Development of Antiresorptive Agent-Related Osteonecrosis of the Jaw After Dental Implant Removal: A Case Report

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Dental implant treatment is a highly predictable therapy, but when potentially lethal symptoms or complications occur, dentists must remove the implant fixture. Recently, reports on antiresorptive agent-related osteonecrosis of the jaw have increased in the field of dental implants, although the relationship between dental implant treatment and antiresorptive agents remains unclear. Here, we report a case of antiresorptive agent-related osteonecrosis of the jaw that developed after dental implant removal. A 67-year-old Japanese woman with a medical history of osteoporosis and 7 years of oral bisphosphonate treatment was referred to our hospital with a chief complaint of painful right mandibular bone exposure. A family dentist removed the dental implants from the right mandible using a trephine drill without flap elevation in August 2016. However, the healing was impaired; she was referred to our hospital 3 months after the procedure. We performed a sequestrectomy of the mandible under general anesthesia. In conclusion, this patient's course has two important implications: First, the removal of dental implants from patients who are prescribed oral bisphosphonates for long durations can cause antiresorptive agent-related osteonecrosis of the jaw. Second, meticulous procedures are required to prevent and treat the development of antiresorptive agent-related osteonecrosis of the jaw after dental implant removal.

Key Words: dental implant removal, bisphosphonate, antiresorptive agent-related osteonecrosis of the jaw, osteoporosis

INTRODUCTION

Bisphosphonates (BPs) have been used widely, efficiently, and safely for the treatment of osteoporosis, malignant hypercalcemia, bone metastasis of solid cancers, and multiple myeloma bone diseases.[1–3] Despite the benefits of BPs, BP-related osteonecrosis of the jaw (BRONJ) was first reported as a severe side effect in 2003.[4] Recently, increasing clinical reports of osteonecrosis of the jaw related to non-BP antiresorptive medications (eg, denosumab or cathepsin K inhibitors) coined the term "antiresorptive agent-related osteonecrosis of the jaw" (ARONJ),[5] with a mounting number of implant-related ARONJ cases described.[6–12] However, there are still few reports about the relationship between ARONJ and dental implant removal.[7,13] Our patient, treated with long-term oral BP, developed ARONJ after the removal of dental implants. We should be aware of this possibility of ARONJ after dental implant removal. This report also discusses preventive measures for dental implant removal-related ARONJ.

CASE REPORT

In November 2016, a 67-year-old Japanese woman was referred to our hospital with a chief complaint of painful right mandibular bone exposure. The patient was diagnosed with osteoporosis in 2009 and treated by her family doctor with 35 mg of oral alendronate weekly. Following her family doctor's instructions, she discontinued the medication in March 2016. She had no other medical history and no history of using a steroid. The family dentist began dental implant treatment began in the maxilla and mandible in February 2015. Two and three implants (CAMLOG Promote, ALTADENT Corp, Osaka, Japan) were placed in the posterior regions of the maxilla and mandible in February 2015 and May 2015, respectively. The surgical procedure was uneventful and achieved primary stability of all implants. The final prostheses were retained by

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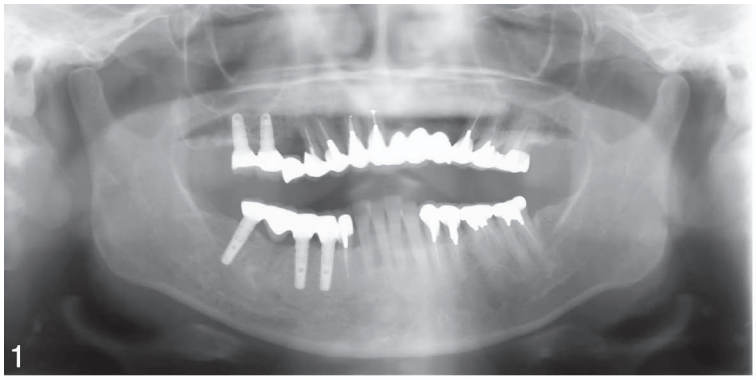
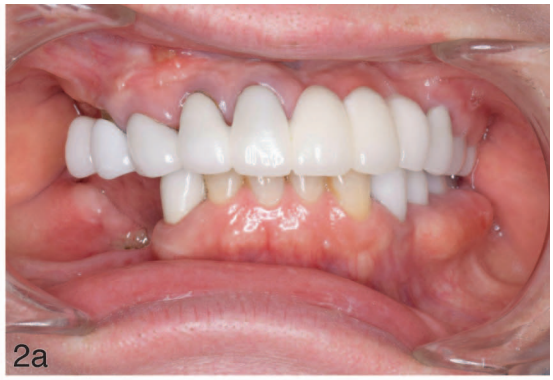
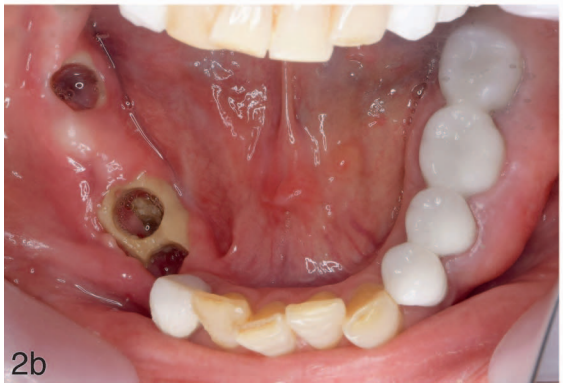
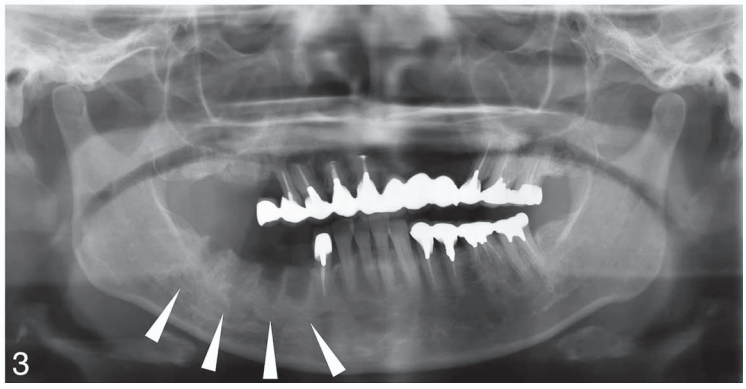
DOI: 10.1563/aaid-joi-D-18-00032









Figures 1–3. Figure 1. Panorama XP obtained at the time of dental implant removal shows no obvious abnormal findings around the dental implant fixtures. **Figure 2.** The intraoral view from the first visit shows widespread exposed necrotic bone in the right mandible (a and b). **Figure 3.** Panorama XP obtained at the first visit reveals that the removal sockets of 3 implant fixtures remain and extensive sclerosis is recognized around the sockets in the right mandible (white arrowhead).

screws in the maxilla and mandibular abutments in August 2015 and March 2016, respectively.

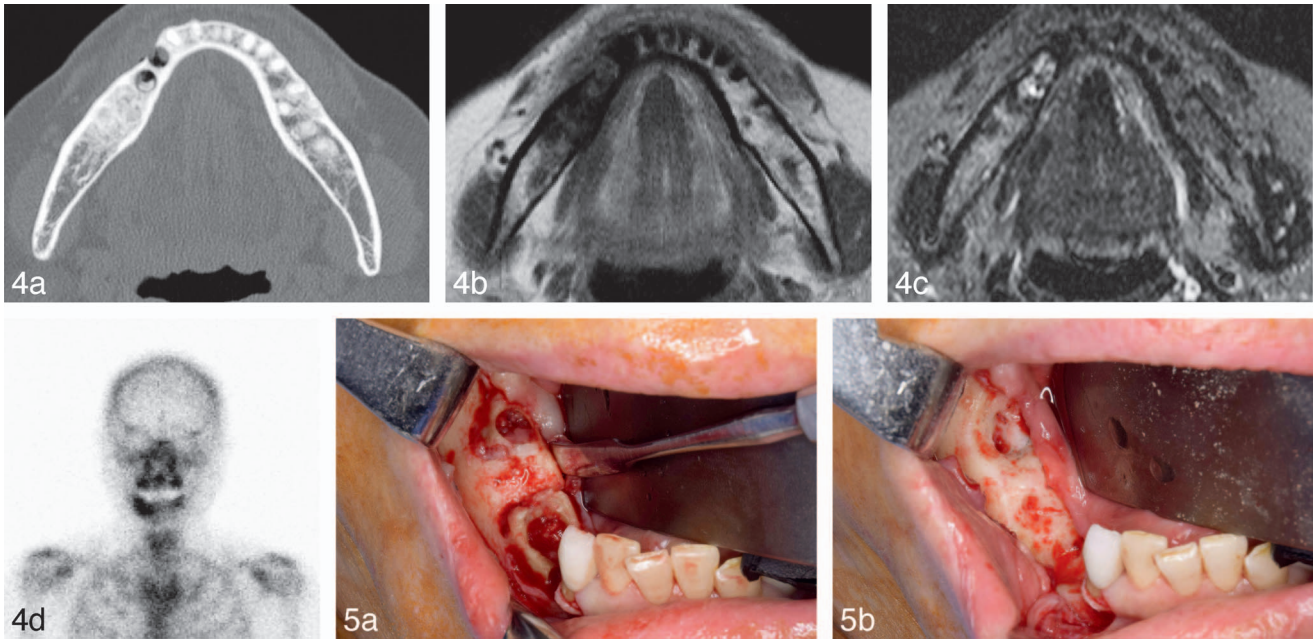
In May 2016, the patient started to complain of right shoulder and right upper arm pain. However, while neither the family dentist nor an oral and maxillofacial surgeon at another university hospital observed any gingival swelling, bone exposure, occlusal problems, or abnormal findings on panorama XP (Figure 1), the patient expressed a strong desire for the removal of all dental implants. As a result, all dental implants were removed from the right maxilla and mandible in July 2016 and August 2016, respectively. Maxillary implants were removed using a trephine drill with flap elevation and primary closure; however, the mandibular implants were removed using a trephine drill without flap elevation or suturing for primary wound closure.

The healing was impaired; therefore, she was referred to our hospital 3 months after the procedure. The clinical examination revealed widespread exposed necrotic bone in the right mandible and no paralysis of the right lower lip (Figure 2a and b). The maxilla had healed well and showed no exposed necrotic bone. Panorama XP showed no abnormality of the right maxilla, but the removal sockets from the 3 implant fixtures remained, and extensive sclerosis was recognized around the sockets in the right mandible (Figure 3). Computed tomography (CT) showed some sequestra in the sockets and increased bone marrow density spreading from the midline to the third molar area of the right mandible (Figure 4a). Magnetic resonance imaging (MRI) showed low intensity on T_1-weighted images and moderately high intensity on T_2-weighted images in the bone marrow of the right mandible (Figure 4b and c). Bone scintigraphy showed a focus of increased radiotracer uptake in the right mandible (Figure 4d).

Despite conservative treatment with oral antibiotics (clindamycin), healing did not progress, and bone exposure persisted for 8 weeks, after which a clinical diagnosis of stage 2 ARONJ was made. In June 2017, we performed a sequestrectomy of the mandible with the patient under general anesthesia. After flap elevation, the bone sequestra around the implant removal cavities were eliminated using a steel bur (Figure 5a and b). The affected bone was resected until bleeding was observed; then, the edges of the remaining bone were rounded off. Careful wound closure was carried out without any graft materials. Pathological findings of the surgical specimen revealed that the bone was nonvital, and the osteocyte lacunae were empty (Figure 6a and b). Colonies of *Actinomyces* sp. adhered to the surface (Figure 6c and d). There was no recurrence in the right mandible 7 months postoperatively (Figure 7a and b).

Discussion

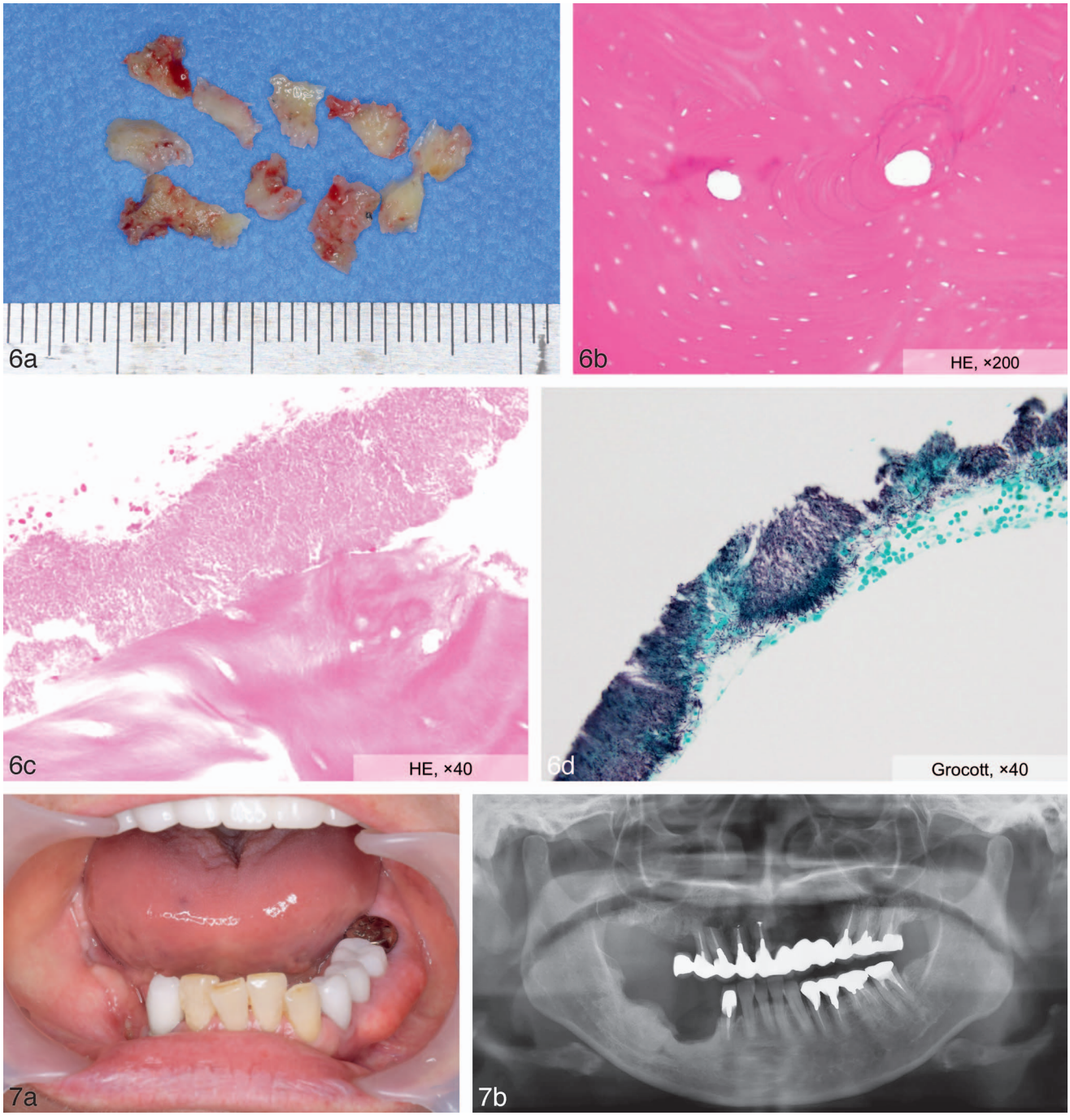
BPs have been used widely, efficiently, and safely for the treatment of osteoporosis, malignant hypercalcemia, bone metastasis of solid cancers, and multiple myeloma bone diseases.[1,2] BPs have been proven especially effective in



Figures 4 and 5. Figure 4. (a) Computerized tomography shows some sequestra located in the sockets and increased bone marrow density spreading from the midline to the third molar area of the right mandible. (b) T_1-weighted magnetic resonance imaging (MRI) shows low intensity in the right mandibular bone marrow. (c) T_2-weighted MRI shows moderately high intensity in the right mandibular bone marrow. (d) Bone scintigraphy shows a focus of increased radiotracer uptake in the right mandible. **Figure 5.** An intraoperative view of the sequestrectomy. (a) After flap elevation, (b) bone sequestra around the implant removal cavities were eliminated with a steel bur.

preventing bone loss and reducing fractures in men and postmenopausal women with established osteoporosis.[14] Despite the benefits of BPs, BRONJ was first reported as a severe side effect of BPs in 2003.[4] Recently, the term "ARONJ" has been used because of clinical reports of osteonecrosis of the jaw related to non-BP antiresorptive medications, such as denosumab or cathepsin K inhibitors.[5] While dental implant treatment is a highly anticipated therapy in widespread use, an increasing number of implant-related ARONJ cases have been described.[6–12] However, there are still few reports about the relationship between ARONJ and dental implant removal,[7,13] and there is scarce information on ARONJ associated with dental implants.

This is a rare and valuable report describing a case of ARONJ that developed after dental implant removal. The course of this patient has two important implications: First, the removal of dental implants from patients undergoing long-term oral BP therapy can cause ARONJ. The main causative factor reported for ARONJ was tooth extraction.[15] However, Marx[6] reported that 25.2% of ARONJ cases occurred spontaneously without any apparent dental disease, treatment, or trauma, and 3.4% originated from dental implant placement. In general, patients undergoing intravenous BP therapy have a higher risk of ARONJ while patients undergoing oral BP therapy have a lower risk.[6,15] Nevertheless, Lazarovici et al[8] reported that only 59% of patients who developed ARONJ associated with dental implant placement were undergoing intravenous BP therapy, whereas 41% were undergoing oral BP therapy. The authors deduced that the difference in the ratio between cases caused by tooth extraction vs dental implant placement occurred because dental implant placement usually was not performed for patients undergoing intravenous BP treatment after alarming reports on the occurrence of ARONJ. In fact, at present, experts' opinions suggest that dental implants should be avoided in patients with cancer who are treated with intravenous BPs.[16] Lopez-Cedrun et al[11] investigated 9 patients with ARONJ who underwent oral BP therapy and dental implant placement, and alendronate was the BP most often associated with the development of ARONJ. In the study, they suggested that the duration of treatment with oral BPs was an influential factor in the onset of ARONJ, and the appearance of ARONJ may depend not only on the duration of treatment but also on other risk factors because the range of intervals was wide. Interestingly, patients who underwent dental implant placement during and after treatment with oral BPs developed ARONJ more rapidly than did those who underwent implant placement before treatment with oral BPs.[17] Moreover, both the surgical insertion of dental implants and the presence of the dental implant itself in the bone are potential risk factors for the development of ARONJ.[18–21] Additionally, peri-implantitis might precipitate the occurrence of ARONJ in patients undergoing BP therapy. Most dental implants associated with ARONJ were located in the posterior regions of the mandible.[8,10,11,18] In the present case, when the family dentist performed dental implant placement, 6 years had already passed since she started oral BP, and the type of BP was alendronate. While the patient's maxillary and mandibular implants were removed around the same time, ARONJ developed in the mandible but not in the maxilla. These results are consistent with previous reports. Therefore, the removal of dental implants can cause ARONJ not only in patients treated with intravenous BPs but also in those treated



Figures 6 and 7. Figure 6. (a) Surgical specimen of the necrotic bone. (b) The bone is nonvital and the osteocyte lacunae are empty. (c and d) Colonies of *Actinomyces* sp. adhere to the surface of the bone. **Figure 7.** (a) Intraoral view 7 months postoperatively reveals that there was no recurrence in the right mandible. (b) Panorama XP obtained 7 months postoperatively reveals that the affected bone has been resected and there is no recurrence in the right mandible. HE indicates hematoxylin and eosin.

with long-term oral BPs. Therefore, patients must be provided with a full explanation of the potential risks of ARONJ development, and great attention should be paid to long-term oral hygiene.

Second, a meticulous procedure is required to prevent and treat the development of ARONJ after dental implant removal. ARONJ is classified into 3 stages, and the diagnostic criterion for stage 2 is exposed and necrotic bone or erythema in the region of exposed bone with or without purulent drainage.[16] Based on this criterion, the present case was diagnosed as stage 2 ARONJ. The primary treatment strategy for stage 2 ARONJ includes the use of oral antimicrobial rinses in combination with antibiotic therapy.[16] However, the bone specimen from the affected site was occluded with biofilms comprised mainly of bacteria and occasionally yeasts; bacteria identified included *Fusobacterium* sp., *Bacillus* sp., *Actinomyces* sp., *Staphylococcus*

sp., and *Streptococcus* sp.[22] In cases in which systemic antibiotic therapy has failed, operative therapy directed at reducing the volume of colonized necrotic bone may serve as a beneficial adjunct to antibiotic therapy.[16]

In the present case, systemic antibiotic therapy did not lead to healing and bone exposure persisted; moreover, the surgical specimen showed *Actinomyces* sp. on the bone sequestra. In clinical situations, various implant removal methods using different tools have been introduced, such as a scalpel; bur and forceps only; bur, forceps, and elevator; trephine drill; and implant removal kit.[23,24] If drilling alveolar bone must occur during the implant removal process, it must be conducted with care under saline irrigation to minimize surrounding alveolar bone damage.[24] In the present case, the family dentist removed the maxillary implants using a trephine drill with flap elevation and primary closure, but the mandibular implants were removed using a trephine drill without flap elevation or suturing for primary wound closure. Lazarovici et al[8] suggested that patients who developed ARONJ associated with dental implants should undergo long-term antibiotics treatment, and their dental implants should be removed only if treatment fails to alleviate the signs and symptoms of ARONJ.[17] To prevent the development of ARONJ after dental implant removal, the most important factor is meticulous procedure to minimize harm to the remaining bone and surrounding gingiva. After dental implants are removed and the edges of the remaining bone are rounded, a mucoperiosteal flap is elevated and moved to perform primary closure.[25,26] Especially when treating patients undergoing intravenous or long-term oral BP therapy, careful procedures are required to prevent the development of ARONJ after dental implant removal. Unfortunately, once ARONJ developed after dental implant removal in the present case, the necrotic bone had to be removed to a level where bleeding compact bone was covered by the mucoperiosteal flap and there was an adequate mucoperiosteal flap to allow for primary closure. Moreover, in some cases, more aggressive alveolar bone removal is needed to perform primary closure with a mucoperiosteal flap.

In the present case, there was no visible dental implant or surrounding tissue abnormality before implant removal except for pain in the shoulder and upper arm. Considering that pain is the main presenting symptom in most patients with ARONJ undergoing oral BP treatment,[11] there might have been an invisible abnormality around the dental implant in the present case at the time of dental implant removal. A limitation of this case report is that we cannot completely rule out the possibility that ARONJ existed at the time of implant removal. Thus, further study of ARONJ is required to evaluate its relationship with dental implant treatment.

In conclusion, this patient's course has two important implications: First, removal of dental implants in patients undergoing long-term oral BP therapy can cause ARONJ. Second, a careful procedure is required to prevent and treat the development of ARONJ after dental implant removal. Therefore, patients at risk should be given a full explanation of the potential risks of dental implant failure and ARONJ development. Furthermore, patients treated with long-term oral BPs who undergo dental implantation should be followed carefully and for a long duration.

Abbreviations

ARONJ: antiresorptive agent-related osteonecrosis of the jaw
BP: bisphosphonate
BRONJ: bisphosphonate-related osteonecrosis of the jaw
CT: computed tomography
MRI: magnetic resonance imaging

Note

There is no conflict of interest.

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