Review Article

# Symposium: Imaging modalities for drug-related osteonecrosis of the jaw (6), assessment of mandibular metabolism due to long-term administration of an anti-resorptive agent by bone scintigraphy (secondary publication)[☆],[☆☆]

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**A R T I C L E  I N F O**

**S U M M A R Y**

It is not yet known why anti-resorptive agent-related osteonecrosis specifically affects the jaw. Here we assessed changes in the bone metabolism of the mandible in response to long-term bisphosphonate (BP) therapy, and we compared the bone metabolism changes of the mandible with those of other bone sites using a quantitative analysis by bone scintigraphy. The region of interest was selected by identifying without an abnormal accumulation of the mandible, humerus, second and fourth lumbar vertebrae, iliac crest, intertrochanteric femur and diaphysis. Bone scintigraphy images were quantified using a value we termed the 'bone uptake value (BUV)'. In the low-dose bisphosphonate (LBP) group (n = 21), the patients were undergoing osteoporosis treatment with low-dose BP. The high-dose BP (HBP) group consisted of 12 bone metastasis patients undergoing high-dose BP treatment. The Control group was 47 subjects with oral disease who had never been treated with an anti-resorptive agent. Our analyses demonstrated that with long-term BP administration, the bone metabolism of the iliac crest and intertrochanteric femur was suppressed but that of the mandible was enhanced. There was no significant difference in bone metabolism with either the low-dose BP or high-dose BP treatment. The effects of the long-term administration of BP were site-specific.

## 1. Introduction

Anti-resorptive agents such as bisphosphonate (BP) and denosumab are the first-line agents for treating osteoporosis, contributing not only to the prevention of fractures in osteoporosis patients but also to an improved health-related quality of life. In addition, anti-resorptive agents decrease the number and frequency of skeletal-related complications in patients with bone metastasis, and thus are often administered over a long term. However, the long-term administration of BP is known to increase the risk of anti-resorptive agent-related osteonecrosis of the jaw (ARONJ) and atypical femoral fracture (AFF) [1–3].

The pathophysiology of both ARONJ and AFF has not been fully elucidated, but the common hypothesis is that an inhibition of osteoclast differentiation and function and increased apoptosis lead to decreased bone resorption and remodeling [1–3]. Although anti-resorptive agents may influence systemic bone remodeling, it is not clear why ARONJ develops at the jaw and AFFs occur in the femur. The mechanisms underlying biomechanical or biological site-specificity are also considered to be one of the causes of ARONJ and AFF, and it is also speculated that the effects of anti-resorptive agents on bone metabolism are site-specific.

Bone scintigraphy is the gold-standard nuclear imaging technique for the diagnosis of fracture lesions in osteoporosis and metastatic bone tumors, and it is indispensable to medical routine examinations for the radioisotope evaluation of bone-related disor-

**Table 1**
Characteristics of the LBP, HBP and control groups.

| | Sex (M:F) | Median age | ARONJ or not | Disease | BP | Median BP administration period (months) |
|---|---|---|---|---|---|---|
| LBP n = 21 | 1:20 | 82.0 | ARONJ:12 not ARONJ:9 | Osteoporosis | Low dose of BP | 41.0 |
| HBP n = 12 | 6:6 | 74.0 | ARONJ:12 | Breast cancer: 6 Prostate cancer: 6 Other cancer: 2 | High dose of BP | 60.5 |
| Control | 26:21 | 73.0 | not ARONJ | Osteomyelitis: 25 Oral carcinoma: 20 Other: 2 | – | – |

ARONJ: Anti-resorptive agent-related osteonecrosis of the jaw, LBP: Low-dose bisphosphonate, HBP: High-dose bisphosphonate.

ders such as bone cancer metastasis, fractures, and osteomyelitis of malignant tumor. The radioisotopes $^{99m}$Tc-methylene diphosphonate ($^{99m}$Tc-MDP) and $^{99m}$Tc-hydroxymethylene diphosphonate ($^{99m}$Tc-HMDP) used in bone scintigraphy are adsorbed at the site(s) where bone metabolism is accelerated, and they reveal bone metabolism which cannot be captured by another imaging modality.

However, bone scintigraphy image acquisition and interpretation criteria differ among institutions worldwide, leading to differences in reported results. Moreover, bone scintigraphy-based diagnoses involve a degree of subjectivity, and visual analyses have been left to qualitative. In order to objectively evaluate bone metabolism, it is necessary to quantify the bone accumulation counts and normalize the bone accumulation counts between images with different time phases.

In this report, we have normalized each pixel level of images obtained by bone scintigraphy at the radiopharmaceuticals' dosage and patients' body weights. We performed a quantitative analysis and we report a summary of our evaluation of changes in bone metabolism affected by long-term treatment with low-dose BP and high-dose BP at the mandible, femur and other bones.

## 2. Patients and methods

### 2.1. Patients

The eligibility of all patients was based on their fulfillment of all of the following criteria: ≥50 years old, had never undergone radiation therapy or steroid therapy, could walk independently and had no history of surgery or metastasis to a femur. In the LBP group (n = 21, one male, 20 females; median age 82 years), the patients were undergoing osteoporosis treatment with low-dose BP, i.e., alendronate, risedronate, minodronate, and ibandronate. The HBP group (n = 12, six males, six females; median age 74 years) was bone metastasis patients who were undergoing high-dose BP treatment, i.e., zoledronate. Both groups of patients were treated at Kagawa University Hospital from October 2012 to December 2016. The median administration of BP in the LBP and HBP groups was 41.0 and 60.5 months, respectively (Table 1).

The Control group patients (n = 47) had never been treated with BP or another anti-resorptive agent. They had been diagnosed with oral disease that required bone scintigraphy prior to treatment at Kagawa University Hospital during the same study period (Oct. 2012–Dec. 2016).

### 2.2. Bone scintigraphy

For all of the patients and controls, bone scintigraphy was performed using dual-head single-photon emission computerized tomography/computerized tomography (SPECT/CT) (Symbia T16;

Siemens Healthcare, Erlangen, Germany) fitted with low-energy, high-resolution, parallel-hole collimators. Whole-body images were obtained approx. 4 h after a single intravenous injection of 740 MBq $^{99m}$Tc-MDP. We used the anterior planar images of bone scintigraphy for the quantification of the bone uptake of radiopharmaceuticals. The region of interest (ROI) was selected by identifying the area without an abnormal accumulation of $^{99m}$Tc-MDP and without overlap with other bones of the mandible, humerus, second and fourth lumbar vertebrae, iliac crest, intertrochanteric femur, and diaphysis (Fig. 1).

We quantified the bone scintigraphy images by using a parameter that we termed the 'bone uptake value (BUV),' calculated as the bone accumulation of radiopharmaceutical by correcting each pixel value of the bone scintigraphy. We used the software BUV ver. 2 (Technical Society for Quantitative Bone Scintigraphy and FujiFilm RI Pharma) to calculate the BUV, using the following formula:

BUV = (pixel value of TBS image × CCF [Bq/Kg]) × coefficient of time/(dose of injection [MBq]/body weight [kg])

Where TBS is total body scan, and CCF is cross calibration factor. The primary endpoint of this study was the patient groups' mean BUV.

## 3. Results

In the Control group, no significant difference in the mean BUV of the mandible, humerus, second and fourth lumbar vertebrae, iliac crest, intertrochanteric femur and diaphysis was observed between the males and females. In the LBP group, no significant difference in the mean BUV of the mandible, humerus, second and fourth lumbar vertebrae, iliac crest, intertrochanteric femur and diaphysis were observed between the ARONJ patients (n = 12) and the patients without ARONJ (n = 9).

In the Control group, as shown in Fig. 2 there was no significant difference in the BUVs of the second and fourth lumbar vertebrae, humerus and iliac crest, intertrochanteric femur and diaphysis; however, the BUVs were significantly different between the mandible and the second and fourth lumbar vertebrae, between the mandible and the humerus and iliac crest, and between the mandible and the intertrochanteric femur and diaphysis (p < 0.001). The metabolism of the mandible was thus higher than that of the femur (which is part of the appendicular skeleton), but the metabolism of the lumbar vertebrae (which are part of the axial skeleton) was enhanced more than that of the mandible (Fig. 2).

As illustrated in Fig. 3, the mandibular BUV of the LBP group was significantly elevated compared to that of the Control group (mean BUV, 0.63 vs. 0.42, respectively; p = 0.004). A suppression of the bone metabolism was observed in the LBP patients' mean BUV compared to the Control group at the iliac crest (mean BUV, 0.12 vs. 0.19, respectively; p = 0.005) and the intertrochanteric femur (mean
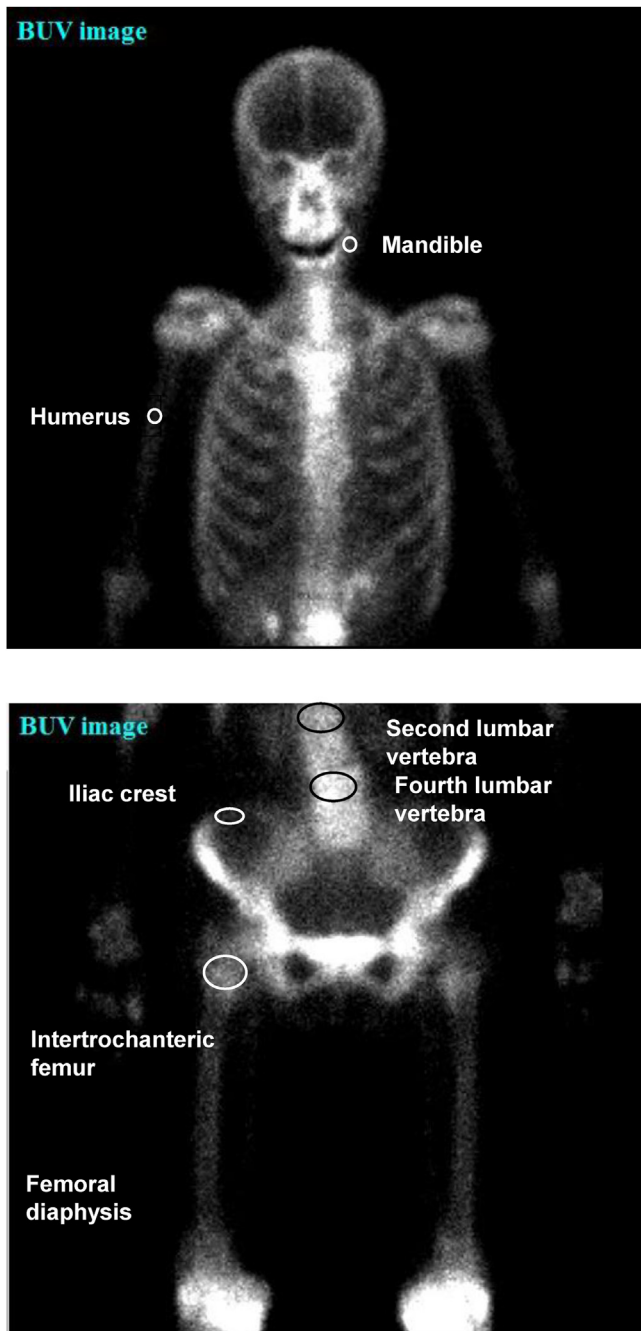
**Fig. 1.** ROIs at bone scintigraphy.

## 4. Discussion

In their report on mandibular metabolism in mice, Goldberg et al. noted that the bone turnover of calvaria and femur was higher than that of the mandible, and the bone turnover rates of calvaria and femur were suppressed by ovariectomy (OVX), whereas the mandible was not affected by OVX [4]. Kubek et al. reported that in healthy mice, the mineral apposition rate (MAR) in the alveolar bone of the mandible was approx. 50% lower than that of the trabecular bone of the mandible and approx. 20% lower than that of the femur. In addition, the MAR of alveolar cortical bone among OVX mice was significantly higher than that of normal mice, and the MAR of trabecular bone of the mandible and femur were not affected by OVX [5].

The bone turnover in beagle dogs was 84% lower in the non-alveolar region compared to the alveolar region [6]. In a study of bone metabolism in 11 healthy humans (median age 63 years old), the standardized uptake values (SUVs) from normal skeletons in NaF18-PET/CT bone scans (which detect sites of high bone remodeling in a manner identically to that of bone scintigraphy) revealed that various skeletal sites have different normal SUV values [7]. The SUVs of the lumbar vertebrae, thoracic vertebrae, and cervical vertebrae were higher than that of the femoral head, and the SUVs of the humeral head and parietal bone were lower than that of the femoral head; jaw bone scan were not done [7].

In the present study, the bone metabolism of normal bone in the 47 control patients was similar to that described in previous reports; i.e., the bone metabolism of the lumbar vertebrae was higher than that of the femur. However, the bone metabolism of the mandible was faster than that of the femur (part of the appendicular skeleton), and the bone metabolism of the lumbar vertebra (part of the axial skeleton) was facilitated more than that of the mandible. Physiological bone regeneration is based on an average 4% turnover per year in cortical bone (which represents roughly 75% of the entire skeleton) and an average 28% turnover per year in trabecular bone (which represents roughly 25% of the skeleton) [8]. The volume ratio of cortical to cancellous bone of the mandible by computed tomography was 22:78 [9] In another study of 90 Chinese females (average age 66.9 years), the percent cortical bone volume of the femoral neck were 42.04–45.95%, respectively [10], whereas the cross sectional area of lumber vertebrae was 9.66 cm$^2$ in women and 12.46 cm$^2$ in men, cortical thickness ranged from 180 to 600 μm, so most of the lumber vertebrae consist of cancellous bone [11–13].

We suspect that that study [7] also identified enhanced bone metabolism of lumbar vertebrae due to a larger proportion of cancellous bone compared to that of the mandible. The mandible has more cancellous bone than the femur. And we surmise that inflammatory responses due to periodontitis and periapical periodontitis were always present in alveolar bone of our study's aged controls, and thus it is possible that the bone metabolism of the entire mandible was higher than that of the femur. Regarding the bone metabolism of normal bone, the bone metabolism in each part of the elderly skeleton also seems to differ depending on environmental factors such as aging-related lifestyle, exercise habits, differences in nutritional intake, and the presence or absence of teeth. An extensive review of the available data is necessary to clarify the influences of these factors.

The elimination half-life (T1/2) of the BP alendronate is 1.66 h, and the T1/2 of the BP zoledronate is multiphasic, with 0.2 and 1.4 h representing early and late phases, respectively [14,15]. BP binds to bone rapidly by chelating calcium ions on hydroxyapatite surfaces [16]. After bone uptake of BP, the BP is released when the bone in which it is deposited is resorbed by osteoclasts. Thus, the half-life of a BP in bone is very long, ranging among different species from 1 to 10 years, depending largely on the rate of bone turnover [17].

BUV, 0.21 vs. 0.27, respectively; p = 0.002) (Fig. 3). There were no significant differences in the mean BUVs of the second and fourth lumbar vertebrae, the humerus, and the diaphysis.

Similar to the LBP group, the HBP group (Fig. 4) also showed an increase in mandibular BUV compared to the Control group (mean BUV, 0.64 vs. 0.42, respectively; p = 0.014), and suppression of the bone metabolism was observed at the iliac crest (mean BUV, 0.11 vs. 0.19, respectively; p = 0.028) and the intertrochanteric femur (mean BUV, 0.19 vs. 0.27, respectively; p = 0.009). There were no significant differences in the mean BUV of the second and fourth lumbar vertebrae, the humerus, and the diaphysis (Fig. 4). In the comparison of the LBP and HBP groups' data, there was no significant difference in BUV of the mandible, iliac crest or intertrochanteric femur (Fig. 5).
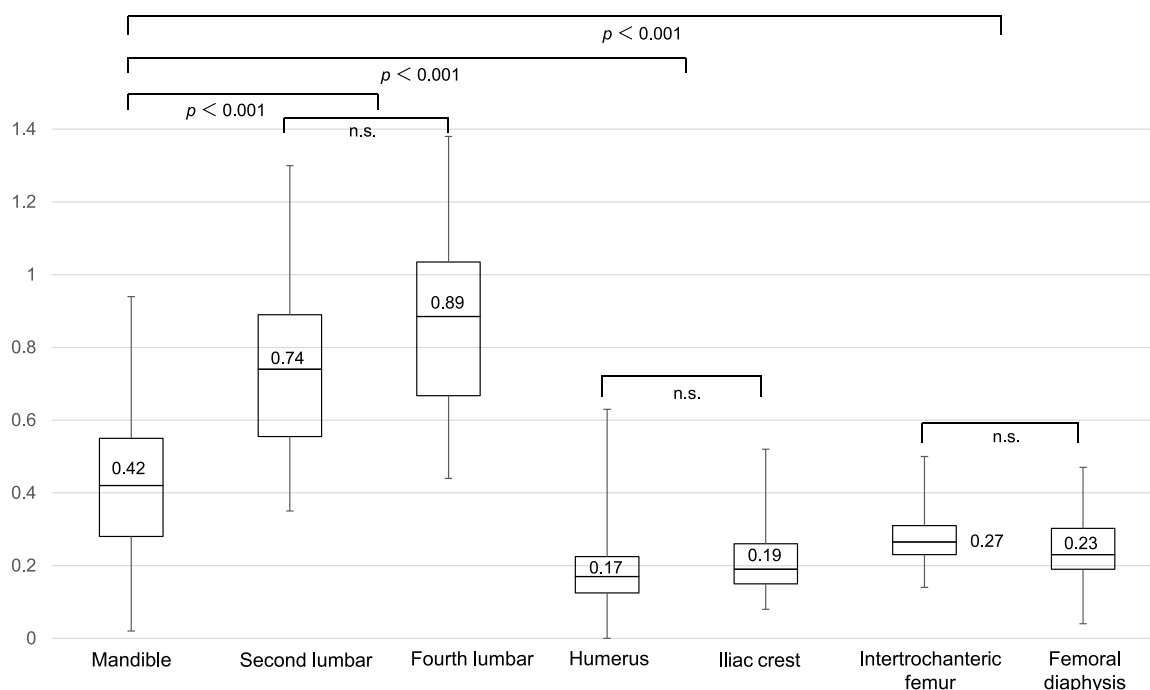
**Fig. 2.** Each site's bone uptake value (BUV) level in the Control group. There was no significant difference in the BUVs of the second and fourth lumbar vertebrae, humerus and iliac crest, intertrochanteric femur and diaphysis. However, the BUVs were significantly different between the mandible and the second plus fourth lumbar vertebrae, between the mandible and the humerus and iliac crest, and between the mandible and the intertrochanteric femur and diaphysis (p < 0.001).
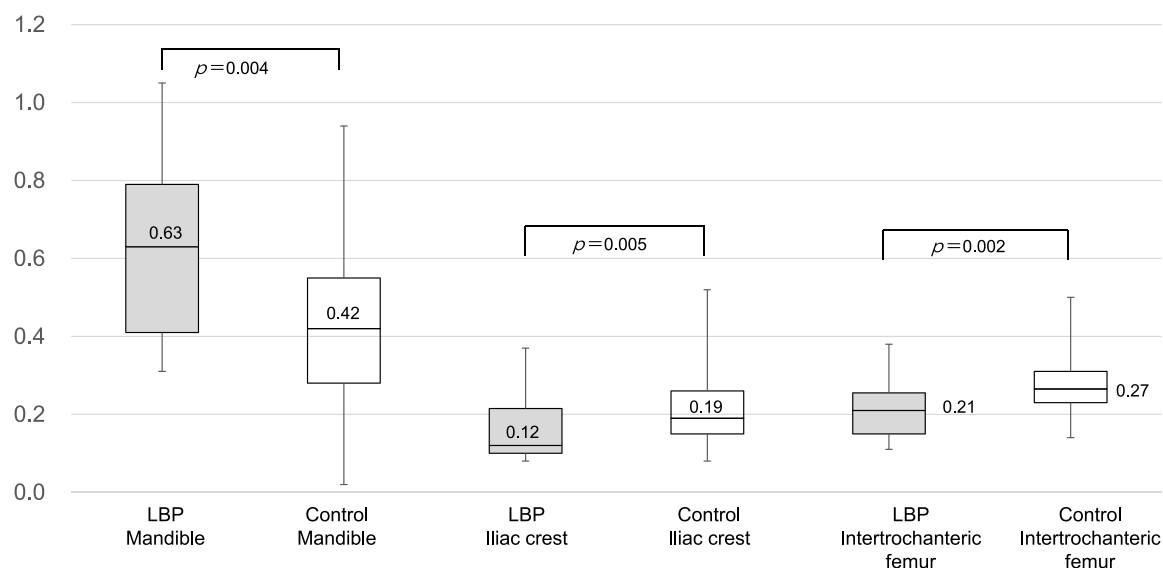


**Fig. 3.** Each site's mean BUV in the LBP group. The mandibular BUV was elevated compared to that of the Control group, and suppression of the bone metabolism was observed in the iliac crest and the intertrochanteric femur.

The first use of a therapeutic BP in humans was to inhibit ectopic calcification, and the next clinical use of a BP was as a bone-targeting radionuclide for nuclear imaging. A BP is conjugated to a technetium isotope (such as the currently used isotopes ^{99m}Tc-MDP and ^{99m}Tc-HMDP), and the radionuclide rapidly accumulates in areas of high bone metabolism due to the high binding affinity of BP to bone mineral [16].

Compounds such as ^{99m}Tc-MDP, ^{99m}Tc-HMDP, and BP have P–C–P backbones, which have chemical stability. The mechanism of these compounds' accumulation in bone is by both chemical adsorption onto the surface of the hydroxyapatite in bone and an uptake mediated by osteoblast-like cells [18]. Adsorption of ^{99m}Tc-MDP by bone was reported to be affected by the local pH, and it

is thus possible that acidification could explain the mechanism of increased ^{99m}Tc-MDP deposition [19]. At bone where metabolism is accelerated, an acidic environment is formed by hydrogen ions released from osteoclasts, local acidosis caused by an inflammatory disease, and tumor growth due to bone resorption by promoted osteoclasts when a tumor has metastasized to bone, so that a radionuclide seems to accumulate more than at normal sites as shown by bone scintigraphy.

BP binds preferentially to bones that have high turnover rates, and the distribution of a BP in bone is not homogeneous; the BP uptake is greater in trabecular bone compared to cortical bone due to the greater blood flow, surface area, and bone turnover in trabecular bone [17]. The binding affinity of BPs in areas of bone
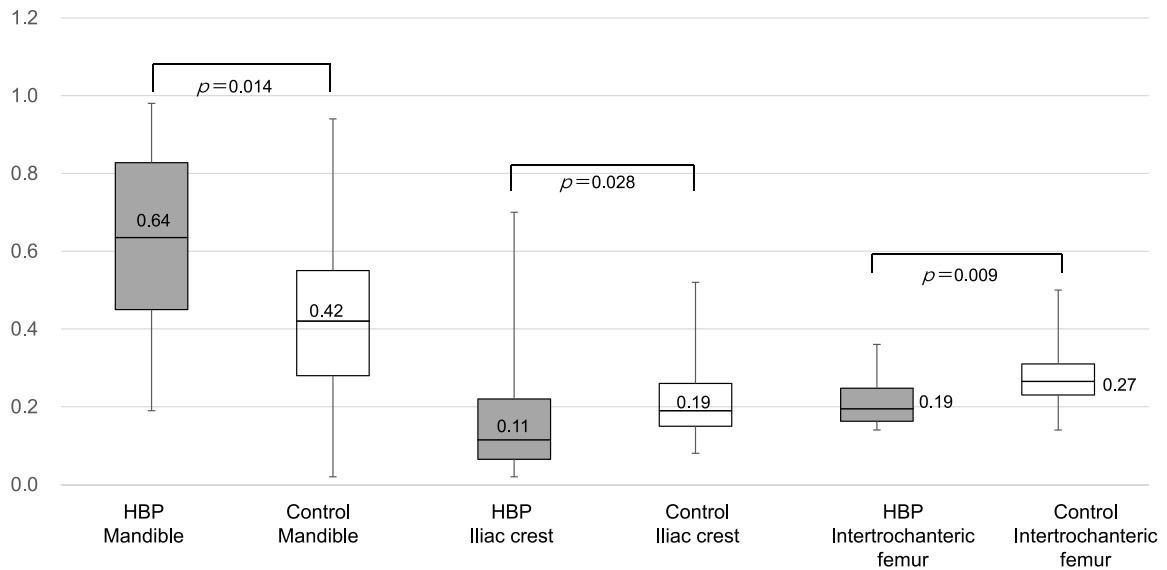
**Fig. 4.** Each site's mean BUV in the HBP group. The HBP patients showed an increase in mandibular BUV compared to the Control group, and suppressed bone metabolism was observed in the iliac crest and in the intertrochanteric femur.
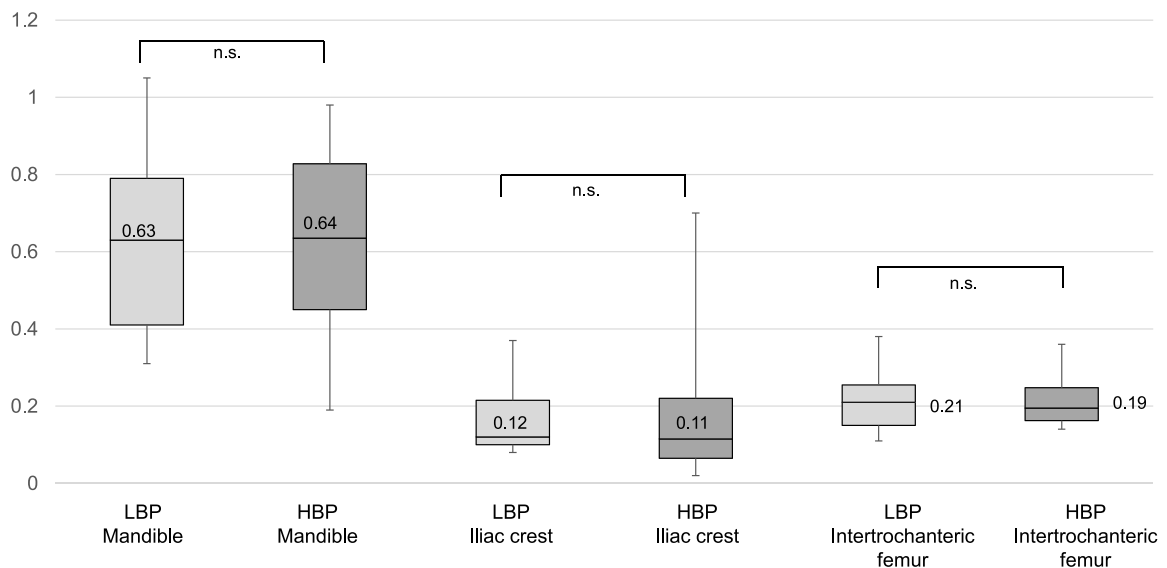


**Fig. 5.** Comparison of each site's mean BUV between the LBP and HBP groups. There was no significant between-group difference in BUVs in the mandible, iliac crest or intertrochanteric femur.

metastasis or high bone turnover is high compared to healthy bone [16]. In beagles treated with a BP for 3 years, the intracortical bone formation rate of the overall mandible was inhibited, due mainly to a suppression of turnover in the alveolar bone region [6]. In an investigation of 45 female patients with breast cancer, it was reported that before BP treatment the bone turnover of the patients' maxilla and femur was greater than that of the mandible, and the bone turnover of each region was not significantly altered after BP treatment [20].

We observed that bone metabolism was suppressed in the femurs of BP-treated osteoporotic patients, but the bone metabolism of the mandible was enhanced, in contrast to the conventional wisdom [21]. In the present study, the effects of the long-term administration of BP were site-specific: the bone metabolism of the iliac crest and intertrochanteric femur was suppressed by the long-term BP treatment whereas that of the mandible was enhanced. Histologically recognized osteonecrosis

occurs in the normal mandible of animals without extraction, and it has been reported that the increase in the osteonecrotic area where does not lead to bone exposure is found in a BP administration [22]. In general, cells undergo necrosis when the intracellular pH decreases due to increasing lactic acid production under the condition of enhanced glycolytic metabolism due to hypoxia.

We speculate that in the present study, $^{99m}$Tc-MDP might have accumulated at the mandible due to the local acidification by osteonecrosis which had not leaded in bone exposure induced in BP treatment. In addition, the distribution of BP to the mandible after BP administration to rats was higher than that of the appendicular and axial skeleton [23], and it was reported that substantial amounts of BP accumulate on bone surfaces at physiological pH and that significant amounts could be released by acidification produced by osteoclasts [24]. It is likely that the accumulation of $^{99m}$Tc-MDP observed at the mandible is attributable to acidification due to BP release from bone by long-term BP treatment. The

question of why a long-term administration of a BP would enhance the bone metabolism of the mandible remains unanswered. Further study of the influence of long-term treatment with a BP on bone metabolism is necessary.

One of the hypotheses that attempt to explain ARONJ in the jaws is the oversuppression of bone resorption, and an increased remodeling rate in the jaw may explain the differential predisposition for ONJ to occur in the jaw compared to other bones in the axial or appendicular skeleton [2,3]. In the present study, the metabolism of the mandible was higher than that of the appendicular skeleton, but the metabolism of the lumbar vertebra, which is part of the axial skeleton, was more enhanced than the metabolism of the mandible in patients administered BP. Two studies conducted in Korea reported that the ratio of the cancellous bone in the maxilla was higher than that in the mandible, at 33.0%–49.0% versus 27.0%–47.8%, respectively [25,26]. Cancellous bone may show more rapid turnover than cortical bone.

Consistent with this theory, maxilla should be have a high incidence rate of ARONJ than the mandible, but ARONJ is approx. threefold more likely to appear in the mandible compared to the maxilla actually [2,3]. The prevalence of ARONJ in osteoporotic patients receiving long-term oral BP therapy was reported at 0.001%–0.01%, and the prevalence in patients with cancer was 1.3% [27–29]. Our present analyses no significant difference in effects on bone metabolism between low-dose and high-dose BP. In addition to an oversuppression of bone resorption by antiresorptive agents, the pathophysiology of ARONJ seems to involve a number of mechanisms such as the specificity and genetic factors of the jaw, which is susceptible to infection due to pre-existing inflammatory dental disease.

Sites that show a significant accumulation of a $^{99m}$Tc-BP analog (e.g., $^{99m}$Tc-MDP and $^{99m}$Tc-HMDP) may also absorb a high amount of a BP. Many inflammatory dental diseases such as periodontal disease and periapical pathology occur in the jaw. Since many radionuclides have been shown bone scintigraphy to be accumulated in such lesions, BP seems to be adsorbed at the sites of inflamed lesions as well. When the local concentration of BP is high and an acidic environment increases BP accumulation, the cytotoxicity becomes strong. Increasing concentrations of both high concentrations of BP and local acidic milieu led to a significant decrease in cell viability and activity [30]. An increase in an acidic oral environment due to inflammatory dental disease in the jaw and an increase in the adsorption amount of BP due to low pH in the jaw have been speculated to be one of the causes of the occurrence of ARONJ, and in our present study, the long-term administration of BP increased the BUV of the mandible, and it therefore seems possible that the risk of ARONJ may increase further with a long-term administration of BP. It is also possible that the disease becomes serious as more BP accumulates in ARONJ lesions.

## 5. Conclusion

Our analyses revealed that the effects of the long-term administration of BPs were site-specific. Bone metabolism did not change in the second and fourth lumbar vertebrae, the humerus, or the diaphysis. The bone metabolism of the iliac crest and intertrochanteric femur was suppressed by long-term BP treatment, but the bone metabolism of the mandible was enhanced. Basic studies of the influence of the long-term administration of a BP on the jaw remain necessary.

## Conflict of interest statement

The authors declare that no competing financial interests exist.

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