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# Risk assessment of medication-related osteonecrosis of the jaw by alveolar bone mineral density

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**Objectives: Osteosclerosis and a high bone mineral density (BMD) have been proposed as risk factors for medication-related osteonecrosis of the jaw (MRONJ). In the present study, we measured the alveolar BMD (al-BMD) of teeth indicated for extraction on dental radiographs using BMD analysis software and investigated the relationship between al-BMD and MRONJ.**

**Materials and Methods: We measured al-BMD on dental radiographs using BMD analysis software (Bone Right) in 100 bone-modifying agent (BMA)-treated patients who visited our department for tooth extraction between November 2020 and May 2023. Fifteen patients treated with BMA for more than 4 years underwent tooth extraction 2 months after their cessation.**

**Results: In 100 patients who underwent tooth extraction, only one patient on high-dose anti-resorptive agents (ARAs) developed MRONJ. al-BMD was significantly higher in MRONJ patients than in non-MRONJ patients. No significant change was observed in al-BMD before and 2 months after the cessation of BMA.**

**Conclusion: Patients who developed MRONJ after tooth extraction had higher al-BMD before tooth extraction, and a relationship between MRONJ and osteosclerosis cannot be ruled out. On the other hand, al-BMD did not change before and after the cessation of BMA, and MRONJ did not occur in patients treated with low-dose ARAs, suggesting that the cessation of BMA is not necessary. (J Osaka Dent Univ 2024; 58: 153-164)**

**Key words: Medication-related osteonecrosis of the jaw (MRONJ); Alveolar bone mineral density (al-BMD); Bone-modifying agent (BMA); Anti-resorptive agent (ARA); Osteoporosis**

## INTRODUCTION

In 2003, Marx *et al.* was the first to show a relationship between osteonecrosis of the jaw (ONJ) and high-dose bisphosphonates (BPs).[1] Many studies subsequently reported bisphosphonate-related osteonecrosis of the jaw (BRONJ).[2, 3] In addition to BP preparations, a relationship was indicated between the human anti-RANKL antibody preparation, denosumab (DMB) as a bone resorption inhibitor and ONJ and, thus, anti-resorptive agent-related ONJ was proposed. Romosozumab, a humanized anti-sclerostin monoclonal antibody, and angiogenesis inhibitors are currently indicated as etiological factors for ONJ. Necrosis of the jaw related to the administration of these drugs was defined as medication-related osteonecrosis of the jaw (MRONJ) in 2014. Many position papers on the pathogenesis, treatment, and prevention of MRONJ have been formulated and updated. However, a method to prevent MRONJ has not yet been established.[2-7] The discontinuation of medication prior to tooth extraction is recommended for patients receiving long-term treatment with anti-resorptive

agents (ARAs) due to the risk of MRONJ;[1-3, 6-14] however, this lacks any supportive evidence.

Osteosclerosis of the jaw and a high alveolar bone mineral density (al-BMD) have been reported as risk factors for MRONJ.[15] Dual-energy X-ray absorptiometry (DEXA), which is primarily used to measure BMD in the Department of Orthopedics, requires special equipment and, thus, is not available for dental treatment. Although computed tomography (CT) and cone beam computed tomography (CBCT), which are frequently performed in dental practice, are useful for evaluating ONJ or osteosclerosis,[16] an objective BMD assessment is difficult. In the present study, we measured al-BMD on dental X-ray images, which are routinely used for general dental treatment, using the BMD analysis software, Bone Right®, and investigated the relationship between al-BMD, as a parameter of BMD, and the development of MRONJ. We also examined the effects of the discontinuation of ARAs on the onset of MRONJ by measuring al-BMD before and after their cessation in patients receiving long-term treatment with ARAs, which is considered to increase the risk of developing MRONJ.

## MATERIALS AND METHODS

### Patients

100 BMA-treated patients (total: 143 teeth) who consulted the Second Department of Oral and Maxillofacial Surgery, Osaka Dental University Hospital for tooth extraction between November 2020 and May 2023 were included in the study. Among 45 patients who had received BMAs for more than 4 years, tooth extraction was conducted after the discontinuation of BMA for 2 months, in accordance with the Position Paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw,[7] on 15 in whom the attending physician considered discontinuation possible. In all patients, premedication with antimicrobial drugs was performed before tooth extraction. The extraction socket was closed to the extent possible. The same dentist certified by the Japanese Society of Oral and Maxillofacial Surgeons was responsible for tooth extraction. Concerning antimicrobial drugs, a previous study indicated the involvement of the oral flora in the onset of BRONJ,[17] while another reported that most of the microorganisms isolated from patients with MRONJ were susceptible to penicillin antibiotics;[3] therefore, penicillin antimicrobial drugs were selected as the first-choice treatment. Macrolides were used when the administration of penicillin antimicrobial drugs was not possible, such as allergy.[5, 18] Patients with symptoms of MRONJ in the initial consultation and those who had undergone irradiation of the jaw were excluded.

### Assessment and measurement of al-BMD

Al-BMD on dental X-ray images was measured using Bone Right® (second-class medical device: 228-ALBZX 00002000).[19, 20] An aluminum step wedge was attached to a dental X-ray film, and imaging was conducted according to the parallel method using an indicator (Figs. 1 and 2). Bone around the tooth to be extracted, which is the most important risk factor for the onset of MRONJ,[2, 21-24] was selected as the site for the al-BMD measurement. Regarding the timing of imaging, when the administration of BMA was discontinued, imaging was conducted before its discontinuation and immediately before tooth extraction (2 months after cessation of BMA). In other patients, imaging was performed immediately before tooth extraction. Alveolar bone adjacent to the tooth to be extracted and apical alveolar bone were adopted as the site of measurement on dental X-ray images (Fig. 3). Measurements were conducted on the adjacent mesial surface.

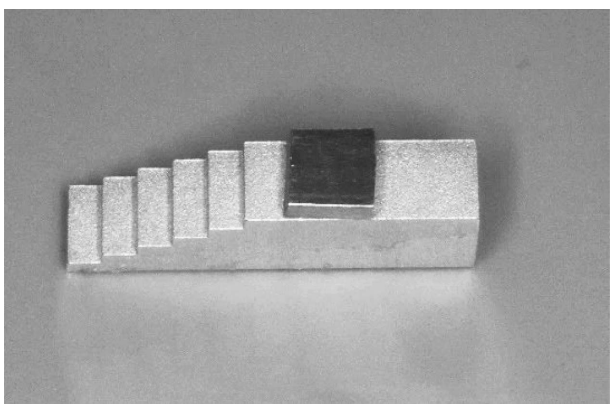


**Fig. 1 An aluminum step wedge for calibration.**

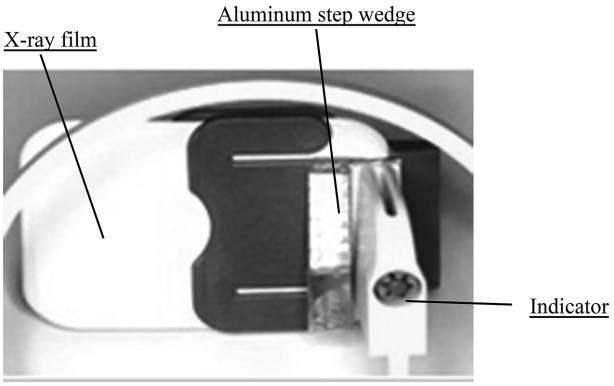



**Fig. 2 Method of the film set-up.** An aluminum step wedge attached to a film. The film was fixed using an indicator and dental x-ray images were taken.

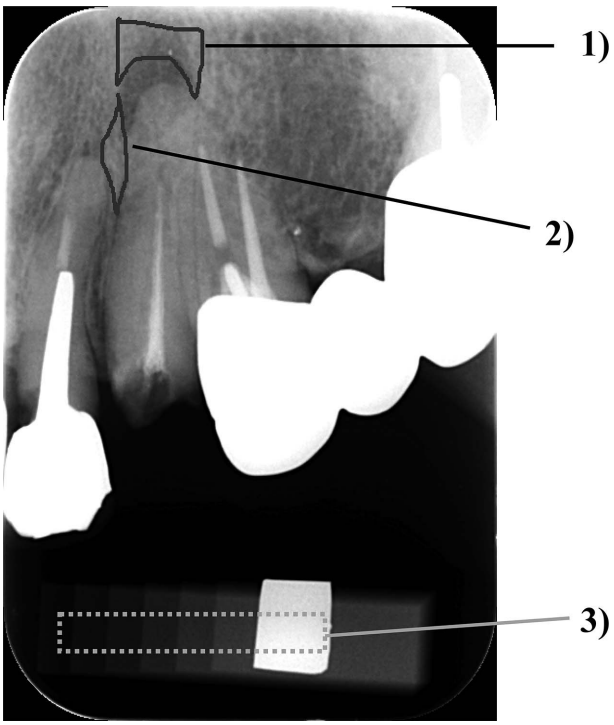



**Fig. 3 Measurement sites on Dental X-ray.** Dental X-ray before tooth extraction (Left side maxillary canine). 1) apical alveolar bone, 2) proximal alveolar bone, 3) used for image enhancement. In dental x-ray images, al-BMD measurement ranges were defined for alveolar bone proximal and apical to the tooth to be extracted. The aluminum step wedge was set as an indicator and al-BMD was measured.

When tooth duplication made measurements difficult, measurements were taken at a distal area. When a periapical lesion was present, the area setting was performed while avoiding the lesion site.

The dental X-ray images obtained were initially converted to digital data standardized with a brightness of 256 steps and pixel count of 300 dpi. Using Bone Right, image brightness was measured on image data with the aluminum step wedge as an index. After correcting/normalizing the brightness of the image to be measured, analyses were performed and al-BMD was measured. This series of processes allowed for differences in the area and brightness of the measurement region to be corrected/normalized, thereby facilitating an examination of serial changes in BMD of the same patient or a comparison of BMD among patients.[5, 20] The measurement of al-BMD with Bone Right was conducted by a third person blinded to patient backgrounds.

### Patient evaluation

We examined al-BMD with respect to the administration method and dose of BMA, the effects of discontinuation, and the presence or absence of MRONJ onset. We also compared al-BMD before and after the cessation of BMA in BMA-discontinued patients. As controls, al-BMD for healthy teeth ($n=64$) was measured in 7 non-BMA-treated patients and compared with that for teeth to be extracted in BMA-treated patients.

### Statistical Analysis

The Mann-Whitney U test and Kruskal Wallis H-test were performed using Excel statistical file software (ystat2018, Tokyo, Japan) to identify significant differences between groups. Data are presented as the mean$\pm$SD. $p<0.05$ was considered to indicate a significant difference.

## RESULTS

### Patient characteristics

Subjects consisted of 6 males and 94 females. Ages ranged between 49 and 92 years, with a median of 80 years. Regarding the administration of BMA, 45 subjects had received BMA for ≥4 years and 55 for $<4$ years (Fig. 4). The primary disease for treatment with BMA was osteoporosis in 96 patients (96%). Four patients (4%) received BMA for malignant tumors: bone metastasis from breast

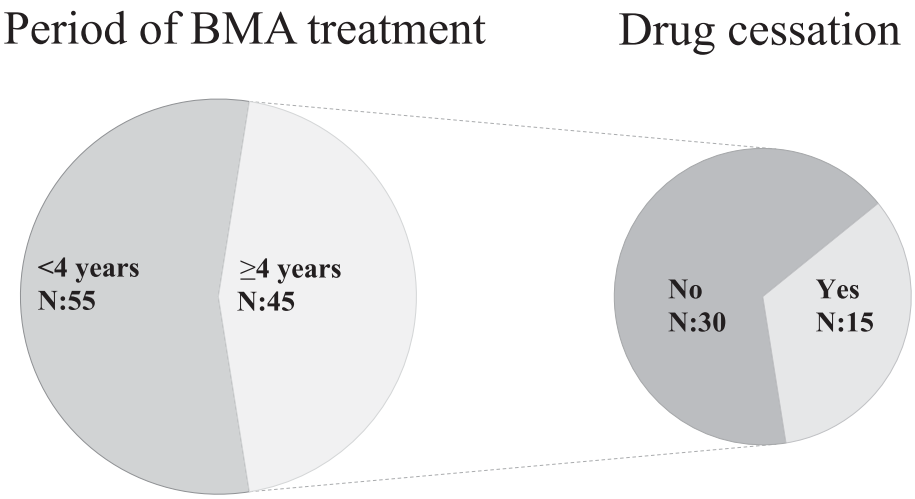



**Fig. 4 Period of BMA treatment.** 45 out of 100 patients had been treated with BMA for more than 4 years and 55 for less than 4 years. Fifteen out of 45 patients treated with BMA for more than 4 years were cessation of BMA for 2 months.

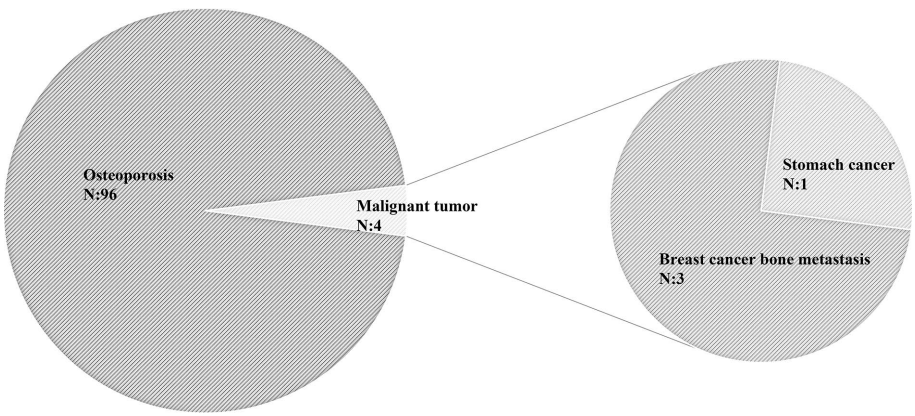



**Fig. 5 Underlying diseases treated with BMA.** The primary disease for BMA was osteoporosis in 96 out of 100 patients and malignancy in 4. 3 out of the 4 patients treated with BMA for malignant tumors had bone metastases from breast cancer and 1 had stomach cancer.

cancer in 3 and stomach cancer in 1 (Fig. 5). In 15 of the 45 patients who had received BMA for ≥4 years, tooth extraction was conducted 2 months after their cessation in accordance with the Position Paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw[7] and only when the attending physician considered BMA discontinuation possible.

## BMA type

91 out of 100 subjects were administered ARAs. 76 patients received the following BPs: alendronate in 30 patients, risedronate in 17, minodronate in 17, ibandronate in 9, and zoledronate in 3. Further-

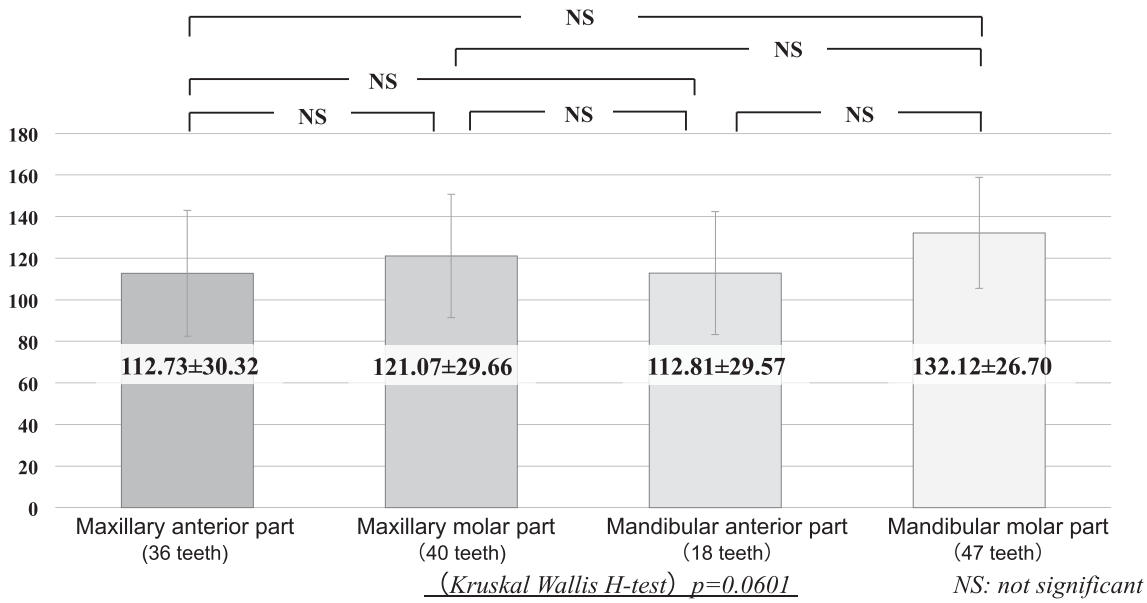
**Table 1 Types of BMA.** BMA used for treatment were ARAs in 91 out of 100 patients, romosozumab in 8, and nintedanib ethanesulfonate in 1. Regarding ARAs, 30 patients received alendronate, 17 risedronate and minodronate, 15 denosumab, 9 ibandronate, and 3 zoledronate.

| Type of BMA | | N |
|---|---|---|
| ARAs | | 91 |
| | Alendronate | 30 |
| | Risedronate | 17 |
| | Minodronate | 17 |
| | Ibandronate | 9 |
| | Zoledronate | 3 |
| | Denosumab | 15 |
| Romosozumab | | 8 |
| Nintedanib ethanesulfonate | | 1 |

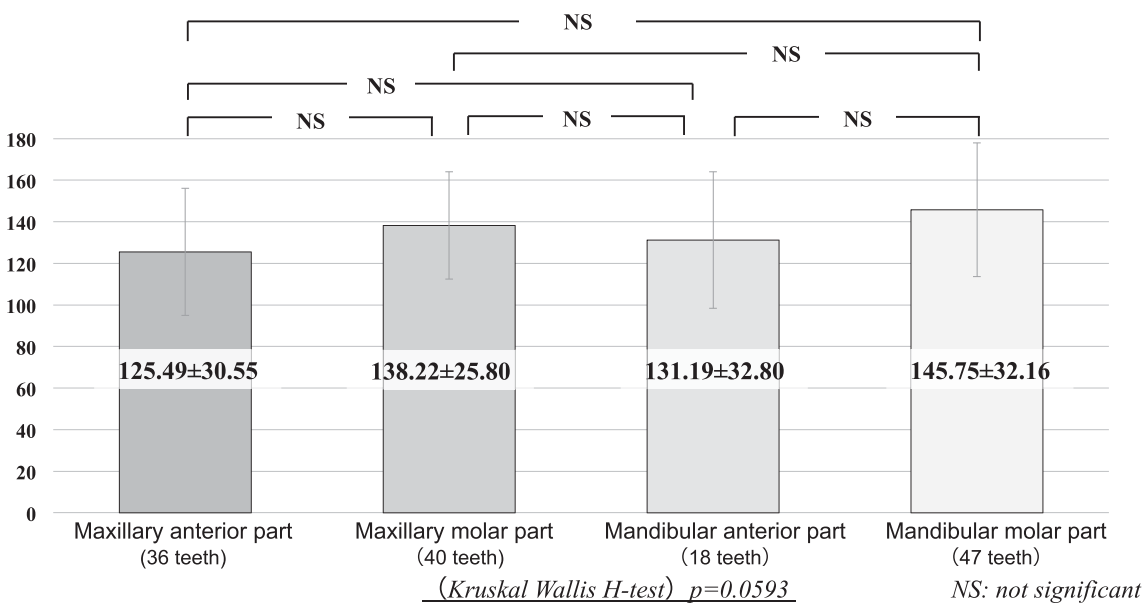
more, DMB was administered to 15 patients. Of the 91 ARA-treated patients, a high dose was used in 3 and a low dose in 88. BMAs other than ARAs included romosozumab in 8 patients and Ofev in 1. Drugs that had primarily been used within 1 year before the initial consultation were defined as drugs that had been used (Table 1).

**Comparison of al-BMD at different sites**

We investigated whether the measurement of al-




**al-BMD of proximal alveolar bone before tooth extraction in non-MRONJ cases.**




**al-BMD of apical alveolar bone before tooth extraction in non-MRONJ cases.**

**Fig. 6 Comparison by site of al-BMD.** al-BMD of proximal alveolar bone before tooth extraction in non-MRONJ cases. al-BMD of each part in proximal and apical alveolar bone were compared using the Kruskal Wallis H-test, and no significant differences were found in all groups.

BMD using Bone Right was quantitative regardless of sites in the present study. Among the 141 teeth of BMA-treated patients without MRONJ, the site of imaging was classified into 4 groups: the maxilla, mandible, anterior part, and molar part. Proximal and apical al-BMD were measured. Analyses were performed using the Kruskal-Wallis H-test. No significant differences were observed between the different sites (Fig. 6-1 and Fig. 6-2), suggesting that the measurement of al-BMD using Bone Right® is

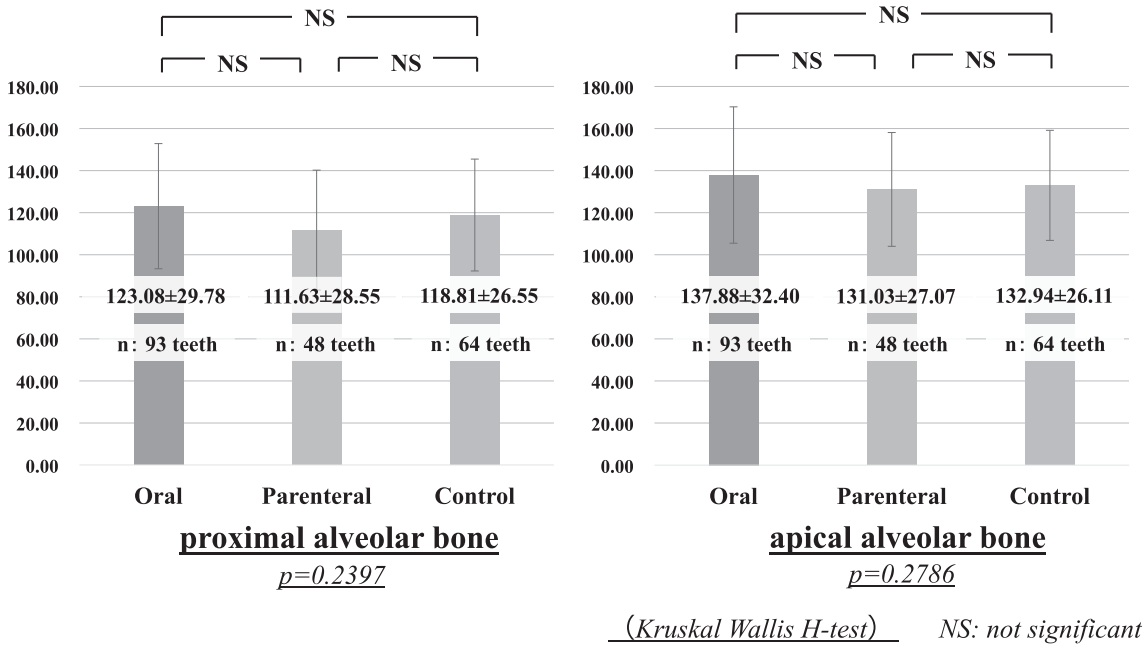



**Fig. 7 Comparison of al-BMD between control and non-MRONJ cases.** No significant differences in proximal and apical alveolar bone between non-BMA users (control) and non-MRONJ cases.

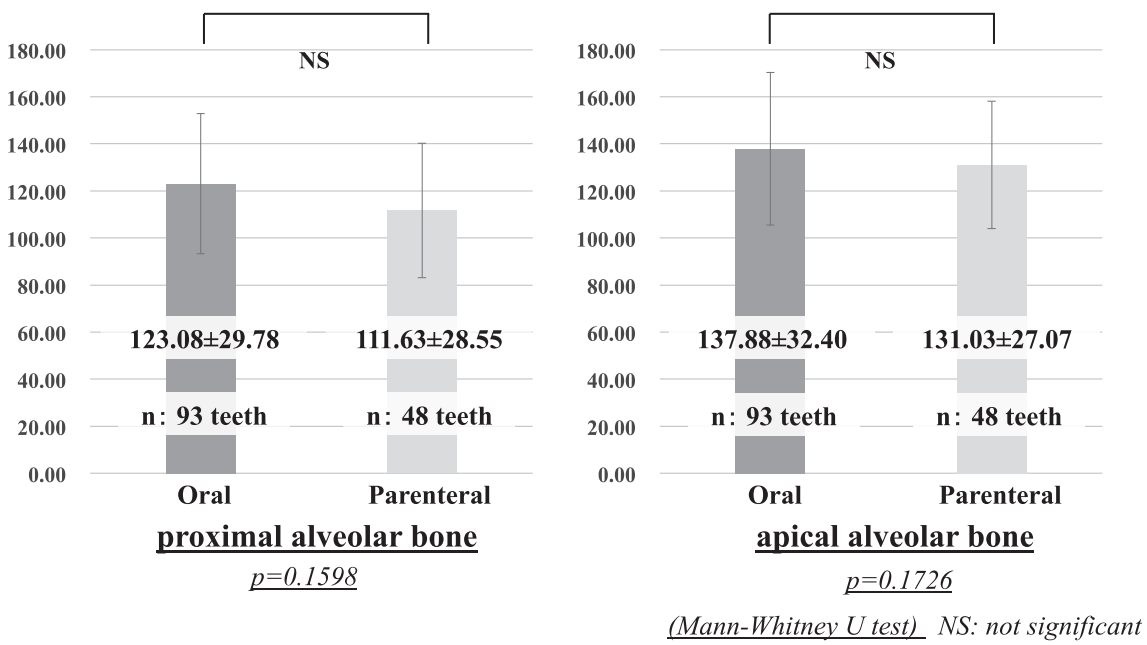



**Fig. 8 al-BMD by the route of BMA administration in non-MRONJ cases.** No significant differences in al-BMD in both proximal and apical alveolar bone due to the method of BMA administration in non-MRONJ patients.

quantitative regardless of sites. In the controls (7 non-BMA-treated patients, 64 teeth), median apical and proximal al-BMD values were 132.94 and 118.81, respectively, which did not significantly differ from the values obtained for BMA-treated patients without MRONJ (Fig. 7).

**Relationship between the route of BMA administration and al-BMD**

We examined the relationship between the route of

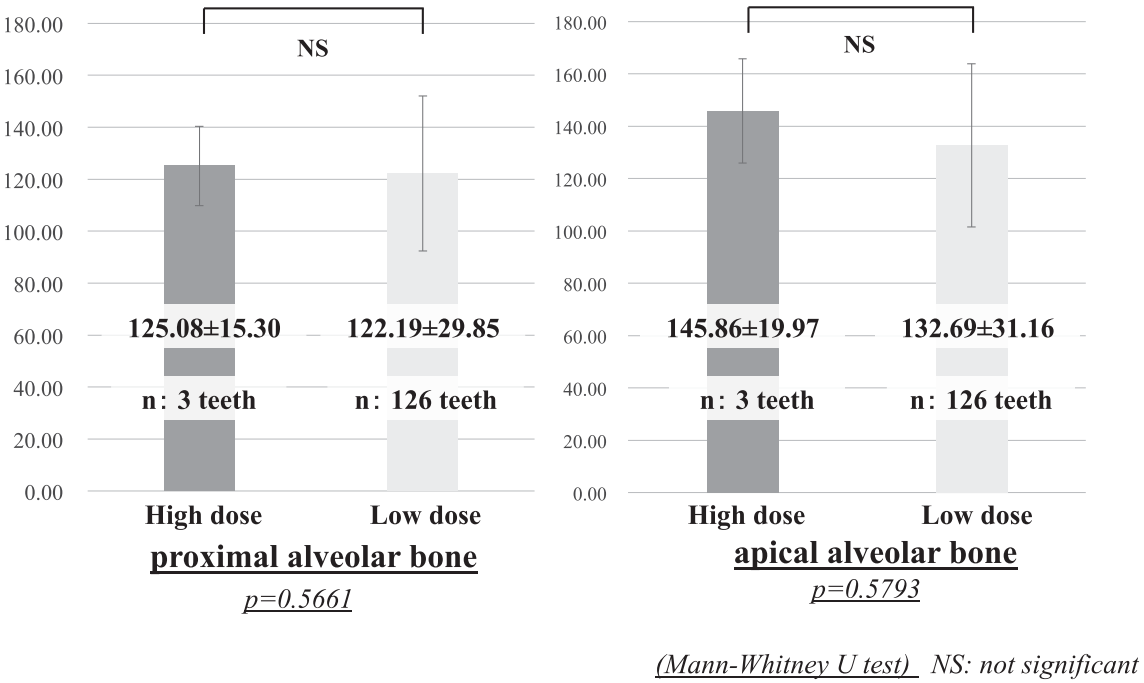



**Fig. 9 al-BMD by ARA doses in non-MRONJ cases.** No significant differences in al-BMD of proximal and apical alveolar bone in non-MRONJ cases classified by ARA doses.

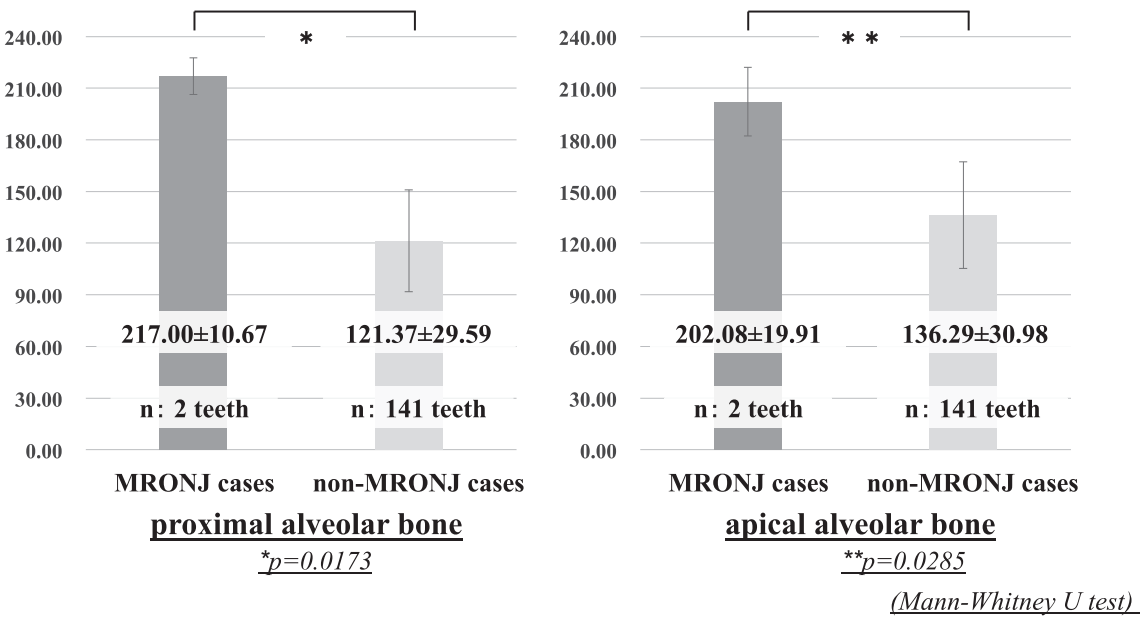



**Fig. 10 al-BMD in MRONJ and non-MRONJ cases just before tooth extraction.** al-BMD of both proximal and apical alveolar bone were significantly higher in MRONJ cases than in non-MRONJ cases.

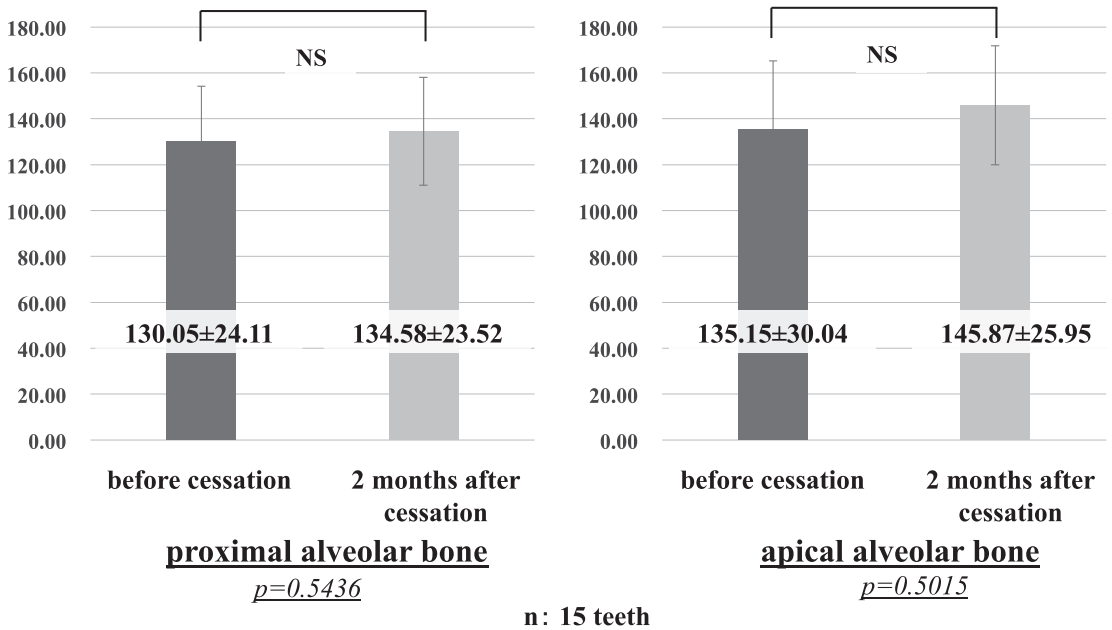



**Fig. 11 al-BMD before and after BMA cessation in non-MRONJ cases.** In cases of BMA cessation in non-MRONJ cases, no significant differences were observed in al-BMD of both proximal and apical alveolar bone before and after cessation.

BMA administration and al-BMD in the 141 teeth of non-MRONJ patients. The results obtained revealed no significant BMA administration method-related differences in proximal or apical al-BMD (Fig. 8).

**Relationship between ARA doses and al-BMD**

We investigated the relationship between ARA doses and al-BMD in the 129 teeth of ARA-treated patients without MRONJ and found no significant differences in proximal or apical al-BMD related to differences in the dose of ARA (Fig. 9).

**Comparison of al-BMD between MRONJ and non-MRONJ patients**

Among 100 subjects, stage 2 MRONJ occurred in 1 patient who had received high-dose DMB (2 teeth), whereas epithelization was noted 2 months after surgery in the other 99 (141 teeth), and MRONJ did not occur. Proximal and apical al-BMD were significantly higher in MRONJ patient than in non-MRONJ patients (Fig. 10).

**Effects of the cessation of BMA on al-BMD**

We examined changes in al-BMD before and after the discontinuation of BMA in 15 non-MRONJ patients (25 teeth) with the 2-month cessation of these agents. No significant changes were noted in proximal or apical al-BMD before and after the discontinuation of BMA (Fig. 11).

## DISCUSSION

High-dose BPs effectively manage hypercalcemia related to bone metastasis from malignant solid tumors, such as multiple myeloma, breast cancer, and prostatic cancer, and skeletal-related events (SREs).[25-27] Furthermore, low-dose BPs have been shown to decrease the incidence of vertebral body or non-vertebral body fractures in patients with osteoporosis.[28, 29] The anti-RANKL antibody "DMB" inhibits osteoclast function and bone resorption. A previous study reported that the low-dose subcutaneous administration of DMB to patients with osteoporosis every 6 months decreased the risk of vertebral body and non-vertebral fractures.[30] Another study indicated that high-dose DMB was more ef-

fective at decreasing the incidence of SREs associated with metastatic bone disease from solid tumors than zoledronic acid.[31] On the other hand, after Marx described BRONJ in 2003,[32] DMB-related ONJ and ONJ related to angiogenesis inhibitors, including bevacizumab and sunitinib, were reported. In 2014, these conditions were defined as MRONJ.[3] Romosozumab, a new monoclonal antibody that has recently begun to be used in patients with osteoporosis, binds to and inhibits sclerostin, a glycoprotein that inhibits bone formation by osteoblasts and promotes bone resorption by osteoclasts, thereby having both pro-osteogenic and antiresorptive effects. It is the first drug to have both bone formation-promoting and bone resorption-promoting effects.[33] However, this drug may also induce ONJ.[5] Therefore, various drugs may contribute to the development of MRONJ.

In patients with osteoporosis, a reduction in BMD of the jaw was noted with a decrease in systemic BMD.[34, 35] Takaishi *et al.* reported a correlation between a decrease in BMD of lumbar vertebrae and a reduction in al-BMD in patients with osteoporosis.[20] Furthermore, hemolytic bone metastasis with a decrease in BMD and sclerotic bone metastasis with an increase in BMD have been shown to coexist in patients with bone metastasis from malignant solid tumors.[36] In patients with bone metastasis from malignant tumors or osteoporosis, bone resorption by osteoclasts is excessively enhanced, and BPs or DMB acts on osteoclasts, inducing a functional disorder. Therefore, BMD increases, resulting in osteosclerosis. This excessive increase in BMD may be a risk factor for MRONJ.[25]

A more detailed understanding of the prodromal state of MRONJ, particularly a risk assessment as diagnostic imaging before the onset of MRONJ, is needed. The Position Paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw reported that CT and CBCT are useful for detecting early changes in cancellous or cortical bones in patients with clinically suspected ONJ, while magnetic resonance imaging (MRI) is applicable for evaluating bone marrow changes or the extent of peripheral soft tissue inflammation.[7] However, facilities with CT or MRI are limited and an objective evaluation method available to general practitioners who may encounter patients with MRONJ at the highest probability needs to be developed. Furthermore, it is often difficult for general practitioners to understand the administration history of BMA, which increases in complexity year by year, and assess the risk of MRONJ. In the present study, we measured al-BMD on dental X-ray images as a simple screening method and examined its relationship with the onset of MRONJ.

Ueda *et al.* indicated that a radiopaque bone change around the site of tooth extraction was a risk factor for the onset of MRONJ.[37] Takaishi *et al.* detected alveolar bone sclerosis at al-BMD of 160 to ≥190, increasing the risk of MRONJ.[25] The present study also showed that al-BMD was significantly higher in patients with MRONJ than in non-MRONJ patients. Although the number of patients was small and further examinations are necessary, the results obtained suggest that high al-BMD before tooth extraction is a risk factor for the onset of MRONJ.

Osteosclerosis primarily induces a functional disorder of osteoclasts. With the sclerotic degeneration of bone marrow in which blood flow is essentially abundant, angiogenesis may be restricted, leading to ischemia or nutritional deficiency and inhibiting the process of wound healing. Takaishi *et al.* reported that al-BMD in non-ARA-treated patients with osteoporosis was 71.4.[20] However, in the present study, no significant difference was observed in al-BMD between healthy controls and BMA-treated patients without MRONJ, indicating that the use of BMA improved al-BMD in patients with osteoporosis to the normal level, whereas MRONJ only occurred in patients with an excessive increase in al-BMD.

The diagnosis of MRONJ and detection of the prodromal symptoms of MRONJ at a stage when clinical findings, such as non-specific pain, are observed, with no conclusive evidence on osteonecrosis, have been raised as an issue.[5] If a cut-off value of al-BMD suggestive of a high risk of MRONJ may be established, it will be useful for predicting

MRONJ. Takaishi *et al.* indicated that al-BMD significantly decreased with age, suggesting its usefulness for osteoporosis screening.[20] They reported that al-BMD (YAM) in osteopenia patients with a young adult mean (YAM) of the lumbar vertebral DEXA value ranging between 70 and 80% was 84.9, while that in osteoporosis patients with a DEXA (YAM) value of ≤70% was 71.4. Furthermore, they indicated that al-BMD (YAM) in healthy adults was 131.7 and that mean al-BMD in patients with MRONJ was 160.8.[15, 19] In the present study, al-BMD in patients with MRONJ was ≥200. Median al-BMD in non-MRONJ patients was similar to that in healthy adults reported by Takaishi *et al.* To establish a cut-off value for the onset of MRONJ, a sufficient number of patients needs to be accumulated in the future. However, if al-BMD is approximately 120 to 130, tooth extraction may be safely performed even in BMA-treated patients. Furthermore, in the present study, we did not examine changes in al-BMD in high-al-BMD patients in whom tooth extraction was not conducted; therefore, this warrants further study. However, if a tooth with high al-BMD is present, tooth extraction must be prophylactically considered before the start of BMA administration.

Many studies proposed that BMA need to be discontinued for a specific period before invasive surgical treatment, including tooth extraction, in order to prevent MRONJ.[1, 2, 3, 6, 7, 10] On the other hand, the discontinuation of BMA in patients with osteoporosis may exacerbate infection during the discontinuation period or increase the risk of adverse events associated with fractures related to a reduction in BMD, and some studies indicated that discontinuation needs to be avoided.[38-41] The effects of the discontinuation of BPs/BMA have been discussed for many years; however, pharmacokinetics differ between the two agents and there is a marked difference in their half-life. Therefore, a consensus has not been reached. In the present study, no significant decrease was observed in al-BMD before and after the discontinuation of BMA. Moreover, BMA had been discontinued in the only patient who developed MRONJ. These results suggest that prophylactic BMA discontinuation before tooth extraction does not always reduce the risk of MRONJ. Discontinuation-related adverse events need to be considered and managed. Therefore, the advantages of BMA discontinuation for MRONJ treatment need to be examined in more detail. Although MRONJ risk assessment methods using CT or MRI have been investigated, an objective risk assessment method has not yet been established. There are still many cases in which tooth extraction is avoided or BMA administration is discontinued. Infectious teeth with a poor prognosis that remain for a long period may exacerbate inflammation of the peripheral jaw, thereby increasing the risk of MRONJ. Quantitative measurements of al-BMD on dental X-ray images, as used in the present study, facilitate current MRONJ risk assessments at all dental clinics regardless of previous complex BMA administration history and may be simpler and more useful than other assessment methods. Furthermore, there is no supportive evidence for the efficacy of prophylactic BMA discontinuation. Based on the results of this study, the prophylactic discontinuation of at least low-dose ARAs may be unnecessary.

## CONCLUSION

In the present study, al-BMD before tooth extraction was high in patients with MRONJ after tooth extraction. We were unable to rule out the possibility that the onset of MRONJ may be associated with osteosclerosis. On the other hand, regarding BMA discontinuation, no changes were observed in al-BMD before and after their cessation, and the onset of MRONJ was not detected in any low-dose ARA-treated patient. Therefore, evidence to support the necessity of discontinuation was not obtained.

**Ethical approval**
The study design was approved by the Ethics Committee of Osaka Dental University, Japan (No.111020).

**Conflict of interest statement**
The authors declare that there are no conflicts of interest.

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