学位論文

Bone metabolism of the jaw in response to bisphosphonate: A quantitative analysis of bone scintigraphy images

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Introduction

Bisphosphonates (BPs) inhibit bone resorption and is widely used for the treatment of cancer with bone metastases and osteoporosis. However, medication-related osteonecrosis of the jaw (MRONJ) is a pathological condition peculiar to the jaw that is associated with BP treatment [1]. The knowledge base and experience in addressing MRONJ has expanded, but the onset mechanism of MRONJ has not been fully elucidated [2, 3]. Among the theories regarding the several potential mechanisms underlying the pathophysiology of MRONJ is the theory of the inhibition of osteoclastic bone resorption by BPs and a subsequent suppression of remodeling. Although BPs may influence systemic bone remodeling, it is not yet known why MRONJ occurs at the jaw. It has been speculated that the influence of a BP on bone metabolism is site-specific, but it is not clear whether there are changes in site-specific bone metabolism due to treatment with a BP. The levels of bone resorption and formation markers decrease with the administration of a BP, and we hypothesized that even in the jaw (which is a frequent site of MRONJ), bone metabolism may be suppressed by BP treatment.

Quantitative measurements have been obtained based on the standardized uptake value (SUV) in the axial bone by radioisotope examination [4, 5]. No report has compared the bone metabolism of the jaw to the bone metabolism of other bone. There are very few studies of the SUV in normal bone and no study of the SUV in individuals at an age at which MRONJ is most

likely to occur. There is also no report regarding the normal values of the SUV of the jaw.

The differences in bone metabolism among the various sites of the jaw (toothless or not) have also not been studied. There are reports of bone metabolism influenced by BPs [6-9], but the influences of periodontal disease and tooth loss on the bone metabolism of the various sites of the jaw are not yet known. The primary objectives of the present study were to (1) examine the changes in the bone metabolism of the jaw in response to BP treatment, and (2) analyze the site-specific bone metabolism in the jaw and other bone sites by using a software program (GI-BONE Application®) for bone SPECT-CT. A secondary objective was to compare the bone metabolism of each part of normal bone.

Patients and Methods

Study design

This was a preliminary, single unit-based, matched case-control study. The study protocol, patient information, and informed consent forms were approved by the Kagawa University Ethical Committee (H24-#106) with informed consent waived. The study was conducted according to the principles of the Helsinki Declaration. We compared the change in the bone metabolism of each part of bone in response to BP treatment by performing a quantitative analysis of bone scintigraphy images among patients who underwent low-dose BP

treatment for osteoporosis (the LBP group; n=17), those treated with high-dose BP for a metastatic bone tumor (the HBP group; n=11), and patients with other oral diseases who required bone scintigraphy, with no history of BP treatment (the control group; n=40). We measured only normal bone and excluded sites with osteomyelitis, oral carcinoma or osteonecrosis of the jaw in all groups. The study's end point was set as the mean SUV of each of these three groups.

Patients

We retrospectively analyzed the data of the patients who underwent bone scans at the first visiting at Kagawa University Hospital during the period from May 2012 to May 2017. The eligibility of all patients was based on fulfilling all of the following criteria: ≥50 years old; had never been treated with denosumab, an angiogenesis inhibitor, radiation therapy, or steroid therapy; no systemic bone disease, and no endocrine disease. The median follow-up time was 26 months.

Bone scintigraphy

Bone scintigraphy was performed using dual-head single-photon emission computerized tomography/computerized tomography (SPECT/CT) (Symbia T16; Siemens Healthcare,

Erlangen, Germany). Planar and SPECT/CT images were acquired 4 hr after a single intravenous injection of 740 MBq ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP). We used the bone scintigraphy SPECT images for the quantification of the bone uptake of ^{99m}Tc-MDP.

We selected the volume of interest (VOI) manually in the three-dimensional cross-section by identifying an intact region of the cervical vertebra, thoracic vertebra, sternum, rib, humerus, temporal bone, alveolar bone of the maxilla (the vital teeth part [MxVTP] and the anodontia part [MxAP]), alveolar bone of the mandible (the vital teeth part [MdVTP] and the anodontia part [MdAP]), mandibular angle, mandibular ramus, and mandibular condyle (Fig. 1). In particular, the VOI of the maxilla and mandible was chosen as a normal oral site without non-vital teeth or apical periodontitis, periodontal disease, or mucosal disease (Fig. 2).

The SUV calculation method

For the quantification of the bone uptake of ^{99m}Tc-MDP, we calculated the SUV by using GI-BONE Application® software (AZE Co., Tokyo). The VOI was set at a site at which no obvious abnormal accumulation of ^{99m}Tc-MDP or any lesion was present, by setting the threshold to 40% after the software program's 'CT Mask' function was implemented. The formula for determining the SUV was as follows:

SUV = radiation concentration (Bq/ml) / dose at the beginning of the scan (Bq)/body weight (g)

Statistical analyses

We compared the mean SUVs of the VOIs among the three patient groups; differences were evaluated using the Kruskal-Wallis test. We compared the mean SUV of each bone part's VOI in the control group; differences were evaluated using the Mann-Whitney U-test. We analyzed SUV differences between the men and women in the control group and differences in patients with and without teeth at the jaw; differences were evaluated using the Mann-Whitney U-test. All analyses were carried out using SPSS 25.0 for Windows (SPSS, Chicago, IL). A p-value of <0.05 was considered significant.

Results

The characteristics of the 68 patients are summarized in Table 1. All 17 patients in the LBP group (one man, 16 women, mean±SD age 80.4 ± 5.72 yrs) were taking low-dose BP for osteoporosis, and the average duration of BP treatment was 41.8 months. In the 11 patients in the HBP group (five men, six women, age 72.3 ± 6.70 yrs), the high-dose BP was used to treat bone metastasis of a malignant tumor: six cases of breast cancer and five of prostate cancer. The average length of the BP treatment was 58.6 months. The control group was 40 patients (23

men, 17 women, age 71.8 ± 10.3 yrs) not treated with a BP. No lesions had occurred in the VOI which we set during the follow-up period. The LBP group consisted of both individuals with and without MRONJ. No significant difference was observed in the mean SUV between the LBP patients with MRONJ and those not affected by MRONJ at any site (data not shown). We therefore tested all of these patients as the LBP group.

The mean SUV of the HBP group was significantly lower at the axial bone of the cervical vertebra ($p=0.006$), thoracic vertebra ($p<0.001$), sternum ($p=0.001$), and rib ($p=0.028$) compared to the corresponding mean SUVs of the LBP and control groups. There was no significant difference among the three groups in the humerus ($p=0.628$) (Fig. 3). The mean SUV of the LBP group was significantly higher at the temporal bone ($p=0.008$) and mandible condyle ($p=0.02$). There was no significant difference among the three groups at the mandibular angle ($p=0.244$) or the mandibular ramus ($p=0.454$) (Fig. 4).

No significant difference was found among the three groups in MxVTP ($p=0.567$) or MdAP ($p=0.137$), but the mean SUV was significantly higher in the LBP group in MxAP ($p=0.028$) and MdVTP ($p=0.038$) (Fig. 5).

The mean SUVs in each bone part in the control group were follows: Among the mean SUVs of each bone part's VOI in the control group, the mean SUV of both MxVTP and MdVTP were significantly higher in the anodontia part ($p=0.025$, $p=0.041$). In the axial bone, the highest

mean SUV was at the cervical vertebra, followed in order by the thoracic vertebra and the sternum. The mean SUVs of the axial bone such as the cervical vertebra, the thoracic vertebra, and the sternum were higher than those of the maxillary and mandibular. The mean SUVs of the mandibular angle, the mandibular ramus, and mandibular condyle were lower than those of MxVTP, MxAP, MdVTP, and MdAP. In our comparison of the men and women, the women showed significantly higher SUVs in the temporal bones ($p=0.047$), but significant differences were not observed between the men and women at other sites (Fig. 6).

Discussion

We hypothesized that the accumulation of ^{99m}Tc-MDP would be reduced in the present BP-treated patients because of the strong suppression of remodeling by their BP treatment. Our present findings do not support this hypothesis. The results of our analyses demonstrate that the bone metabolism of the jaw and temporal bone was enhanced by BP treatment and that a suppression of bone remodeling due to BP was not present in the jaw. That is, contrary to our hypothesis, suppression of bone metabolism by BP treatment was not observed in the jaw.

Another hypothesis is that high levels of BP accumulation lead to a suppression of bone remodeling and an accumulation of large regions of dead or apoptotic osteocytes, which constitute necrotic bone [10-12]. A BP is connected to a technetium isotope (e.g., MDP or

HMDP), and it is possible to approximate a BP's pharmacokinetics. Therefore, the region of accumulation of ^{99m}Tc-MDP in our control group would be expected to be at a site where the effect of BP is strongly exhibited. Because BP strongly suppresses bone remodeling, the region of accumulation should be reduced in the BP-treated groups. If instead the accumulation is increased in the BP groups, other factors may be involved.

It is necessary to know the SUV of normal jaw for the evaluation and early detection of MRONJ by bone scintillation analyses. We took advantage of the rapid uptake of ^{99m}Tc-MDP in new bone formation and provisional calcification [13-20]. Various factors such as the teeth and periodontal tissue and occlusion affect the metabolism of the jaw; the structure of the bone is different between the maxilla and the mandible, and the various factors involved in the SUV of normal jaw have not been studied. The mean SUV of the jaw has not been determined.

Similar to our study, the spine has been reported to have a larger SUV with greater blood flow and turnover compared to the femur and humerus [21-23, 5]. The spine has also been reported to exhibit a high SUV due to mechanical stress and age-related changes [24, 25]. Because the SUVs of normal vertebrae show wide variability, it can be difficult to determine a standard value for normal bone [4]. Suenaga et al. reported that the SUV changed with the use of dentures [26]. We thus speculate that the influence of multiple factors (e.g., occlusal force) appears strongly at the part where teeth remain.

The rate of turnover of the body's entire skeleton is ~10% per year, and an average ~4% turnover per year in cortical bone is estimated; this represents roughly 75% of the entire skeleton. An average 28% turnover per year in trabecular bone, which represents roughly 25% of the skeleton, was also reported [27]. Our observations of the present control group's high mean SUVs in the cervical vertebrae, thoracic vertebrae, and maxillary bone compared to the mandibular bone with a high trabecular bone area are not inconsistent with the above-cited values [27]. The results of our analyses also revealed that in the patients treated with high-dose BP, the mean SUV was significantly lower in the axial bone of the cervical vertebra, thoracic vertebra, sternum, and rib. In light of these lower values, we speculate that the bone metabolism of axial bone was suppressed by the high-dose BP treatment.

Several studies using ^{18}F-NaF or ^{99m}Tc-MDP showed increased SUVs in osteoporotic patients [28, 25, 29-33], suggesting that the bone turnover is increased in osteoporotic patients. Alendronate treatment resulted in significant decreases in bone metabolism and turnover in the lumbar spine [34].

In the present study, the SUV in the humerus and several parts of the jaw were not significantly different between the BP groups and the controls. The influence of BP in this study was a tendency to result in a greater change in a large population of trabecular bone. The mean SUV at the site of MxAP and MdVTP were higher in the LBP group compared to the other two

groups. There was no significant difference in MxVTP, but the SUV of LBP group was the highest than other. Low-dose BP treatment may increase bone metabolism of the jaw. There was no significant difference in MdAP. It is unclear why there was no significant difference in MdAP, but it was clear that bone metabolism was not suppressed even in the anodontia part mandibular.

As no data before the patients' BP treatment were available to us, we could not study sequential data of bone metabolism during BP treatment. In a study of temporomandibular joint dysfunction (TMD), quantitative bone SPECT/CT images showed a high accumulation of the radiotracer [35]. Thus, when clinicians observe a high accumulation of a radiotracer in a patient, the patient should be examined for the presence of TMD.

This study has several limitations. First, the selection bias couldn’t be ruled out due to the retrospective study design. Second, various factors such as the teeth, periodontal tissue, occlusion and TMD cannot be excluded completely. Finally, the number of patients was relatively small, and so limiting the statistical power to detect significant associations.

This study is the first to evaluate the mean SUV of the jaw in detail (e.g., the presence of teeth, the mandible angle, mandibular ramus, and mandibular condyle). We suggest that further studies of a greater number of patients will help elucidate the onset mechanism of MRONJ and contribute to the prevention and early detection of MRONJ by calculating the normal bone SUV

in patients treated with a BP.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (the Kagawa University Ethical Committee (H24–#106)) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Figure Legends

Fig. 1. The volume of interest (VOI) was selected manually in the three-dimensional cross-section by identifying an intact region.

Fig. 2. The VOI of the jaw in detail. The VOI of the maxilla and mandible was chosen as a normal oral site without non-vital teeth or apical periodontitis, periodontal disease, or mucosal disease. MdAP: anodontia part of alveolar bone in mandible, MxVTP: vital teeth part of alveolar bone in maxilla, MdVTP: vital teeth part of alveolar bone in mandible.

Fig. 3. The mean standardized uptake value (SUV) of the trunk bone and humerus. The mean SUV of the high-dose bisphosphonate (HBP) group was significantly lower at the trunk bone of the cervical vertebra, thoracic vertebra, sternum, and rib compared to the corresponding values of the low-dose bisphosphonate (LBP) group and control group.

Fig. 4. The mean SUV of the jaws. The mean SUV of the LBP group was significantly higher at the temporal bone and mandible and the temporomandibular joint.

Fig. 5. The mean SUV of the alveolar. A significantly higher mean SUV was found in the LBP group in the MxAP and the MdVTP . MxVTP: vital teeth part of alveolar bone in maxilla, MxAP: anodontia part of alveolar bone in maxilla, MdVTP: vital teeth part of alveolar bone in mandible. MdAP: anodontia part of alveolar bone in mandible.

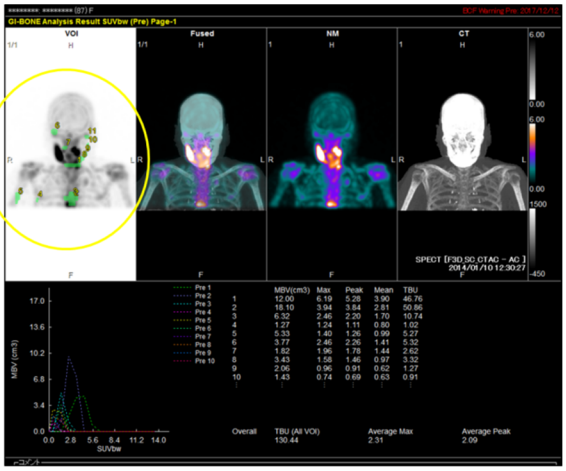
Fig. 6. The value of the mean SUV of the Control group. Between the mean SUV of each part's VOIs in the control group, both the vital teeth part of the maxillary and mandibular alveolar were significantly higher in the anodontia part.

Table 1. The patients' characteristics (n=68)

	Sex	Mean age, yrs	MRONJ or Not	Underlying disease	Antiresorptive agent	Avg. duration of BP administration, mos.
LBP group n=17	M:1 F:16	80.4	MRONJ:10 Not MRONJ:7	Osteoporosis: 17	Low-dose BP	41.8
HBP group n=11	M:5 F:6	72.3	MRONJ:11	Breast cancer: 6 Prostate cancer: 5	High-dose BP	58.6
Control group n=40	M:23 F:17	71.8	Not MRONJ: 40	Osteomyelitis: 20 Oral carcinoma: 18 other: 2	None	–

Data are the number of patients in each group. BP: bisphosphonate, HBP: high-dose bisphosphonate, LBP: low-dose bisphosphonate, mos.: months, MRONJ: medication-related osteonecrosis of the jaw.

Fig. 1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VOI
Fused
NM
CT
SPECT [F3D,SC,CTAC - AC]
2014/01/10 12:30:27
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Overall TBU (All VOI) Average Max Average Peak
130.44 2.31 2.09
MBV (cm3)
SUVbw

Fig. 2

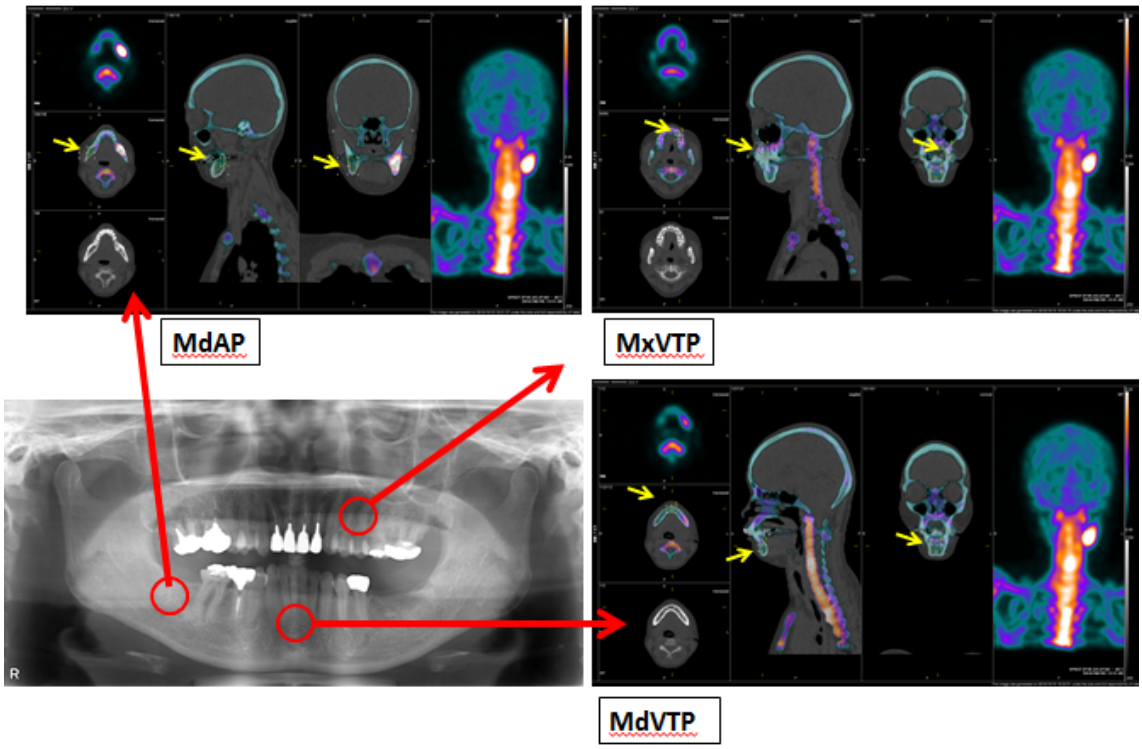


Fig. 3

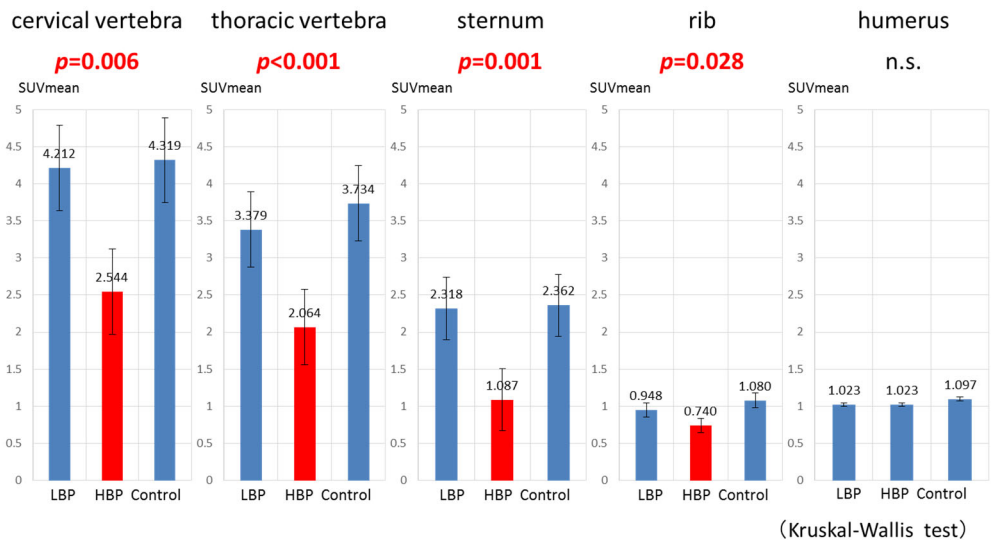

cervical vertebra
p=0.006
thoracic vertebra
p<0.001
sternum
p=0.001
rib
p=0.028
humerus
n.s.
SUVmean
4.212
2.544
4.319
3.379
2.064
3.734
2.318
1.087
2.362
0.948
0.740
1.080
1.023
1.023
1.097
LBP HBP Control
(Kruskal-Wallis test)

Fig. 4

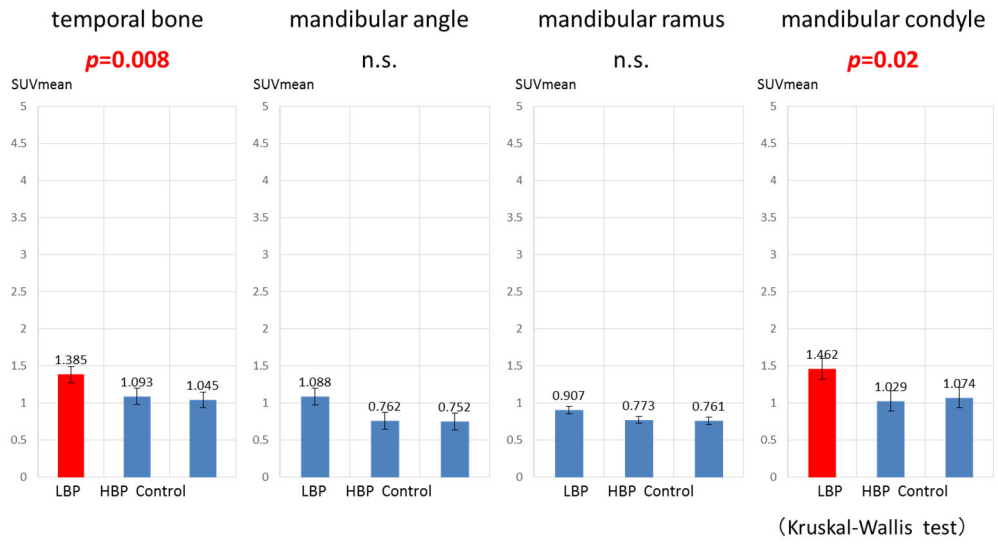
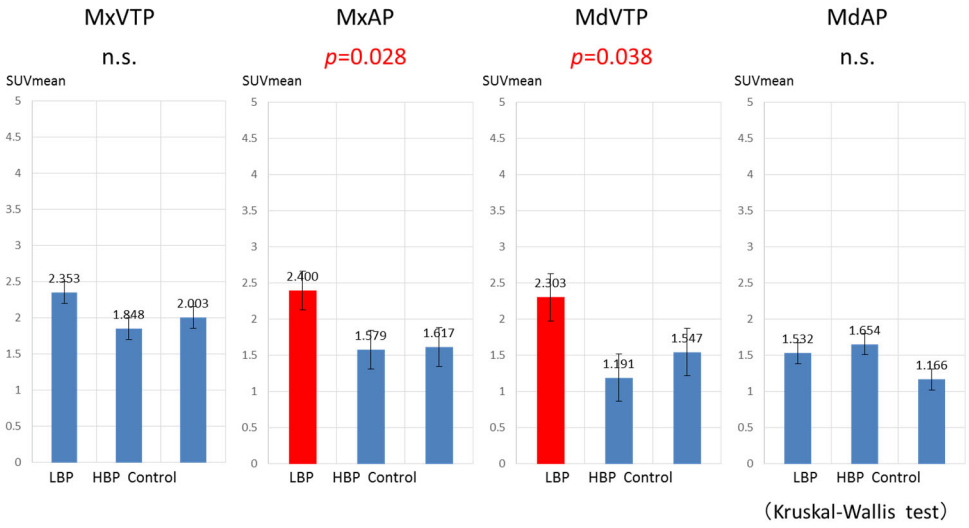

temporal bone
p=0.008
mandibular angle
n.s.
mandibular ramus
n.s.
mandibular condyle
p=0.02
SUVmean
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
1.385
1.093
1.045
1.088
0.762
0.752
0.907
0.773
0.761
1.462
1.029
1.074
LBP
HBP
Control
(Kruskal-Wallis test)

Fig. 5


MxVTP
n.s.
MxAP
p=0.028
MdVTP
p=0.038
MdAP
n.s.
SUVmean
2.353
1.848
2.003
2.400
1.579
1.617
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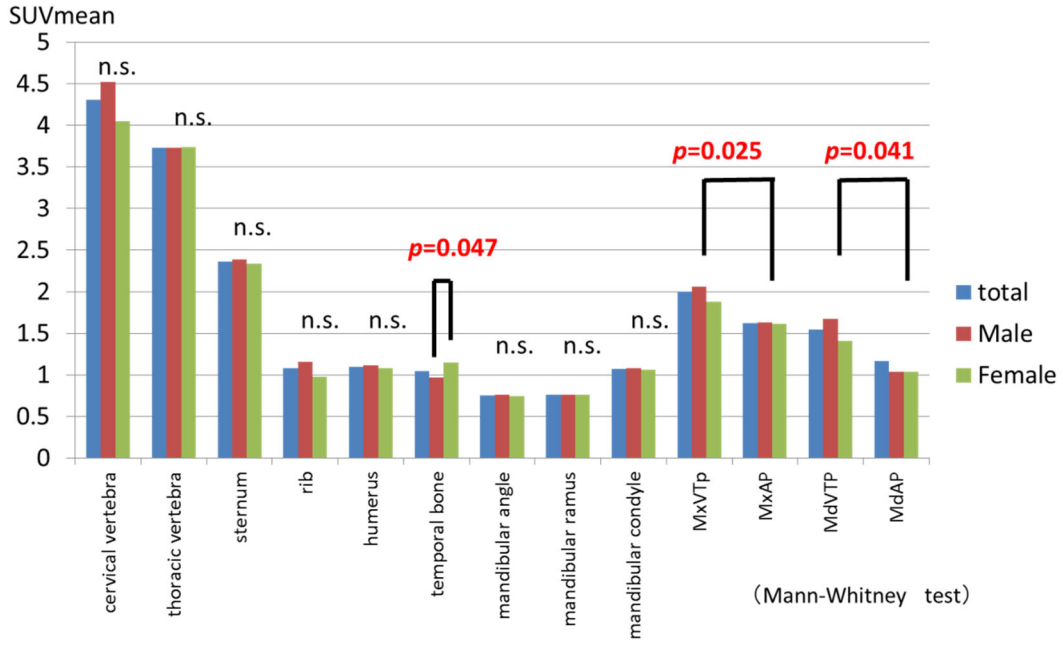
1.191
1.547
1.532
1.654
1.166
LBP HBP Control
(Kruskal-Wallis test)

Fig. 6


SUVmean
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
n.s.
n.s.
n.s.
n.s.
n.s.
p=0.047
n.s.
n.s.
n.s.
p=0.025
p=0.041
cervical vertebra
thoracic vertebra
sternum
rib
humerus
temporal bone
mandibular angle
mandibular ramus
mandibular condyle
MxVTp
MxAP
MdVTP
MdAP
total
Male
Female
(Mann-Whitney test)