Histopathological Effects of Teriparatide in Medication-Related Osteonecrosis of the Jaw: An Animal Study

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Purpose: Osteonecrosis of the jaw after tooth extraction is a major complication in patients using bisphosphonates (BPs) for bone lesions, such as for the treatment of osteoporosis. The purpose of this study was to investigate the histopathologic effects of teriparatide (a synthetic parathyroid hormone) on rats developing osteonecrosis with BP use.

Materials and Methods: Rats (n = 80) that had been injected intraperitoneally with zoledronic acid for 7 weeks were used. Maxillary first molar extractions and bone defects were established in the same region in the eighth week. Teriparatide was administered subcutaneously to prevent osteonecrosis. Animals were sacrificed and histopathologic changes were examined. Osteoblasts, osteoclasts, inflammatory phase of bone healing, and osteonecrotic areas were evaluated.

Results: The osteoclast numbers were larger in the experimental groups (teriparatide administered before and immediately after tooth extraction) than in the control group (administered zoledronic acid). The inflammatory phase of bone healing was more pronounced in the experimental group (teriparatide administered before tooth extraction) than in the control group. There were significant differences in osteoclast numbers and in the inflammatory phase of bone healing between the experimental and control groups ($P < .05$). The osteoblast numbers and osteonecrotic areas were similar in size between the experimental and control groups. There were no significant differences ($P > .05$).

Conclusions: BPs have negative effects on osteoclasts and the inflammatory phase of bone healing, whereas teriparatide was found to be effective in eliminating the negative effects of BPs. Teriparatide had positive effects in preventing osteonecrosis; therefore, teriparatide could be an effective agent for MRONJ.

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Osteonecrosis of the jaws (ONJ) after tooth extraction is a major complication for patients using bisphosphonates (BPs) to prevent or treat metastatic cancer, multiple myeloma, Paget disease, hypercalcemia, and osteoporosis.[1] ONJ associated with BP treatment has been referred to by several acronyms, including BRONJ

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(bisphosphonate-related ONJ), BRON (bisphosphonate-related osteonecrosis), BON (bisphosphonate osteonecrosis), BAONJ (bisphosphonate-associated ONJ), and simply ONJ. The recognition of ONJ as a complication of other drugs, including the receptor activator of nuclear factor-κB ligand inhibitor denosumab and antiangiogenic agents, prompted a special committee of the American Association of Oral and Maxillofacial Surgeons to recommend the term *medication-related osteonecrosis of the jaw* (MRONJ).[2] In many cases, the treatment of MRONJ is unsuccessful, because BPs decrease bone resorption by inhibiting osteoclast function, and the drugs have antiangiogenic effects.[3]

Teriparatide is a new synthetic parathyroid hormone that has been used recently to improve the thickness and quality of bone. It is an alternative to anti-osteoporosis drugs and antiresorptive agents.[4] Teriparatide stimulates osteoclasts and osteoblasts when bone resorption occurs, producing an anabolic effect.[5,6] In the literature, there are few data about the use of teriparatide in cases of MRONJ. Recently, clinical cases were reported that showed teriparatide usage was beneficial in cases of MRONJ.[5-8] Dayisoylu et al[9] and Ersan et al[10] evaluated the effects of teriparatide usage in BRONJ after immediate tooth extraction. However, there is no reported study evaluating the effects of teriparatide usage before tooth extraction and after the occurrence of MRONJ. The hypothesis of this experiment was that teriparatide usage would be beneficial in cases of MRONJ, and the study investigated which period (before tooth extraction, at the time of tooth extraction, and after the occurrence of MRONJ) would be best for teriparatide usage.

Materials and Methods

Ethical approval was obtained from Inonu University animal research ethics committee (Malatya, Turkey).

Eighty Wistar albino male rats were used. Recent studies on MRONJ have used rat models.[9,11-13] In accord with previous animal studies, all rats were injected intraperitoneally with zoledronic acid (0.4 mg/kg once a week) for 7 weeks. In addition, all rats were injected with dexamethasone (1 mg/kg intraperitoneally weekly at weeks 5, 6, and 7). At the end of 7 weeks, the maxillary left first molars were extracted and bone defects with a diameter of 4 mm were created in the same region under general anesthesia. Administration of teriparatide was adjusted in accord with previous studies.[14,15] During the procedures, 15 rats were excluded from the study because they died. The remaining rats were divided into 1 control group and 3 experimental groups. The groups and the procedures performed are presented in Tables 1 to 3.

CONTROL GROUP

The control group was injected with zoledronic acid and dexamethasone. No additional medication or procedure was performed in the control group. Three subgroups were created from the control group according to the time of sacrifice (C-10, week 10, n = 7; C-15, week 15, n = 8; C-17, week 17, n = 8).

EXPERIMENTAL GROUPS (PREOPERATIVE, POSTOPERATIVE, AND OSTEONECROSIS)

These rats were injected with zoledronic acid and dexamethasone. Teriparatide also was administered in these groups.

Preoperative Group

Before the tooth extraction procedure, teriparatide was injected subcutaneously for 3 weeks (0.04 mg/kg twice a week) to prevent osteonecrosis (at weeks 5, 6, and 7). Two subgroups were created from the preoperative group according to the time of sacrifice (Pre-10, week 10, n = 9; Pre-15, week 15, n = 9).

Postoperative Group

After the tooth extraction procedure, teriparatide was injected subcutaneously for 3 weeks (0.04 mg/kg twice a week) to prevent osteonecrosis (at weeks 8, 9, and 10). Two subgroups were created from the postoperative group according to the time of sacrifice (Post-10, week 10, n = 8; Post-15, week 15, n = 8).

Osteonecrosis Group

After MRONJ had occurred, teriparatide was injected subcutaneously for 3 weeks (0.04 mg/kg twice a week) for the treatment of osteonecrosis (at weeks 15, 16, and 17), and the osteonecrosis group was sacrificed at 17 weeks (O-17, n = 8).

Table 1. PROCEDURES APPLIED TO RATS IN THE CONTROL AND EXPERIMENTAL GROUPS

Weeks	Procedure	Dosage
0-7	Intraperitoneal zoledronic acid	0.4 mg/kg 1 time/wk
5-7	Intraperitoneal dexamethasone	1 mg/kg 1 time/wk
8	Tooth extraction and bone defects	
15	Osteonecrosis	

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Table 2. PROCEDURES APPLIED TO THE EXPERIMENTAL GROUPS

Experimental Groups	Period of Teriparatide Application
Preoperative	wk 5-7 (before tooth extraction)
Postoperative	wk 8-10 (immediately after tooth extraction)
Osteonecrosis	wk 15-17 (after occurrence of osteonecrosis)

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HISTOPATHOLOGIC ANALYSES

All animals were euthanized intravenously with an overdose of ketamine. The maxillary molar region of each rat was extracted as a specimen and fixed with 10% neutralized formalin solution for 48 hours. After fixation, bone specimens were decalcified in 10% formic acid at room temperature for 48 hours. Samples were obtained from the necrotic region of decalcified specimens and placed in blocks. The samples were embedded in paraffin wax and cut in a sagittal direction into 4-μm sections. The sections were stained with hematoxylin and eosin. Histopathologic changes in the groups were examined at weeks 10, 15, and 17. Osteoblasts and osteoclast numbers, the inflammatory phase of bone healing, and osteonecrotic areas were evaluated at magnifications of $\times$100 and $\times$200.[16]

STATISTICAL ANALYSIS

Analyses of the data were performed with SPSS 20.0 (SPSS, Inc, Chicago, IL). Variables were analyzed by 1-way analysis of variance and the Kruskal-Wallis test. A statistical level of significance of .05 was used in all cases.

Results

Histopathologic features of MRONJ are shown in Figure 1.

OSTEOBLASTS

At week 10, a statistically significant difference in osteoblast numbers was detected between the C-10 and Pre-10 groups (P = .043). The C-10 group had considerably larger numbers of osteoblasts than the Pre-10 group. Osteoblast numbers were larger in the C-10 group than in the Post-10 group, but the difference was not statistically significant (P = .133). At week 15, osteoblast numbers were larger in the C-15 group than in the Pre-15 and Post-15 groups, but the difference was not statistically significant (P = .331). At week 17, osteoblast numbers were smaller in the C-17 group than in the O-17 group, but the difference was not statistically significant (P = .767). Numbers of osteoblasts are shown in Figure 2.

OSTEOCLASTS

At week 10, a statistically significant difference in osteoclast numbers was detected between the C-10 and Pre-10 groups (P = .037) and between the C-10 and Post-10 groups (P = .009). The C-10 group had a significantly smaller number of osteoclasts than the Pre-10 and Post-10 groups. At week 15, a statistically significant difference in osteoclast numbers was detected between the C-15 and Pre-15 groups (P = .012) and between the C-15 and Post-15 groups (P = .049). The C-15 group had a considerably smaller number of osteoclasts than the Pre-15 and Post-15 groups. At week 17, osteoclast numbers were larger in the C-17 group than in the O-17 group, but the difference

Table 3. DRUG ADMINISTRATION AND TIME OF SACRIFICE

Groups	0-5 wk	5-7 wk	8 wk	8-10 wk	10 wk	15 wk	15-17 wk	17 wk
C-10 (n = 7)	Z	Z, D	E	—	S	—	—	—
C-15 (n = 8)	Z	Z, D	E	—	—	S	—	—
C-17 (n = 8)	Z	Z, D	E	—	—	—	—	S
Pre-10 (n = 9)	Z	Z, D, T	E	—	S	—	—	—
Pre-15 (n = 9)	Z	Z, D, T	E	—	—	S	—	—
Post-10 (n = 8)	Z	Z, D	E	T	S	—	—	—
Post-15 (n = 8)	Z	Z, D	E	T	—	S	—	—
O-17 (n = 8)	Z	Z, D	E	—	—	—	T	S

Abbreviations: C-10, control group sacrificed at week 10; C-15, control group sacrificed at week 15; C-17, control group sacrificed at week 17; D, dexamethasone; E, extraction; O-17, osteonecrosis group sacrificed at 17 weeks; Post-10, postoperative group sacrificed at week 10; Post-15, postoperative group sacrificed at week 15; Pre-10, preoperative group sacrificed at week 10; Pre-15, preoperative group sacrificed at week 15; S, time of sacrifice; T, teriparatide; Z, zoledronic acid.

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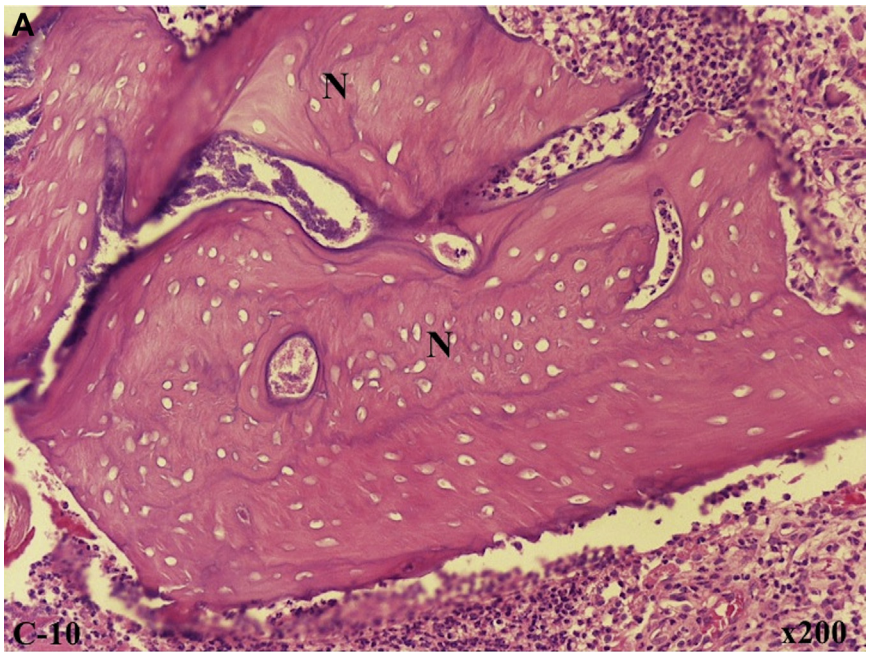

FIGURE 1. Histologic sections of the extraction socket of the first maxillary molar and its surroundings (hematoxylin and eosin stain; magnifications, ×100, ×200). *A*, In the C-10 group, the osteonecrosis area had increased, and osteoblasts were present. In addition, osteoclasts were not observed. **(Fig 1 continued on next page.)**

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was not statistically significant (P = .422). Numbers of osteoclasts are shown in Figure 3.

INFLAMMATORY PHASE OF BONE HEALING

At week 10, a statistically significant difference in the inflammatory phase of bone healing was detected between the C-10 and Pre-10 groups (P = .011). The C-10 group showed a considerably decreased inflammatory phase of bone healing than the Pre-10 group. The inflammatory phase of bone healing was less in the C-10 group than in the Post-10 group, but the difference not statistically significant (P = .172).

At week 15, the inflammatory phase of bone healing was greater in the C-15 group than in the Pre-15 group, but less than in the Post-15 group. However, no statistically significant differences were observed among these groups (P = .688).

At week 17, the inflammatory phase of bone healing was less in the C-17 group than in the O-17 group, but the difference was not statistically significant (P = .674). Results of the inflammatory phase of bone healing are shown in Figure 4.

OSTEONECROTIC AREA

The osteonecrotic area was assessed histologically. At week 10, the osteonecrotic area was larger in the C-10 group than in the Pre-10 and Post-10 groups, but the difference was not statistically significant (P = .324). At week 15, the osteonecrotic area was larger in the C-15 group than in the Pre-15 and Post-15 groups, but the differences were not statistically significant (P = .587). At week 17, the osteonecrotic area was smaller in the C-17 group than in the O-17 group, but the difference was not statistically significant (P = .653). The osteonecrotic areas are shown in Figure 5.

Discussion

BPs have been used to prevent skeletal complications of osteoporosis and metastatic bone disease.[17] Recent studies have shown that BPs have side-effects, such as MRONJ, atrial fibrillation, provocation of an acute-phase response, and renal failure.[18] MRONJ is one of the most important complications and was first reported in 2003.[1] More recently, MRONJ has been noted more commonly, but its true incidence remains undetermined.[19,20] MRONJ emerges in the jawbone, but the condition is not clearly understood. However, many factors are involved, including the presence of oral microflora, the higher turnover rate of the jawbone than of most other bones, the easily traumatized oral mucosa, and infection.[21] In addition, dental extraction or dentoalveolar surgery increases the incidence of MRONJ,[22] but MRONJ also can occur spontaneously.[23,24]

Bone remodeling occurs with the cooperation of osteocytes, osteoblasts, and osteoclasts. Damage can develop in the alveolar bone after a tooth extraction

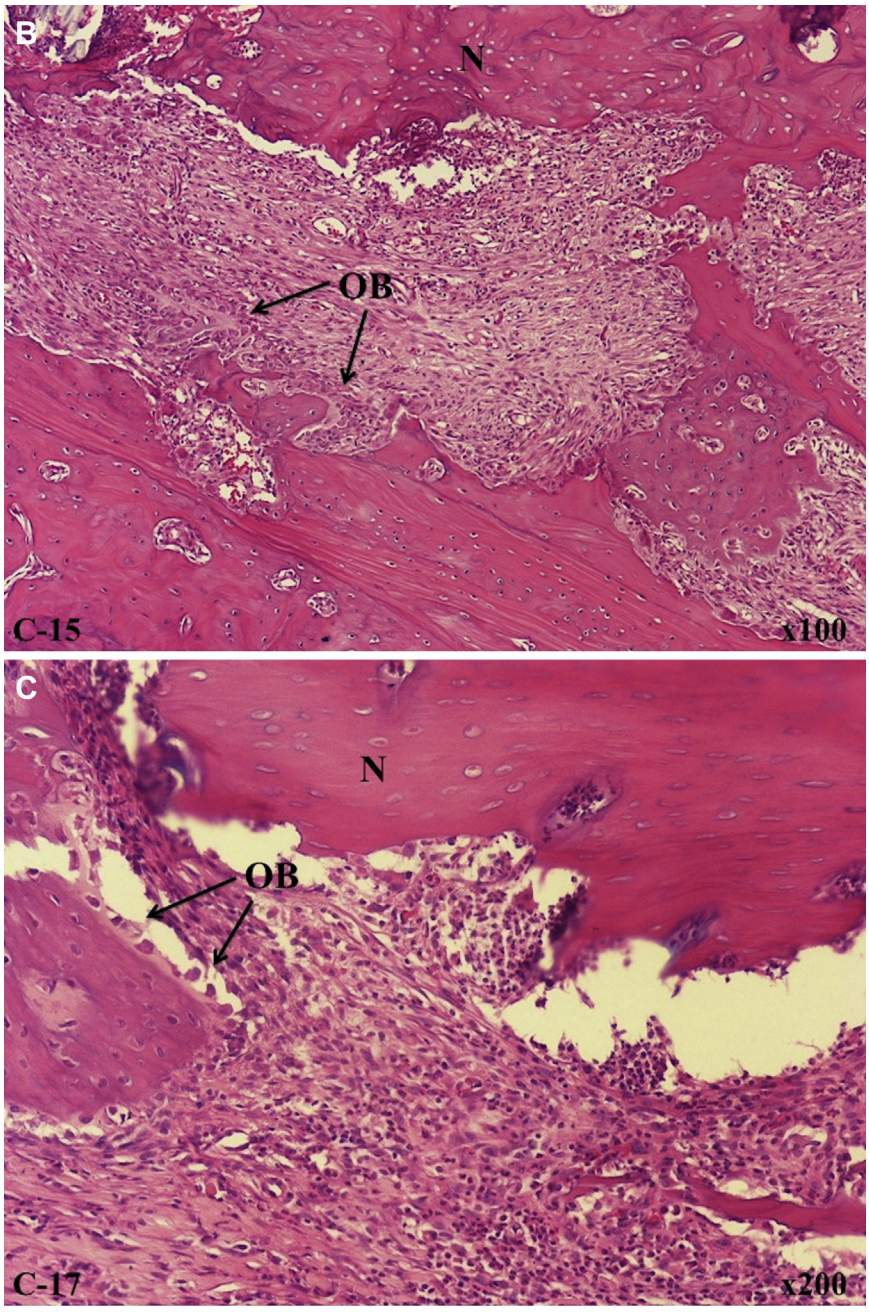

FIGURE 1 (cont'd). *B*, In the C-15 group, there were osteoblasts and few osteoclasts in the osteonecrotic areas. *C*, In the C-17 group, osteoblasts and osteoclasts were seen in the osteonecrotic areas. **(Fig 1 continued on next page.)**

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or other dental alveolar surgery; thus, osteoclasts are induced for bone repair,[16,25] and then bone resorption is initiated by the osteoclasts. Moreover, osteoblasts are stimulated during bone remodeling.[26]

Although the pathophysiology of MRONJ is unclear, there have been many hypotheses, including suppression of bone turnover, an antiangiogenesis effect, immune deficiency, and infection.[27] In bone metabolism, pyrophosphates are hydrolyzed during cellular functions. BPs accumulate in bone, but BPs are resistant to hydrolysis; hence, they suppress bone turnover.[28] The mechanism of this suppression is not fully understood, but there are several factors, including inhibition of osteoclasts, maturation of precursor cells, and decreased activity and numbers of osteoclasts.[3,29] This situation also leads to apoptosis of osteoclasts. Furthermore, recent studies have reported that BPs inhibit the activity and numbers of osteoblasts.[30,31] The result of this inhibition of osteoblasts and osteoclasts is decreased bone resorption.

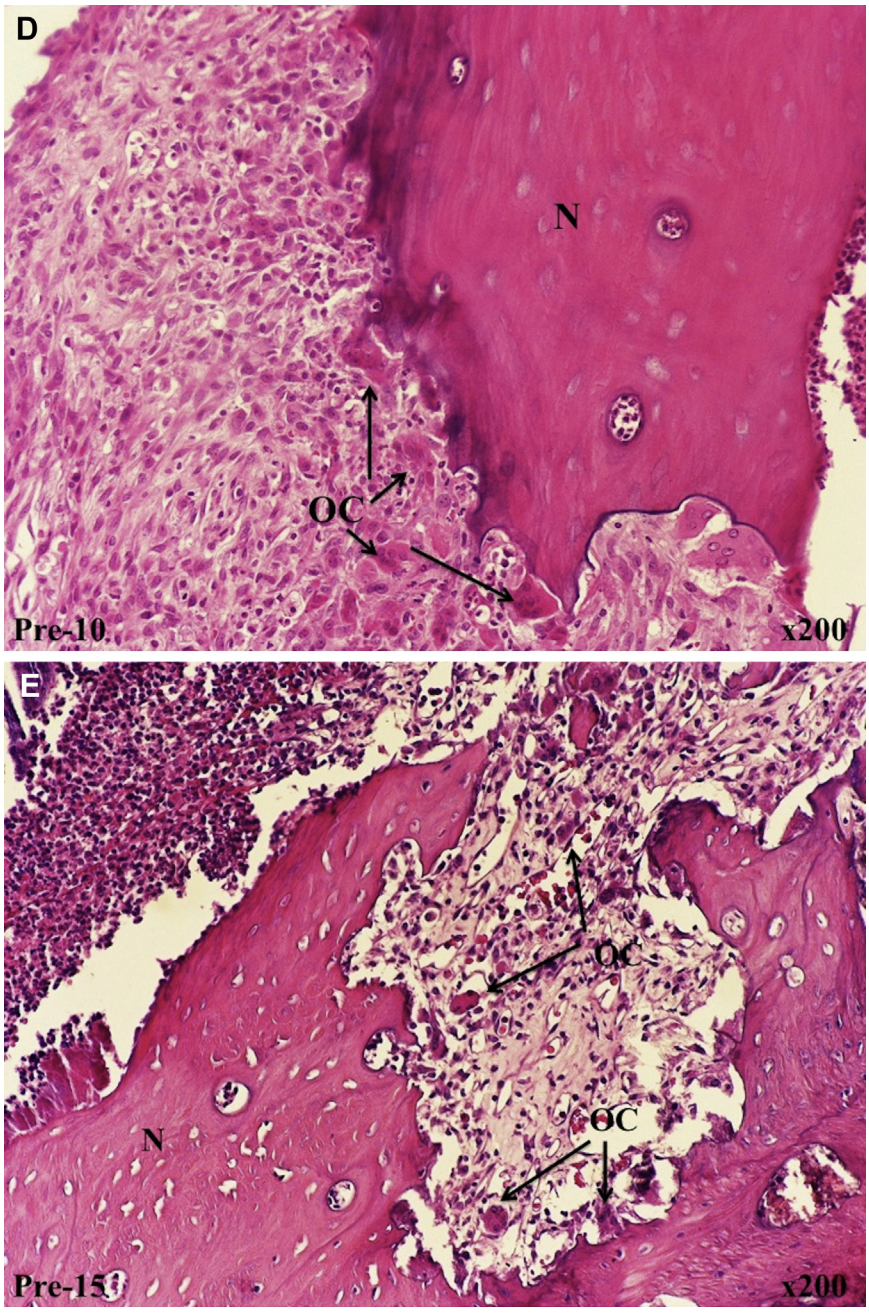

FIGURE 1 (cont'd). *D, E,* In the Pre-10 and Pre-15 groups, smaller osteonecrotic areas were observed, with osteoblasts and numerous osteoclasts. **(Fig 1 continued on next page.)**

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Teriparatide is a new synthetic parathyroid hormone recently introduced to improve the thickness and the quality of bone.[4] Parathyroid hormone regulates the metabolism of calcium and phosphate and is responsible for bone formation. This drug is used to prevent bone resorption in cases in which mineral density is low or the quality of bone is inferior, as in osteoporosis. Unlike other antiresorptive agents, it also exerts an anabolic effect on bone. When osteoclast stimulation initiates bone resorption, osteoblasts are stimulated simultaneously, resulting in an anabolic effect.[32] This effect has resulted in the use of this agent in cases of MRONJ and periodontal bone defects.[5-8] Research has shown no serious clinical side-effects associated with this agent; however, the risk of osteosarcoma owing to its anabolic effect on bone should be considered.[32] To date, no clinical case of osteosarcoma related to teriparatide use has been reported. However, this risk should be considered carefully in patients at increased risk of osteosarcoma development.

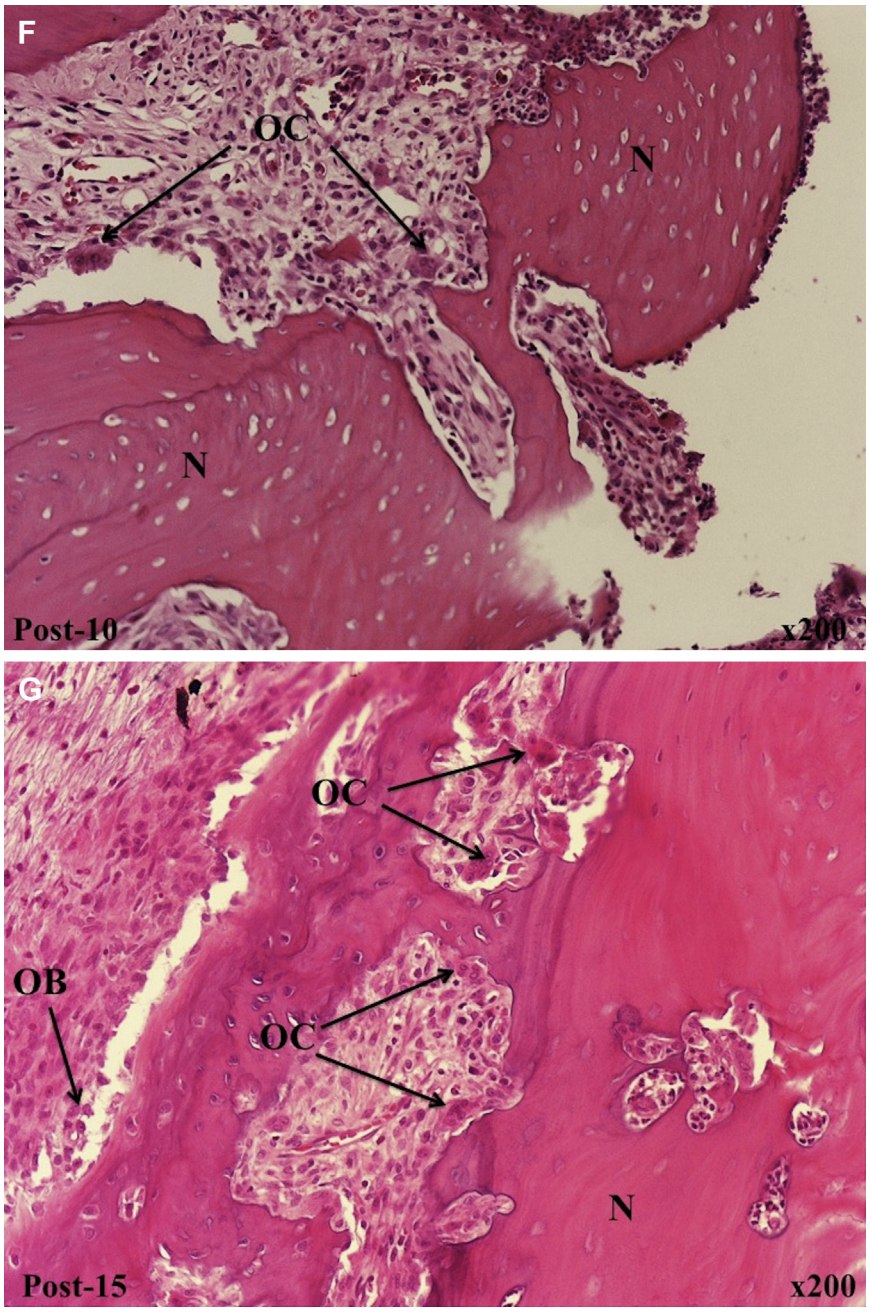

FIGURE 1 (cont'd). *F, G,* In the Post-10 and Post-15 groups, smaller osteonecrotic areas were observed, with osteoblasts and numerous osteoclasts. **(Fig 1 continued on next page.)**

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The administration of teriparatide to treat MRONJ has been reported in a few case reports, and there are 2 animal studies related to use of this drug. In the present study, teriparatide was assessed for the prevention and treatment of MRONJ.

The osteoblast numbers decreased in the Pre-10 group at week 10, but there were no meaningful differences among the groups at week 15. Thus, the smaller osteoblast numbers at week 10 increased by week 15. In terms of osteoblasts, between BPs and teriparatide, similar effects were observed. These findings are consistent with those of Dayisoylu et al.[9]

The osteoclast numbers in the experimental groups administered teriparatide (Pre-10, Post-10, Pre-15, and Post-15) were considerably larger than those in the control groups. The number of osteoclasts also decreased in the control groups at weeks 10 and 15 (C-10 and C-15). The negative effects of BPs on osteoclast resorption are part of the mechanism of MRONJ. However, the positive effect of teriparatide on

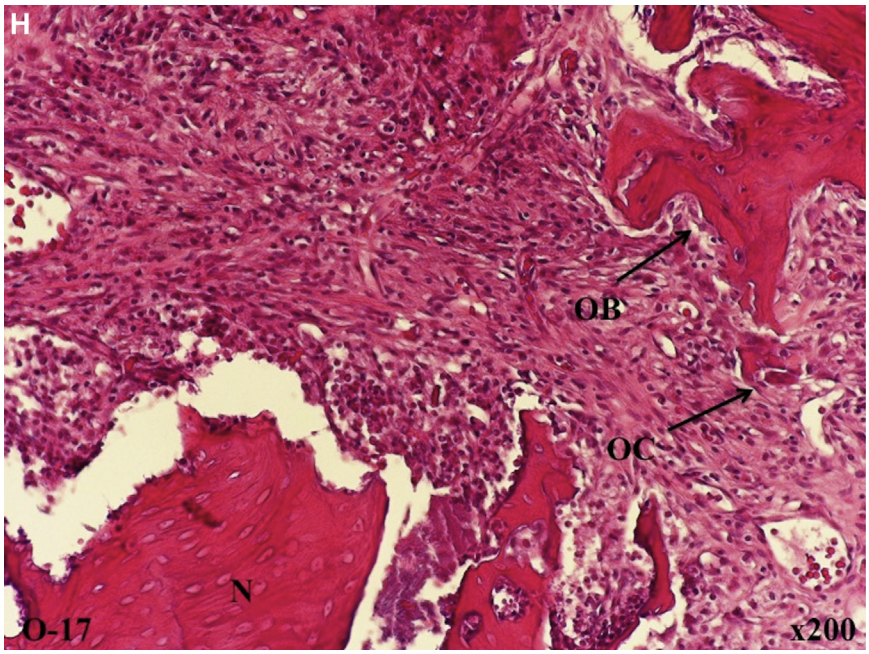

FIGURE 1 (cont'd). *H*, In the O-17 group, osteoblasts and osteoclasts were observed in the osteonecrotic areas. C-10, control group sacrificed at week 10; C-15, control group sacrificed at week 15; C-17, control group sacrificed at week 17; N, necrosis; O-17, osteonecrosis group sacrificed at week 17; OB, osteoblast; OC, osteoclast; Post-10, postoperative group sacrificed at week 10; Post-15, postoperative group sacrificed at week 15; Pre-10, preoperative group sacrificed at week 10; Pre-15, preoperative group sacrificed at week 15.

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osteoclast formation can help to prevent the development of MRONJ. Conversely, after MRONJ develops, teriparatide administration was found not to be effective at week 17. Dayisoylu et al[9] reported similar effects on osteoclasts between BPs and teriparatide. The authors found that teriparatide exerted positive effects on osteoclasts at weeks 10 and 15.

At week 10, the Pre-10 group exhibited a superior inflammatory phase of bone healing compared with the C-10 group, but at week 15, the inflammatory phase of bone healing was similar in the Pre-15 and C-15 groups. Moreover, the other groups showed similar effects at weeks 15 and 17.

In all groups, in terms of the histologic osteonecrotic area, similar effects were observed. Dayisoylu et al[9] and Ersan et al[10] reported that osteonecrotic areas were larger in the BP group than in the teriparatide group.

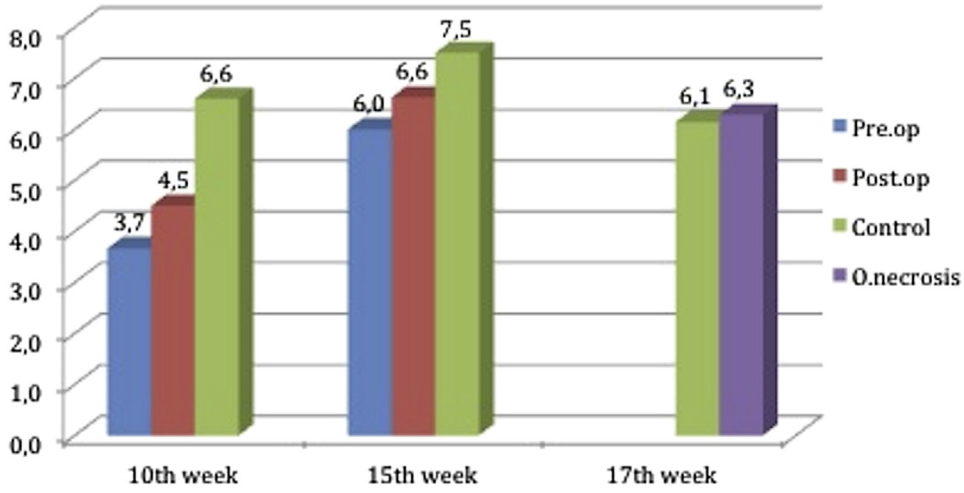

FIGURE 2. Osteoblast numbers. Control, control groups sacrificed at weeks 10, 15, and 17; O.necrosis, osteonecrosis group sacrificed at 17 weeks; Post.op, postoperative groups sacrificed at weeks 10 and 15; Pre.op, preoperative groups sacrificed at weeks 10 and 15.

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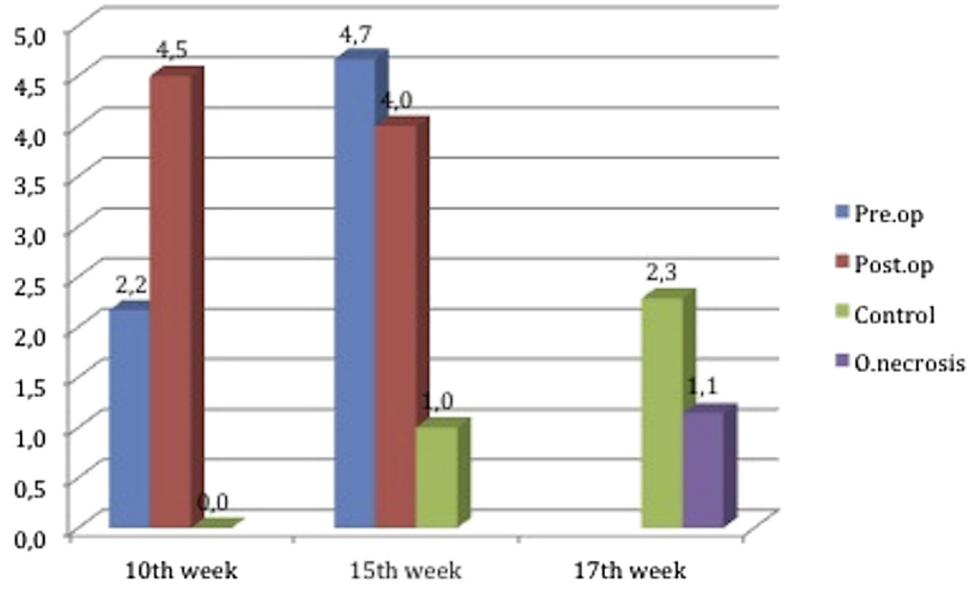

FIGURE 3. Osteoclast numbers. Control, control groups sacrificed at weeks 10, 15, and 17; O.necrosis, osteonecrosis group sacrificed at 17 weeks; Post.op, postoperative groups sacrificed at weeks 10 and 15; Pre.op, preoperative groups sacrificed at weeks 10 and 15.

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Although the potential impact of teriparatide on bone healing is not exactly known, recent studies have reported that teriparatide stimulates bone turnover and increases bone mass. The resolution of MRONJ and bone healing by teriparatide could be attributed to osteoclast activity. Teriparatide had a positive impact on the resolution of the inflammatory response of bone healing, but the mechanism of action of teriparatide is unknown. Bashutski et al[33] reported that teriparatide exerted positive effects on healing bone defects in the oral cavity. Teriparatide was reported to be effective in the healing of necrotic wounds in rats administered BPs and steroids by Kuroshima et al.[34] In other studies, Kuroshima et al[35] reported that teriparatide promotes healing of the tooth extraction socket. Kuroshima et al[34] in a study associated with BPs and steroids reported that osteoblasts were considerably increased and osteoclasts and necrotic bone were decreased by teriparatide after BP and steroid use.

According to the results of this study, the numbers of osteoclast were decreased in the control groups

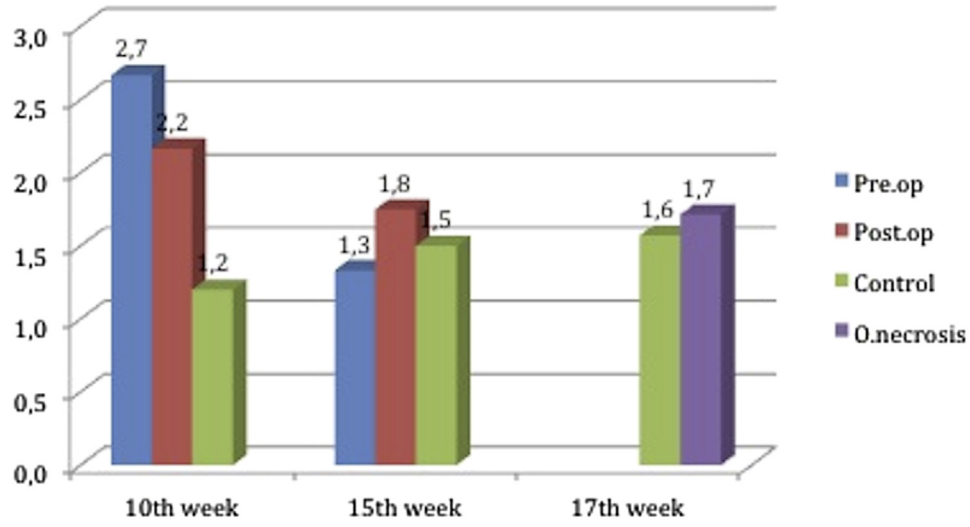

FIGURE 4. Results of the inflammatory phase of bone healing. Control, control groups sacrificed at weeks 10, 15, and 17; O.necrosis, osteonecrosis group sacrificed at 17 weeks; Post.op, postoperative groups sacrificed at weeks 10 and 15; Pre.op, preoperative groups sacrificed at weeks 10 and 15.

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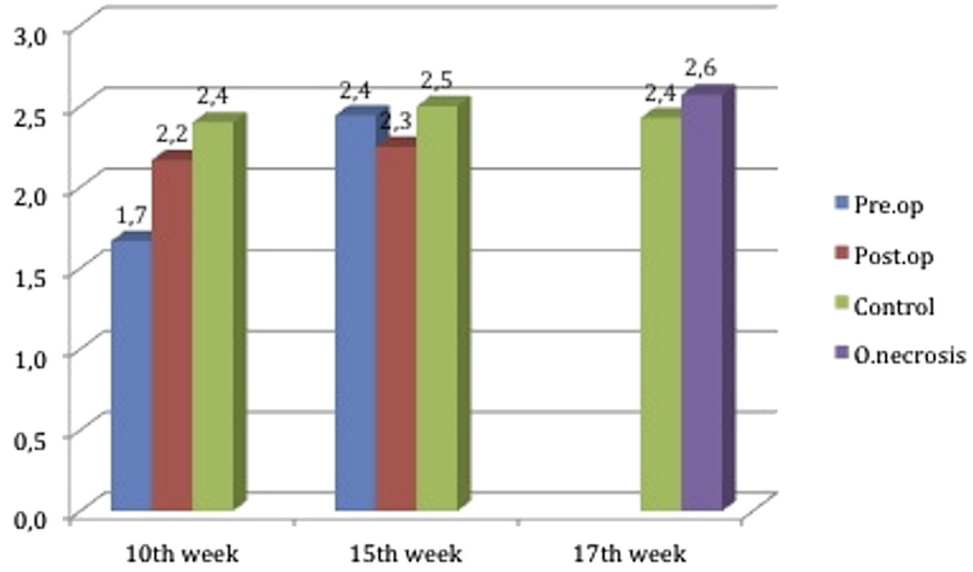

FIGURE 5. Osteonecrotic areas. Control, control groups sacrificed at weeks 10, 15, and 17; O.necrosis, osteonecrosis group sacrificed at 17 weeks; Post.op, postoperative groups sacrificed at weeks 10 and 15; Pre.op, preoperative groups sacrificed at weeks 10 and 15.

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that were given BP without any treatment. The authors believe that the decreased number of osteoclasts was related to the apoptotic effects of BP on osteoclasts. Conversely, teriparatide had an anabolic effect on osteoclasts. This result is important for MRONJ, because osteoclasts are inactive in this condition.

Teriparatide administered before and immediately after tooth extraction might decrease the risk of developing osteonecrosis. Prospective randomized studies are needed to evaluate the long-term effectiveness of teriparatide.

BPs have negative effects on osteoclasts and the inflammatory phase of bone healing, whereas teriparatide has positive effects. Before the development of osteonecrosis, teriparatide showed positive effects on the prevention of osteonecrosis; after the development of osteonecrosis, teriparatide did not show any positive effect on the treatment of MRONJ. Further studies are needed to confirm its effectiveness as prevention.

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