid hormone-administered group (OVX-ZP), ovariectomized, zoledronate-only group (OVX-Z), and sham-operated control group (Control).
BP: bisphosphonates, IP: intraperitoneal, PTH: parathyroid hormone, SC: subcutaneous, 3D: 3-dimensional, CT: computed tomography.

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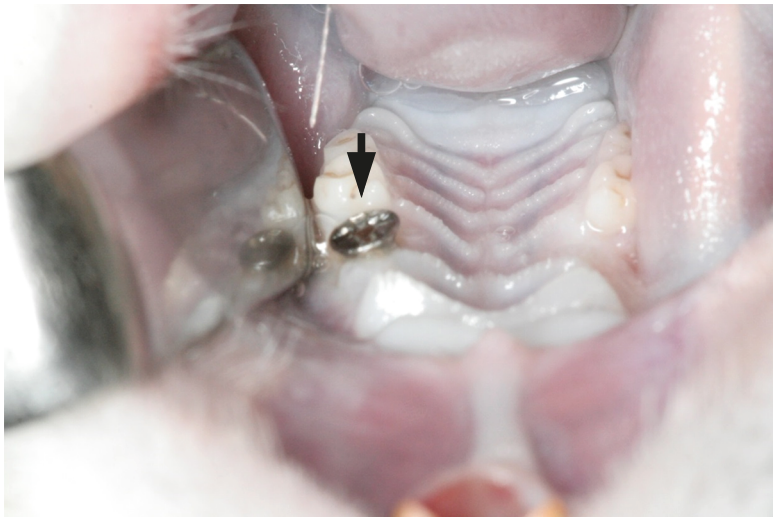

Figure 2. Placement of the implant screw in the maxilla. The implant screw (arrow) was installed into the healed socket site of the left maxillary first molar extracted 4 weeks previously in an ovariectomized and bisphosphonate-administered rat or a sham-operated control rat.

3 days postoperatively, 5 mg/kg of gentamicin (Kukje Pharma Co., Seongnam, Korea) and 5 mg/kg of ketoprofen (Bukwang Pharm aceutical Co., Seoul, Korea) were administered intramuscularly.

For rats in the OVX-ZP group, 30 μg/kg of PTH in vehicle was administered via subcutaneous injection in the dorsum beginning on the day after implant placement. The same volume of normal saline was administered to rats in the OVX-Z group and the sham-operated control group. The amount of PTH was titrated based on our previous studies [27,28]. Four weeks later, all animals in each group were killed with carbon dioxide, and the alveolar bone including the screw implant was collected from each animal. Five bone blocks were used for the histomorphometric analysis, and the remaining blocks were kept for the micro-CT analysis.

Preparation of histologic and histomorphometric analysis

Alveolar bone blocks, including screw implants, were removed from the maxillae, fixed in neutrally-buffered 10% formalin (Sigma-Aldrich) for 48 hours, dehydrated by graded ethanol concentrations, and then embedded in methyl methacrylate (Heraeus Kulzer, Wehrheim, Germany). After polymerization, tissue specimens were sectioned along the longitudinal axis of the implant body at a thickness of approximately 35±5 μm and stained with Masson trichrome for microscopic observation. An experienced examiner without knowledge of the specimens' group of origin performed the histologic and histomorphometric analyses. Images were captured using a microscope equipped with a digital camera (Leica Microsystems, Heerbrugg, Switzerland). Parameters were analysed with i-Solution software (IMT Technology, Vancouver, Canada). The bone-to-implant contact ratio (BIC, %) was defined as the percentage of bone contacted along the total length of the implant. Bone area/tissue area (BA/TA, %) was defined as the percentage of bone area per tissue area within the thread region.

Micro-CT assessment

Specimens were scanned with a high-resolution micro-CT scanner (Skyscan 1173, Bruker MicroCT, Kontich, Belgium) in the axial direction vertical to the longitudinal axis of the implant, as previously described [27,28]. An image pixel size of 5.33 μm was obtained at

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130 kV and 45 μA with a 1.0-mm aluminium filter and a 5,000-ms exposure time. Three-dimensional (3D) images were restored with the Nrecon reconstruction program (Bruker MicroCT). The region of interest (ROI) was defined as the amount of bone from 1.0 mm below the neck of the screw implant, extending 2.5 mm apically and 0.3 mm outward from the implant perimeter. The following micro-architectural parameters were assessed: bone volume (BV, mm^3), tissue volume (TV, mm^3), bone volume ratio (defined as the ratio of bone volume to tissue volume [BV/TV], %), trabecular thickness (Tb.Th, mm), trabecular number (Tb.N, $1/mm^3$), and trabecular separation (Tb.Sp, mm).

Statistical analysis

All quantitative data are presented as mean±standard deviation. Because the data did not show a normal distribution, the Kruskal-Wallis test was used to investigate potential differences between groups, and the Mann-Whitney test was used for pairs of groups. All statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). *P* values less than 0.05 were considered to indicate statistical significance.

RESULTS

Histological and histomorphometric findings

In the histological findings, no osteonecrotic lesions were found in the control group. However, insufficient healing of the alveolar bone around the implants and an extended osteolytic area were observed in the OVX-Z group. In the OVX-ZP group, although half of the implant surface was covered with bone, less bone fill was found than in the control group. Additionally, the lamellate bone, which extended from the adjacent original bone, was thicker in the OVX-ZP and control groups than in the OVX-Z group (Figure 3).

Histomorphometric measurements revealed that PTH administration affected bone formation around the implant. The BA/TA and BIC values around the implants are shown in Table 1. At 4 weeks, the OVX-ZP group, which was treated with PTH, exhibited more

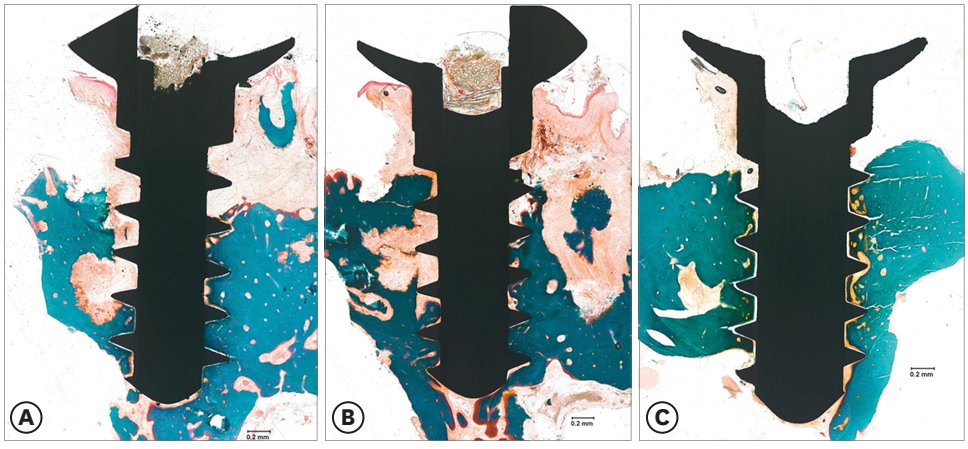

Figure 3. Representative histologic images of the alveolar bone around the implant in the rat maxilla. (A) The OVX-ZP group showed an implant surface partially covered with bone. (B) The OVX-Z group (B) showed impaired healing of the bone around the implant and many necrotic sequestra. (C) The Control group displayed good osseointegration of the implant after 4 weeks (Masson trichrome staining). Group were randomly divided into 3 groups: ovariectomized, zoledronate- and parathyroid hormone-administered group (OVX-ZP, ovariectomized, zoledronate-only group (OVX-Z), and sham-operated control group (Control).

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Table 1. Average values of BA/TA and BIC ratio around implants placed in the maxillae of rats at 4 weeks (n=5)

Variables	Group		
	OVX-ZP	OVX-Z	Control
BA/TA (%)	53.4±4.0[a]	28.9±9.5	67.0±4.7
BIC (%)	50.8±1.4[b]	16.9±2.4	69.3±9.8

All values are presented as mean±standard deviation. Group were randomly divided into 3 groups: ovariectomized, zoledronate and parathyroid hormone administered group (OVX-ZP), ovariectomized; zoledronate only group (OVX-Z), and sham-operated control group (Control).
BA/TA: bone area/tissue area, BIC: bone-to-implant contact.
[a]The BA/TA of group OVX-ZP is significantly greater than that of group OVX-Z (P=0.01). [b]The BIC of group OVX-ZP is significantly greater than that of group OVX-Z (P=0.012).

bone formation than the OVX-Z group. The average BA/TA was 53.4%±4.0% in the OVX-ZP group and 28.9%±9.5% in the OVX-Z group, constituting a statistically significant difference between the groups (P=0.010). The average BIC in the OVX-ZP group was 50.8%±1.4%, which was significantly higher than that in the OVX-Z group (16.9%±2.4%) (P=0.012).

Micro-CT analysis

Micro-CT was performed to assess the bone structure and to examine structural differences in the bones around the implants. Two-dimensional images of the maxillary bone of the OVX-ZP group showed somewhat higher degrees of radio-opacity and partial bone formation around the implants. In contrast, the OVX-Z group displayed compromised healing of the peri-implant bone, as well as defective sequestrum-like bone (Figure 4). In the OVX-ZP group, 3D reconstruction images demonstrated partial coverage of bone around the implants, while the OVX-Z group showed newly-formed bone around the implants (Figure 5).

The values of 3D micro-structural indices of bone around the implants in the maxillae of rats at 4 weeks are shown in Table 2. The BV/TV of the OVX-ZP group was 31.3%±19.8%, which was significantly greater than that (19.4%±9.3%) in the OVX-Z group (P=0.045). However, the OVX-ZP and OVX-Z groups showed no significant difference in Tb.Th (P>0.054) or Tb.Sp (P>0.05), although the Tb.N in the OVX-ZP group was significantly (P=0.024) higher than that in the OVX-Z group.

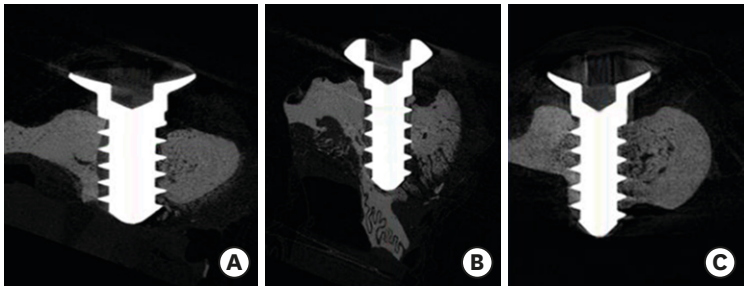

Figure 4. Two-dimensional micro-computed tomography images of the alveolar bone in the rat maxilla. (A) The OVX-ZP group showed somewhat greater radio-opacity and favorable bone formation around the implant. (B) The OVX-Z group displayed defective bone and compromised healing of the bone around the implant. (C) The Control group showed intimate bone-to-implant contact. Group were randomly divided into 3 groups: ovariectomized, zoledronate- and parathyroid hormone-administered group (OVX-ZP), ovariectomized, zoledronate-only group (OVX-Z), and sham-operated control group (Control).

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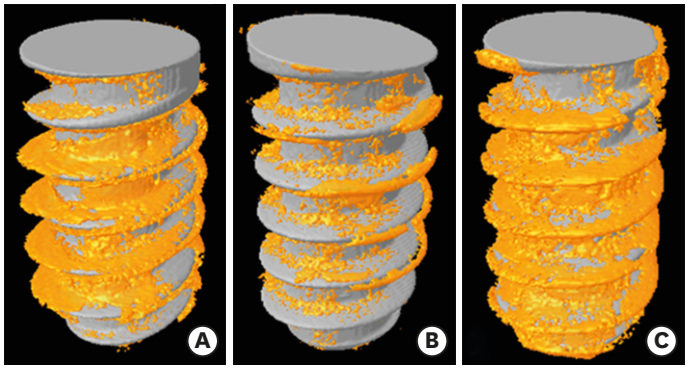

Figure 5. Three-dimensionally reconstructed micro-computed tomography images of the implant and the surrounding bone. (A) The OVX-ZP group demonstrated partial coverage of the implant by peri-implant bone. (B) The OVX-Z group showed poor formation of the new bone around the implant. (C) The Control group displayed massive formation of the bone around the implant (gray color: titanium screw implant; yellow color: peri-implant bone). Group were randomly divided into 3 groups: ovariectomized, zoledronate- and parathyroid hormone-administered group (OVX-ZP), ovariectomized, zoledronate-only group (OVX-Z), and sham-operated control group (Control).

Table 2. Average values of 3D micro-structural indices of bone around implant placed in maxillae of rats at 4 weeks (n=5)

Variables	Group		
	OVX-ZP	OVX-Z	Control
TV (mm^3)	6.97±0.06	6.98±0.02	6.99±0.08
BV (mm^3)	2.19±1.39	1.35±0.64	2.48±1.01
BV/TV (%)	31.3±19.8[a)]	19.4±9.3	35.3±14.28
Tb.Th (mm)	0.06±0.004	0.06±0.002	0.07±0.003
Tb.N ($1/mm^3$)	4.3±1.33[b)]	2.2±0.19	5.7±0.95
Tb.Sp (mm)	0.21±0.02	0.29±0.13	0.23±0.02

All values are presented as mean±standard deviation. Group were randomly divided into 3 groups: ovariectomized, zoledronate and parathyroid hormone administered group (OVX-ZP), ovariectomized; zoledronate only group (OVX-Z), and sham-operated control group (Control).
TV: tissue volume, BV: bone volume, BV/TV: bone volume/tissue volume, Tb.Th: trabecular thickness, Tb.N: trabecular number, Tb.Sp: trabecular separation.
[a)]The BV/TV of group OVX-ZP is significantly greater than that of group OVX-Z (P=0.045). [b)]The Tb.N of group OVX-ZP is significantly greater than that of group OVX-Z (P=0.024).

DISCUSSION

Recently, risk assessments and established guidelines for predicting the development of MRONJ after dentoalveolar surgery—including tooth extraction and dental implantation in patients administered BPs—have been documented by the AAOMS [5]. As such, patients who will be on long-term BP therapy over 4 years should be adequately informed about the risk of compromised bone healing and the possibility of developing MRONJ. However, no proven curative strategies exist for MRONJ after dental implantation [6,8,29]. To date, no studies have examined the effect of PTH by simulating clinical circumstances [17,18,20,24]. The aim of this study was to determine the effect of PTH on MRONJ resolution. The onset of MRONJ following dental implant placement can occur after surgery or after a delayed period, depending on the timing of BP administration [13,30,31]. In this study, to minimize the risk of oral infection, zoledronate was not administered until the extraction socket was completely covered by mucosa. The conditions used in this experimental study mimicked the clinical scenario in which the pharmacological effect of BPs accumulates in the edentulous alveolar bone of the osteoporotic patient. As a result, some osteonecrotic sequestra were observed in the peri-implant bone in histologic specimens of the OVX-Z group, despite the

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lack of clinical symptoms such as bone exposure or gingival ulceration. These findings could indicate that dental implants might unavoidably result in localized trauma to the recipient bone site affected by BPs [32].

The dose and route of BP administration in this study were based on those detailed in previous studies [26,33]. Rats in the BP-treated groups were administered an equivalent cumulative dose to a single intravenous administration of zoledronate every 3 to 4 weeks in a human [34]. Considering the rapid healing rate of rodent bone, the dosage frequency was once a week for 6 weeks. Although the pharmacodynamics of the route of administration of zoledronate in rodents is not fully understood, plasma concentrations are known to be relatively low when the intraperitoneal route is used and the period of drug exposure is relatively short [35]. Thus, rats in this study were considered to have received an intraperitoneal dose equivalent to the standard intravenous dose in humans.

The effects of PTH on dental tissues have been studied [21-23], and several treatment options for MRONJ have been recommended [18,19,36]. Although the mechanism by which PTH improves the healing of bone tissue has not been completely elucidated, PTH may regulate bone resorption by increasing osteoclastic activity [37]. PTH exerts a fast-acting, robust stimulatory effect on bone remodeling, even in cases of previous exposure to BPs [38,39]. It has been shown that intermittent PTH use can reduce the development of MRONJ in patients with a history of systemic or long-term oral BP use [20,25,31,36]. The histomorphometric results of the present study demonstrated that intermittent injections of PTH could decrease the amount of osteonecrotic bone around implants. Intermittent PTH injections also enhanced the osseointegration of implants by increasing bone regeneration and volume. The results of the microstructural analysis also revealed that the BV and Tb.Ns values of the OVX-ZP group were higher than those of the OVX-Z group. These results support the premise that PTH can act as an antagonist of the suppressive effect of BPs on bone turnover.

No clinically valid MRONJ was observed in any group in the present study. The experimental animals did not show exposed or probeable bone. However, micro-CT images of the OVX-Z group revealed more prominent peri-implant radiolucency and osteolytic changes around the implants than were observed in the OVX-ZP group. The OVX-Z group also showed a greater extent of osteosclerotic areas and sequestra in 2D images than the OVX-ZP group. We used MRONJ as the basis for our research, and our results still could meet the criteria of at-risk or stage 0 MRONJ as defined by the AAOMS. Thus, our experimental results could still be used to assess the benefits of PTH for the treatment of MRONJ [5].

The microstructural parameters of the alveolar bone at the implant sites in the OVX-ZP group showed increased bone formation, as demonstrated by higher Tb.N and Tb.Th values, although the difference was not statistically significant. In addition, the BV/TV of bone as calculated by micro-CT matched the percentage of bone as assessed in the histomorphometric analysis [40]. These results support the claim that PTH can actively promote anabolic bone deposition [41], suggesting that PTH can be used in the management of MRONJ because it augments effective bone remodeling.

The present study had several limitations that hinder the generalizability of the results. First, the number of experimental animals was not sufficient to allow us to perform statistical analyses based on the mean values of measurements or to draw statistically significant conclusions related to some parameters. Further studies using a greater number of

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experimental animals are needed to allow for more statistically meaningful results. Second, the experimental period was too short to observe the prolonged effect of PTH, including its safety and efficacy. Future experiments are also needed to determine the long-term side effects, most effective dosage, and optimal interval of PTH administration for the prevention and treatment of MRONJ. Third, the administration of 30 μg/kg of PTH is already known to increase the cancellous bone volume in the proximal metaphyses of OVX rats [2]. However, to clarify the action of PTH, more refined protocols are needed in terms of the duration, dose, pattern, and frequency of PTH administration. Finally, no experimental group received PTH alone. Without such a group, it was difficult to conclude that PTH affected bone turnover in general. However, the use of PTH in healthy patients has not been approved for off-label use in the treatment of MRONJ. Thus, caution is needed when interpreting the results obtained with this animal model.

Despite these limitations, the results of this study revealed that intermittently-administered PTH increased peri-implant bone formation in the maxillae of osteoporotic rats administered BPs. The clinical significance of this finding is that intermittent PTH administration may aid in the effective treatment of MRONJ, particularly when elective dental implant installation is planned for patients with a history of long-term BP usage for the treatment of osteoporosis.

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