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Risk of osteomyelitis of the jaw induced by oral bisphosphonates in patients taking medications for osteoporosis: A hospital-based cohort study in Japan

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ABSTRACT

Oral bisphosphonates (BPs) represent the first line of prevention and treatment for osteoporosis. However, several studies have reported osteonecrosis of the jaw (ONJ), also known as osteomyelitis of the jaw (OMJ), as a side effect of these drugs. Although absolute risk is suggested to be low, information to date on the relative risk or attributable risk has in fact been limited. Here, we estimated risk of oral BPs for OMJ in osteoporosis patients taking oral BPs compared with other osteoporosis drugs. Using an electronic medical records retrieval system and manual confirmation of OMJ, we conducted a retrospective cohort study of patients taking medications for osteoporosis at Kyoto University Hospital between November 2000 and October 2010. To evaluate relative risks of oral BPs for OMJ, logistic regression analysis was performed and odds ratios (ORs) and 95% confidence interval (CIs) were estimated. In addition, sensitivity analyses were performed according to hierarchical diagnosis. A total of 4129 patients (59.6%) were prescribed BPs while 2794 (40.3%) received other osteoporosis drugs. Absolute risk for OMJ was estimated to range from 0.46% to 0.99% (95% CIs: 0.25–0.66 to 0.69–1.2) among patients receiving oral BPs and 0.071% to 0.17% (95% CIs: 0–0.17 to 0.022–0.33) among patients receiving other osteoporosis drugs. The attributable risks of oral BPs for OMJ were estimated to range from 0.38% to 0.81% (95% CIs: 0.38–0.39 to 0.80–0.81). ORs (95% CIs) adjusted for confounding factors were 5.0 (1.9–12.9) to 6.0 (1.3–26.1) for confirmed cases only. In terms of absolute and attributable risks, the risk of oral BPs for OMJ is considered to be less than 1% in patients with osteoporosis. However, oral BPs may increase the risk of OMJ compared with patients treated with other osteoporosis medications and the risk of side effects should be kept in mind.

Introduction

Bisphosphonates (BPs) are used for a range of conditions involving the bone, such as osteoporosis and bone metastases of malignant cancer, and their efficacy in increasing bone mineral density, preventing further bone fractures, and reducing bone pain has been confirmed [1,2]. Nevertheless, in 2003 Marx reported bisphosphonate-related osteonecrosis of the jaw or bisphosphonate-induced osteonecrosis of the jaw as a side effect of BP treatment [3]. Since this initial report, the association between BP exposure and the incidence of osteonecrosis of the jaw (ONJ) and osteomyelitis of the jaw (OMJ) has been clarified in several case series, reviews, epidemiologic studies and clinical trials [4–16]. Here, we group OMJ together with ONJ for case ascertainment, as in previous studies and a review [15–17].

Several studies have reported prevalence of OMJ on intravenous administration of BPs ranging from 0.7% to 18.6% [6–8]. In contrast, surveillance data reported that estimated prevalence or incidence in patients treated with oral BPs (alendronate) ranged from 0.01% to 0.04% [9], or approximately 0.7 cases per 100,000 person-years' exposure [10]; while several studies reported a prevalence or incidence of OMJ on oral BP administration ranging from 0.05% to 4.3% [11–13], or 3.0 to 6.3 cases per 100,000 person-years [14]. These data suggest that the risk of OMJ is much lower in patients receiving oral than intravenous BPs. However, the low incidence of OMJ among BP-naïve patients precludes any direct estimation of the risk ratio of OMJ among osteoporosis patients treated with oral BPs, and few reports have described the relative risk of oral BPs for OMJ [14,15].

Oral BPs are the drug treatment of first choice in osteoporosis [18], a condition which affects more than 75 million people in the United States, Europe and Japan [19]. Nevertheless, effective decision making on the risks of oral BPs is hampered by a lack of information for both patients and the physicians who prescribe them. It is therefore of

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interest to evaluate the particular risk of OMJ as a side effect of oral BPs and to offer clinically relevant information to patients, physicians and dentists.

Here, we conducted a historical cohort study of patients diagnosed with and treated for osteoporosis at Kyoto University Hospital using an electronic medical records (EMR) retrieval system. Our purpose was to estimate specific risks for OMJ in osteoporosis patients taking oral BPs compared with other osteoporosis medications, with comprehensive data extraction and manual confirmation of OMJ.

Material and methods

Study design and cohort

We conducted a retrospective cohort study of patients diagnosed with osteoporosis at Kyoto University Hospital between November 2000 and October 2010. Among these patients, analysis was limited to those aged 20 years or older who had been treated with osteoporosis medications. This criterion was based on previous findings that age at first onset of BP-induced OMJ was approximately 20 years [20–23]. Eligible patients were identified using their ID at Kyoto University Hospital, and dental and medical records were examined by two reviewers from September 2011 to December 2011.

Data extraction

We used an electronic medical records retrieval system to extract data from the EMR [24]. This system retrieves electronic data for both outpatients and inpatients at Kyoto University Hospital, including demographic data, diagnosis and 10th edition of the International Classification of Diseases (ICD-10) code [25], medications and injections, laboratory tests, radiological or pathological studies, etc. First, we searched for patients who were diagnosed with osteoporosis as specified by ICD-10 code (Appendix 1) and prescribed osteoporosis medications approved in Japan (Appendix 2). We then extracted the following data for these patients: sex; date of birth; diagnosis; date of diagnosis; names, doses and dates of osteoporosis medications, hypoglycemic agent and insulin, corticosteroids and chemotherapy; and diagnosis related to malignant tumors in the oral region and diabetes as specified by ICD-10 code.

Exclusion criteria

Patients with primary or metastatic tumors or a history of trauma in the maxillofacial region were excluded, because these often induce inflammation of the jaw. Patients with a history of radiation therapy were excluded from analysis of the risk of oral BPs for OMJ, because craniofacial radiation for malignant tumors in the maxillofacial region causes osteoradionecrosis of the jaw [26]. Patients treated with intravenous BPs were also excluded, because our purpose here was to evaluate the risk of OMJ in osteoporosis patients receiving oral BPs.

Definition of OMJ cases

The American Association of Oral and Maxillofacial Surgeons, a task force of the American Society for Bone and Mineral Society and the Canadian Consensus Practice Guideline for Bisphosphonate-associated Osteonecrosis of the Jaw have stated that the hallmark of BP-induced ONJ is exposed necrotic bone in the maxillofacial region that has persisted for more than 8 weeks [27–29]. However, radiographic findings in infected jawbone in patients treated with BPs have shown that it has similar characteristics to those in BP-induced ONJ even if necrotic bone could not be clinically visualized [30,31]. In addition, the presence of osteonecrosis is a common histopathologic finding in both BP-induced ONJ and OMJ [32]. We therefore considered it appropriate to group cases of OMJ together with ONJ, as was done in previous studies and a review [15–17].

Hierarchical diagnostic criteria of OMJ

We proposed interim diagnostic criteria for OMJ in this study, using four hierarchical diagnostic criteria defined as follows: possible cases were diagnosed by increased uptake on technetium bone scan with characteristic signs and symptoms of bone infection and/or findings on dental panoramic X-ray; probable cases were diagnosed by imaging findings on computed tomography (CT) scans which were consistent with findings of possible cases; confirmed cases were diagnosed by a histological picture consistent with OMJ and/or the isolation of a microorganism in samples obtained by extraoral open surgery, percutaneous biopsy of bone, removed bone or intramedullary tissue, or pus aspiration from adjacent tissues, with findings of probable cases; and non-cases were diagnosed if not applicable to the above criteria.

Reconfirmation of OMJ

OMJ was diagnosed independently by two oral and maxillofacial surgeons. To minimize diagnosis bias, the records were examined in the following order: 1. observation of findings on dental panoramic X-ray; 2. observation of findings on technetium bone scan; 3. observation of findings on CT scan; 4. observation of findings of histological study; 5. observation of findings of surgical treatment; and 6. observation of clinical symptoms by checking progress notes. Before reviews, reviewers were trained to diagnose OMJ using a standardized protocol. We then examined inter-examiner reliability of diagnosis using 20 patients with a diagnosis of OMJ who were not included from the study population using kappa statistics. Inter-observer agreement was moderate (kappa value = 0.64 to 0.81).

First, the reviewers examined radiographic imaging and clinical records of patients with diagnoses of an inflammatory condition of the jaws (Appendix 3) to confirm their diagnoses of OMJ. Examination of X-rays, technetium bone scans, and CT scans was done using the Centricity Enterprise web v.3.0 software (GE Health Care, Little Chalfont, Buckinghamshire, England). Next, they examined radiographic imaging and records of patients with diseases possibly related to OMJ (e.g. fracture or cellulitis in the oral and maxillofacial regions, periodontal disease, or osteomyelitis and osteonecrosis in other regions, etc.) as well as records of patients suspected to have OMJ (Appendix 3), in order to decrease the false-negative rate.

In their review, the reviewers examined when oral BPs were prescribed and when OMJ occurred: cases of OMJ which developed before or without prescription of an oral BP were regarded as non BP-induced cases. They also examined whether patients had malignant tumors or any history of craniofacial radiation therapy or trauma in the maxillofacial region. In addition, they collected data concerning BP prescriptions at other hospitals when available from referral letters from physicians, and patients with a confirmed prescription in another hospital were regarded in the same way as those with a prescription in our hospital. Cases with diagnostic disagreement were discussed until they could be classified by consensus into an appropriate case category.

Confounding factors

The following confounding factors were included into the statistical analysis: age, sex, diabetes, steroid use and chemotherapy. Diabetes was diagnosed if the patient had received a diagnosis of diabetes, and had either received any treatment with hypoglycemic medication (hypoglycemic agent and/or insulin) or had an HbA1c ratio $\geq$6.5% [33]. Steroid use was defined as the receipt of any

treatment with corticosteroids, and chemotherapy use as the receipt of any treatment with cancer chemotherapy.

Statistical analysis

Patient characteristics were summarized using descriptive statistics (median, range, interquartile range, 95% confidence intervals (CIs) and percentages). Medians for continuous variables were compared using the Wilcoxon rank-sum test. Proportions across levels of categorical variables were compared using the Fisher exact test. In the analysis of characteristics by case definition, we compared the differences between overall cases and non-cases. Duration of drug administration was calculated by the sum of the number of prescription days. Once-weekly medication was treated as equivalent to 7 days' prescription. The incidence of OMJ was calculated using the cumulative incidence method, which is defined as the number or proportion of a cohort of people who experience the onset of OMJ during a specified time interval [34]. Attributable risk was defined as the difference in the population risk of disease in exposed versus unexposed patients [34]. The relative risk of oral BPs for OMJ was evaluated by logistic regression analysis with OMJ as the dependent variable, and odds ratio (ORs) for OMJ cases and 95% CIs were estimated using three models: Model 1, crude; Model 2, adjusted for sex and age; and Model 3, adjusted for Model 2 and diabetes, steroid, and chemotherapy use. In addition, the following sensitivity analyses were performed: ORs for overall cases; ORs for both probable and confirmed cases; and ORs for only confirmed cases. Goodness-of-fit of the model was examined using the Hosmer–Lemeshow goodness of fit test. All *P* values were two-sided at a significance level of 5%. All statistical analyses were performed using Stata 11.2 software (Stata Corporation, College Station, TX, USA).

Sample size estimation

Almost all previous studies reported that the prevalence or incidence of ONJ or OMJ in patients treated with oral BPs was low, at up to 0.34% [9,11,12]. In contrast, the incidence of ONJ or OMJ among BP-naïve osteoporosis patients was unclear at the time this present study began. Black et al. identified only 1 patient with possible ONJ among 3852 postmenopausal women without BPs (0.025%) [35]. Hence, to compare the proportion of patients receiving oral BPs with those receiving other osteoporosis medications, at least 2842 patients in each group were estimated for inclusion with an alpha set at 0.05 and beta set at 0.10, assuming that the proportion of OMJ in patients receiving BPs was 0.50% and that in patients receiving other osteoporosis medications was 0.025%.

Ethical approval

This study protocol was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine and conducted according to the 'Ethical Guidelines for Epidemiological Research' [36].

Results

A total of 7062 patients treated with osteoporosis medications and aged 20 years or older were included. Among these, the reviewers examined records of 84 patients suspected of having OMJ and 1986 patients with diseases possibly related to OMJ. In their review, they confirmed that 7 patients had been treated with BPs (including 1 patient receiving intravenous BPs) in other hospitals and 6 had a history of craniofacial radiation therapy in the maxillofacial region. No patient was confirmed to have developed OMJ due to trauma in the maxillofacial region or before receiving a prescription of BP. After exclusion of 29 patients with primary or metastatic tumors in the oral region and/or a history of craniofacial radiation therapy and 110 patients receiving intravenous BPs, 6923 (98.0%) eligible patients were entered into the analysis.

Patient characteristics are summarized in Table 1. The total number of patients prescribed oral BPs was 4129 (59.6%), while 2794 (40.3%) received other osteoporosis drugs. Median age was lower ($P=0.022$) and the percentage of females, and steroid and chemotherapy users was higher among those prescribed BPs ($P<0.001$), whereas the prevalence of diabetes did not differ between the two groups ($P=0.15$).

Patient characteristics according to our four case definitions are shown in Table 2. Forty-six patients receiving osteoporosis medications developed OMJ (0.66%, 95% CIs: 0.47–0.85). Compared with non-cases, cases were older ($P=0.049$) but the percentage of females, diabetes patients, and steroid or chemotherapy users did not differ between the two groups ($P>0.05$). All patients who developed OMJ received one or more kinds of nitrogen-containing BPs (NBPs), namely alendronate, risedronate and minodronate. The median duration of BP administration among case patients prescribed oral BPs was longer than that in non-cases. Among the 4129 patients prescribed oral BPs, 19 cases were diagnosed as confirmed, 7 as probable, and 15 as possible, giving an estimated absolute risk (i.e. incidence) of oral BPs for OMJ ranging from 0.46% to 0.99% (95% CIs: 0.25–0.66 to 0.69–1.2). In contrast, among the 2794 patients prescribed other osteoporosis drugs, 2 cases were diagnosed as confirmed, 1 as probable, and 2 as possible, giving an estimated absolute risk ranging from 0.071% to 0.17% (95% CIs: 0–0.17 to 0.022–0.33). The attributable risks of oral BPs for OMJ were estimated to range from 0.38% to 0.81% (95% CIs: 0.38–0.39 to 0.80–0.81).

Table 3 shows sensitivity analyses and adjusted ORs for OMJ according to case definitions. Crude ORs (95% CIs) were 5.5 (2.2–14.1) for overall cases, 5.8 (1.7–19.4) for both probable and possible cases, and 6.4 (1.5–27.7) for confirmed cases only. After adjustment for potential confounding factors, ORs were 5.0 (1.9–12.9) for overall cases, 5.4 (1.6–18.3) for both probable and possible cases, and 6.0 (1.3–26.1) for confirmed cases only. The final multivariable adjusted model was reliable ($P=0.55$ to 0.61 by the Hosmer–Lemeshow test).

Table 1
Characteristics of patients taking medications for osteoporosis at Kyoto University.

	BP administration	Other osteoporosis drugs	*P* value
Number	4129	2794	
Median age (range)	65.0 (20–99)	65.5 (20–97)	0.022
Sex, n (%)			
Male	814 (19.7)	725 (25.9)	<0.001
Female	3315 (80.2)	2069 (74.0)	
Diabetes, n (%)			
Yes	707 (17.1)	442 (15.8)	0.15
No	3422 (82.8)	2352 (84.1)	
Steroid use, n (%)			
Yes	2934 (71.0)	1508 (53.9)	<0.001
No	1195 (28.9)	1286 (46.0)	
Chemotherapy use, n (%)			
Yes	551 (13.3)	256 (9.1)	<0.001
No	3578 (86.6)	2538 (90.8)	
Oral BP administration[a]			
Etidronate, n (%)	548 (13.2)	N.A.	N.A.
Alendronate, n (%)	2871 (69.5)	N.A.	
Risedronate, n (%)	1604 (38.8)	N.A.	
Minodronate, n (%)	38 (0.92)	N.A.	
Duration of administration (days)			
Median duration (IQR)	364.0 (90–966)	439.5 (98–1413)	<0.001

BPs = bisphosphonates; N.A. = not applicable; IQR = interquartile range.
Medians for continuous variables were compared using the Wilcoxon rank-sum test. Proportions across levels of categorical variables were compared using the Fisher exact test.
[a] In some cases, several oral BPs were prescribed for one patient.

Table 2
Demographic and risk factor characteristics of patients by case definition.

	Hierarchical diagnostic criteria			Overall cases	Non-cases	*P* value
	Confirmed cases	Probable cases	Possible cases			
Number	21	8	17	46	6877	
Median age (range)	68.0 (35–84)	74.5 (50–83)	66.0 (23–79)	69.0 (23–84)	65.0 (20–99)	0.049
Sex, n (%)						
Male	3 (14.2)	1 (12.5)	3 (17.6)	7 (15.2)	1532 (22.2)	0.29
Female	18 (85.7)	7 (87.5)	14 (82.3)	39 (84.7)	5345 (77.7)	
Diabetes, n (%)						
Yes	2 (9.5)	1 (12.5)	4 (23.5)	7 (15.2)	1142 (16.6)	1.0
No	19 (90.4)	7 (87.5)	13 (76.4)	39 (84.7)	5735 (83.3)	
Steroid use, n (%)						
Yes	15 (71.4)	6 (75.0)	14 (82.3)	35 (76.0)	4407 (64.0)	0.12
No	6 (28.5)	2 (25.0)	3 (17.6)	11 (23.9)	2470 (35.9)	
Chemotherapy use, n (%)						
Yes	3 (14.2)	0	2 (11.7)	5 (10.8)	802 (11.6)	1.0
No	18 (85.7)	8 (100)	15 (88.2)	41 (89.1)	6075 (88.3)	
Route of administration, n (%)						
Oral BPs	19 (90.4)	7 (87.5)	15 (88.2)	41 (89.1)	4088 (59.4)	<0.001
Other osteoporosis drugs	2 (9.5)	1 (12.5)	2 (11.7)	5 (10.8)	2789 (40.5)	
Oral BP administration[a]						
Etidronate, n (%)	4 (19.0)	0	3 (17.6)	7 (15.2)	541 (7.8)	N.A.
Alendronate, n (%)	15 (71.4)	3 (37.5)	9 (52.9)	27 (58.7)	2844 (41.3)	
Risedronate, n (%)	7 (33.3)	4 (50.0)	9 (52.9)	20 (43.4)	1584 (23.0)	
Minodronate, n (%)	1 (4.7)	1 (12.5)	0	2 (4.3)	36 (0.52)	
Duration of BP administration (days)[b]						
Median days (IQR)	1267 (182–2009)	380 (84–1342)	588 (273–1630)	707 (210–1630)	358.5 (89.5–966)	0.001

BPs = bisphosphonates; N.A. = not applicable; IQR = interquartile range.
Wilcoxon rank-sum test or Fisher exact test were performed to compare the differences between overall cases and non-cases.
[a] In some cases, several oral BPs were prescribed for one patient.
[b] Duration was calculated for 4129 patients treated with oral BPs.

Discussion

We conducted a retrospective cohort study with comprehensive data extraction using an EMR retrieval system and manual confirmation of ONJ according to standardized procedures. We evaluated not just the absolute risk, but also the attributable risk of OMJ induced by the administration of oral BPs. In addition, we estimated the relative risks (ORs) for OMJ, which ranged from 5.0 (95% CIs: 1.9–12.9) to 6.0 (95% CIs: 1.3–26.1) after adjustment for confounding factors. This study provides a significant and comprehensive estimation of the specific risks of OMJ in osteoporosis patients taking oral BPs compared with other osteoporosis medications.

Few reports have examined the relative risk of oral BPs for OMJ, and the risk remains unclear. The Dental Practice-based Research Network (DPBRN) reported an unadjusted OR for ONJ of 15.5 (95% CIs: 6.0–38.7) in two health-care organizations [14], and a Danish group reported an adjusted hazard ratio of alendronate for inflammatory jaw disease of 3.1 (95% CIs: 1.4–6.8) and for etidronate of 2.2 (95% CIs: 1.1–4.3) in Danish population [15]. Our results are consistent with these findings and indicate an increased risk of OMJ in osteoporosis patients treated with oral BPs even after adjustment for confounding factors.

The estimated absolute risk of oral BPs for OMJ in this study was slightly higher than those of previous reports. Among findings to date, surveillance data from Australia estimated a prevalence of ONJ ranging from 0.01% to 0.04% or 0.09% to 0.34% after tooth extraction [9]; a Korean group reported a prevalence ranging from 0.05% to 0.07% among patients treated with oral BPs in a university hospital [11]; and the DPBRN in the US reported the occurrence of ONJ in 6 of 21,163 cohort members who had at least one oral BP dispensed, giving an estimated incidence of approximately 0.028% [14]. On the other hand, another US group reported a prevalence of ONJ of approximately 4% in patients treated with alendronate in a university hospital [13]. Characteristics of our study design include a hospital-based setting; inclusion of patients treated with other osteoporosis medications; classification of OMJ and ONJ cases together; and diagnosis of OMJ according to four hierarchical

Table 3
Adjusted odds ratios for osteomyelitis of the jaw by case definition.

	Osteomyelitis of the jaw		Odds ratio		
	Cases, n (%)	Non-cases, n (%)	Crude	Age- and sex-adjusted	Multivariable-adjusted
Possible cases ≥					
Oral BPs (+)	41 (89.1)	4088 (59.4)	5.5 (2.2–14.1)	5.5 (2.1–14.1)	5.0 (1.9–12.9)
Oral BPs (−)	5 (10.8)	2789 (40.5)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Probable cases ≥					
Oral BPs (+)	26 (89.6)	4103 (59.5)	5.8 (1.7–19.4)	5.9 (1.7–19.5)	5.4 (1.6–18.3)
Oral BPs (−)	3 (10.3)	2791 (40.4)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Confirmed cases only					
Oral BPs (+)	19 (90.4)	4110 (59.5)	6.4 (1.5–27.7)	6.4 (1.4–27.7)	6.0 (1.3–26.1)
Oral BPs (−)	2 (9.5)	2792 (40.4)	1.0 (ref)	1.0 (ref)	1.0 (ref)

BPs = bisphosphonates; ref = reference.
Odds ratios (95% confidence interval) are shown.
These multivariate odds ratios for osteomyelitis of the jaw were adjusted for age, sex, diabetes, and steroid and chemotherapy use.

diagnostic criteria. Estimated incidence among the studies may vary by setting, design, or population. Additionally, incidence might also be influenced by dental hygiene [37], albeit that our present and previous studies have not examined dental hygiene at the population level. Clinical decision making for osteoporosis patients should be done in consideration of the risk and benefit of oral BPs in the target population.

BPs can be classified into two groups, with different molecular modes of action, namely NBPs and non-nitrogen-containing BPs (NNBPs) [1]. In this study, we confirmed that all patients who developed OMJ received one or more kinds of NBPs. Several clinical studies have also shown that NBP use is associated with an increased risk of ONJ [6,8,11,16]. Further, NBPs were shown to exert a strong negative effect on human oral keratinocytes at different cellular levels in vitro compared to NNBPs [38]. These results indicate that patients taking NBPs have a higher risk of OMJ than those receiving NNBPs even among oral bisphosphonate users. However, although a few studies have shown the occurrence of ONJ or increased incidence of inflammation of the jaw in users of oral NNBPs (i.e. clodronate or etidronate) [9,15], the risk of oral NNBPs for OMJ remains unclear. Further investigation in a different population is required to examine the hypothesis that patients taking oral NNBPs have a lower risk of OMJ than those receiving oral NBPs.

An additional characteristic of this study was our proposal of four interim hierarchical diagnostic criteria for OMJ. In general, OMJ is diagnosed by the presence of a compatible clinical picture; consistent imaging findings on plain radiographs and/or computed tomography scans and/or increased uptake on technetium bone scan; and a histological picture consistent with OMJ and/or the isolation of microorganisms in samples obtained by extraoral open surgery, percutaneous biopsy of bone, removed bone or intramedullary tissue, or pus aspiration from adjacent tissues [39]. Diagnosis is often difficult, however, particularly in the early stage [26], and these criteria are not always consistently applied to different stages of OMJ. Osteomyelitis is caused by a certain inciting focus that enables the infection to propagate and has various clinical expressions, and the clinical and laboratory features of infections are not always present [26,40]. This background explains why diagnostic imaging has long played a major role in the investigation of suspected osteomyelitis [41]. To date, however, the accuracy of radiographic imaging for OMJ has not been clarified. Accordingly, we set priority on these radiographic findings for OMJ with reference to previous reviews of osteomyelitis in the other regions [40,41]. A review of osteomyelitis reports as follows: plain radiographs should always be the first step in the imaging assessment of osteomyelitis, but sensitivity or specificity is low; scintigraphic procedures are an essential part of the diagnostic procedure; and CT scans are a useful adjunct to conventional radiography when findings are normal in cases clinically suspected to have skeletal infection [40]. In addition, there is an agreement that the objective standard for diagnosing osteomyelitis is bone biopsy and culture [41]. On the other hand, a review of OMJ reports that routine radionuclide bone scans have low specificity and other problems that may be mitigated by the addition of CT scans, because increased uptake on blood flow phase images may be seen with soft tissue infection or at surgical sites in the jaw, etc. [26]. These reviews indicated that CT scans were of greater value in diagnosing OMJ than technetium bone scans or plain radiographs, but that the highest priority was given to a histological picture consistent with OMJ and/or the isolation of a microorganism in samples obtained at surgical treatment.

Data extraction from EMR in this study was conducted using an EMR retrieval system [24]. In two previous large cohort studies of the risk of oral BPs, data were extracted from a health maintenance organization database and an administrative claims database [14,15]. However, these databases have not been designed for medical research, and EMR data are richer than information in claims databases [42]. In addition, outcome was diagnosed using codes for osteomyelitis [15], but automated data extraction without human intervention has not reached a suitable level of accuracy [43]. In this study, two oral and maxillofacial surgeons diagnosed cases by chart review with observation of imaging findings. Furthermore, to guard against false-negative cases, they examined a total of 1986 patients (28.1%) among the included patients. This comprehensive data extraction process and manual confirmation of OMJ likely improve the reliability of our results.

Several limitations of this study warrant mention. First, selection bias is inherent to single-center studies, and the present study was additionally subject to inherent referral bias toward the selection of more severe cases, given that our department is a lead institution for oral and maxillofacial surgery in Kyoto City. A positive aspect of this limitation, however, is that almost all patients likely consult our department in the clinical problem of oral and maxillofacial regions. Additionally, OMJ is an uncommonly encountered clinical condition, and such patients are likely to be referred to our clinic to establish a diagnosis. The impact of selection bias is thus somewhat unclear. Second, although our estimation models were adjusted for confounding factors, including diabetes, and steroid and chemotherapy use [28,44], no adjustment was made for other possible confounding factors related to OMJ, such as smoking, immune disorders, or oral BP dose, etc. [14,27]. However, several studies reported that there was no association between dose of oral BP or other risk factors and inflammation of the jaw [15,45], and risk factors of BP-induced OMJ are controversial. Further investigation is required to clarify other risk factors for oral BP-induced OMJ. Third, we might have overestimated the risk of oral BPs. In the chart review, we confirmed 6 patients treated with oral BPs in other hospitals; however, other patients who were treated without oral BPs in our hospital may have received oral BPs in other hospitals. We therefore performed sensitivity analyses with exclusion of these patients, but the significant results did not change (data not shown). Fourth, due to the limited number of events, the 95% CIs of estimated ORs were wide. This prevents the drawing of reliable conclusions from the results, and indicates the need to assess relative risks in a larger number of patients with OMJ.

Conclusions

In terms of absolute and attributable risks, the risk of oral BPs for OMJ is considered to be less than 1% in osteoporosis patients. However, oral BPs may increase the risk of OMJ compared with patients treated with other osteoporosis medications, and the extent of side effects should be kept in mind. This study provides important information for patients, physicians and dentists involved in the treatment of osteoporosis using oral BPs.

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TY participated in the design of the study, performed the statistical analysis and drafted the manuscript. MY participated in the design of the study, checked the statistical analysis and helped to draft the manuscript. KY participated in the design of the study, and programmed and extracted data from the hospital database using the EMR retrieval system. KS and KA participated in the design of the study and performed the chart review. ES participated in the design of the study and helped to draft the manuscript. KG and KT participated in the design of the study. TN participated in the design and checked the statistical analysis. KB participated in the design of the study and was the principal investigator of the study. All authors have read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.bone.2012.08.115.

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