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ORIGINAL ARTICLE

A retrospective study of osteomyelitis and osteonecrosis of the jaws and its etiologic implication of bisphosphonate in Asians

Sung Ok Hong[1] · Chae-Yoon Lee[2] · Junho Jung[3] · Deog-Yoon Kim[4] · Christian Walter[3] · Yong-Dae Kwon[5]

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Abstract
Objective The objective of this study were to find the annual case trend of inflammatory jawbone diseases and to investigate the impact of medication-related osteonecrosis of the jaws (MRONJ).
Material and methods A retrospective study of 372 patients diagnosed with inflammatory jawbone condition except for alveolar osteitis from 2007 to 2015 was initiated. History taking and investigation of etiologic factors MRONJ, osteoradionecrosis (ORN), odontogenic infection, foreign body, and trauma were investigated. A separate analysis showed the number of MRONJ cases in two age groups (under 70 years; 70 years and over) and serum C-terminal peptide (s-CTX) values that were found.
Results The results showed that the number of MRONJ cases was significantly larger in the older age group ($p < 0.05$). Regarding gender and sites of lesions, MRONJ was significantly frequent in the female and the mandible ($p < 0.05$). The R^2 values for the regression analysis for MRONJ ($R^2 = 0.9234$) and odontogenic etiology ($R^2 = 0.0427$) signified linear increase in the number of MRONJ cases, whereas bone lesions due to traditional odontogenic etiology stayed stationary.
Conclusion The number of MRONJ has escalated, and most of the patients are elderly people. The current trend of inflammatory conditions of the jaw may have changed since the advent of MRONJ.
Clinical relevance Long-term bisphosphonate therapy became a major risk factor for the osteomyelitis and osteonecrosis of the jaws. Thorough medical history, taking would be essential and communication with prescribing physicians should be emphasized during the dental treatment planning.

Keywords MRONJ · Osteoporosis · Inflammatory jawbone disease · Bisphosphonates

✉ Yong-Dae Kwon
yongdae.kwon@gmail.com

[1] Department of Dentistry (Oral & Maxillofacial Surgery), International St. Mary's Hospital, Catholic Kwandong University, Incheon, South Korea

[2] Department of Oral & Maxillofacial Surgery, Graduate School, Kyung Hee University, Kyungheedaero 26, Seoul 02447, South Korea

[3] Department of Oral & Maxillofacial Surgery, Universitätsmedizin Mainz, Augustusplatz 2, Mainz 55131, Germany

[4] Department of Nuclear Medicine, School of Medicine, Kyung Hee University, Kyungheedaero 26, Seoul 02447, South Korea

[5] Department of Oral & Maxillofacial Surgery, Center for Refractory Jawbone Diseases, School of Dentistry, Kyung Hee University, Kyungheedaero 26, Seoul 02447, South Korea

Introduction

Osteomyelitis of the jaws is a common disease in oral and maxillofacial surgery departments all over the world so that the literature about this topic is vast with unfortunately lots of different definitions as well. It is an inflammatory process of the periosteum, cortex, cancellous bone, and endosteum that can result in osteonecrosis [1] that can occur as acute or as a primary or secondary chronic osteomyelitis [1]. There is a multitude of reasons for osteomyelitis such as medications, radiation, odontogenic sources, and traumas, and in some cases, the cause remains unknown [2].

The medication-related osteonecrosis of the jaws (MRONJ) became a focus after the first description of the bisphosphonate-related osteonecrosis of the jaws by Marx in 2003, but several other active agents can cause osteonecrosis

such as sunitinib, bevazicumab, or denosumab. Sunitinib is an oral, small-molecule, multitargeted receptor tyrosine kinase (RTK) inhibitor that was approved by the Food and Drug Administration (FDA) for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST) [3]. Bevacizumab is a humanized monoclonal IgG1 antibody, which works as an angiogenesis inhibitor of all endothelial growth factors, and is prescribed for the treatment of advanced cancer including metastatic colon and non-small cell lung cancers [4]. Denosumab is a receptor activator of nuclear factor kappa-B ligand inhibitor (RANKL inhibitor) that is used in similar indications as bisphosphonates such as malignant diseases to the bone and especially osteoporosis. These antiangiogenic drugs cause MRONJ with individual administration or in combination with bisphosphonates (BPs) possibly because of oral mucosa breakdown, impaired angiogenesis, and bone remodeling [5–10].

Due to the aging society in developed countries, osteoporosis is one of the main reasons for the prescription of bisphosphonates and denosumab. In the USA, more than 50 % of all people older than 80 have either an established osteoporosis or an osteoporosis. At the age of 65 years, 20 % are affected [11]. In Germany, more than 200×10^6 defined daily dosages are prescribed per year and alendronate, which has its indication for osteoporotic patients, has a share of nearly 70 % so that osteoporosis is the main cause for bisphosphonate use [11]. Other FDA-approved treatment options are estrogen hormone therapy (ET/HT), estrogen agonist/antagonists such as raloxifene, tissue-selective estrogen complexes such as bazedoxifene, and parathyroid hormones [12].

The fifth Korean National Health and Nutrition Examination Survey data from 2010 stated that 67.7 % of Korean women aged 65 years and older and 33.5 % of Korean men aged 75 years and older are at high risk of osteoporotic fractures [13] so that at least 50 % of these patients will eventually take bisphosphonates [14]. In 2008, the number of the patients on bisphosphonate therapy in Korea was reported to be around 600,000, and the incidence of MRONJ in 2010 was estimated to be at least 0.04 % [15]. Of these patients, 78.7 % had a MRONJ due to the oral intake of bisphosphonates [15], being the highest percentage in the world. For example, the percentage in Australia is between 0.09 and 0.34 % [16], in the USA about 4 % [17], and in Germany less than 20 % [2].

In a German study, the percentage of MRONJ among all osteomyelitis and osteonecrosis patients was 10 % for the years 2000 to 2005 but 45 % in the following years from 2005 to 2014 [2]. With rising amounts of prescriptions for bisphosphonates, the prevalence of MRONJ has also increased not only in Western countries but also in Asian countries [18].

On the other side, in most patients, an intraoral triggering factor has been described so that preventive measures have been implemented in many countries, suggesting a dental visit before the first bisphosphonate administration, thus the frequency of new MRONJ has been reduced in many participating departments [19, 20].

The purpose of this study was to analyze the frequency and etiologic background of inflammatory jawbone disease with emphasis on MRONJ in a tertiary hospital in Korea.

Materials and methods

A retrospective study was conducted analyzing all patients with osteomyelitis being treated in the Department of Oral and Maxillofacial Surgery at Kyung Hee University Medical Center, Korea from January 2007 to March 2015. The digital patient data files were searched with the following search terms: osteonecrosis, osteomyelitis, osteoradionecrosis, inflammatory conditions of the jaw. Inclusion criteria were osteomyelitis and osteonecrosis. Exclusion criteria were the existence of simple postextraction alveolar osteitis and MRONJ without visible necrotic bone clinically and on panoramic radiographs (at risk, stage 0 MRONJ [21]).

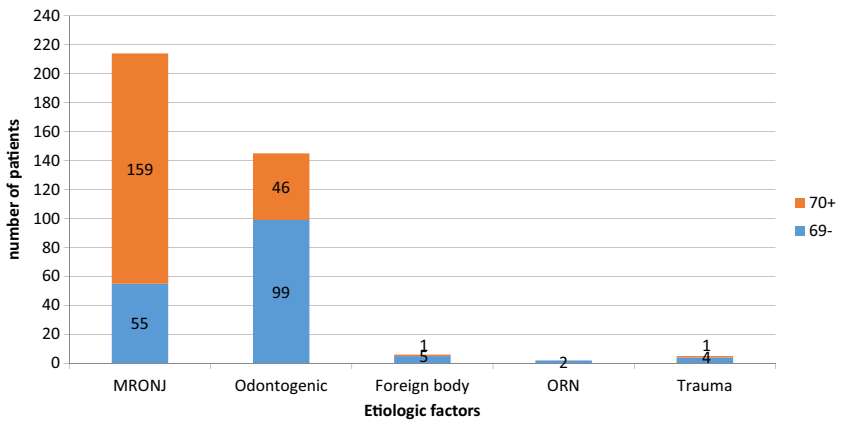

Fig. 1 Investigation of etiologic factors related to inflammatory jawbone diseases over the past 8 years. MRONJ was the most common (57.5 %) and ONJ the second (38.9 %), followed by trauma (1.3 %), foreign body (1.6 %), and ORN (0.53 %)

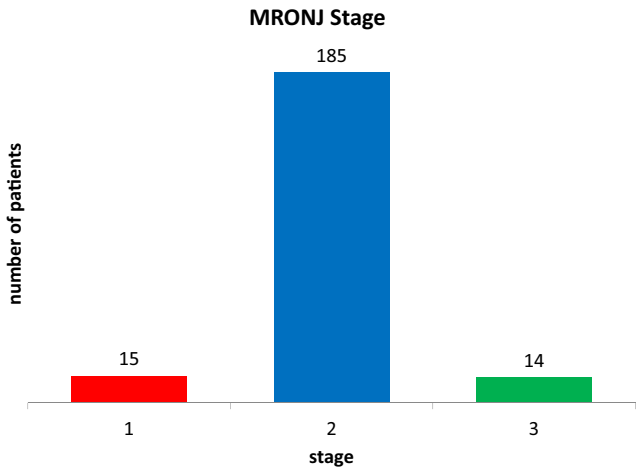

Fig. 2 MRONJ stage distribution: stage 2 (86.4 %) is dominant with 185 people

Regarding the etiology, the patients were separated in one of the following groups: medication-related osteonecrosis (MRONJ); osteoradionecrosis (ORN); odontogenic osteomyelitis, due to foreign bodies; and trauma. [2]. Etiology besides MRONJ were grouped as non-MRONJ and compared. The definition of the American Association of Oral and Maxillofacial Surgeons (AAOMS) was used to define MRONJ, and only stages 1, 2, and 3 were included [21].

Further collected data next to the etiology were demographic data (age, gender), site of the inflammatory bone disease (maxilla, mandible, both jaws), triggering factors, type of bisphosphonates prescribed in MRONJ, mode of bisphosphonate application in MRONJ, medication duration for MRONJ, and serum C-terminal peptide (s-CTX) values that were taken as fasting morning values.

To analyze the distribution of the etiologic factors depending on the age of the patients, those patients were separated into two groups, <70 years and ≥70 years. And the patients with MRONJ were separated into those patients on a long-term medication (≥4 years) and those with a shorter medication intake period (<4 years). The annual number of MRONJ cases was also compared with those of non-MRONJ cases. The year 2015 was excluded due to the limitation in the period of investigation.

The study was approved by the Institutional Review Board (KHD IRB 1411-2).

For statistical analysis, SPSS 17.0 (Chicago, USA) was used. Chi-squared tests were used to analyze associations between age and MRONJ and non-MRONJ cases, and a paired *t* test and a Pearson's chi-square test were used to detect significant relations between the site, stage, and s-CTX values.

Results

Three hundred seventy-two patients (288 female, 84 male) with an average age of 67.58 ± 14.45 years, ranging from 12 to 93, were included. Seventy-eight patients had lesions in the maxilla, 285 in the mandible, and 9 patients in both jaws.

57.5 % of the patients had a MRONJ and 38.98 % odontogenic. The other etiologic factors were rare with $n \leq 13$ (Fig. 1).

MRONJ patients Out of 214 MRONJ patients (202 female, 12 male) with an average age of 74.36 ± 6.89 years ranging from 52 to 93, only 4 received the bisphosphonates due to a malignancy and 210 patients due to osteoporosis. One hundred fifty-nine patients were 70 years and older, and 55 patients were under 70 years old. One hundred fifty-nine patients had the lesion in the mandible (150 patients with one and 9 patients with two or more lesions), 50 patients had the lesion in the maxilla (48 patients with one and 2 patients with two or more lesions), and 5 patients had lesions in both jaws. Only 15 patients had a stage 1, 185 patients a stage 2, and 14 patients a

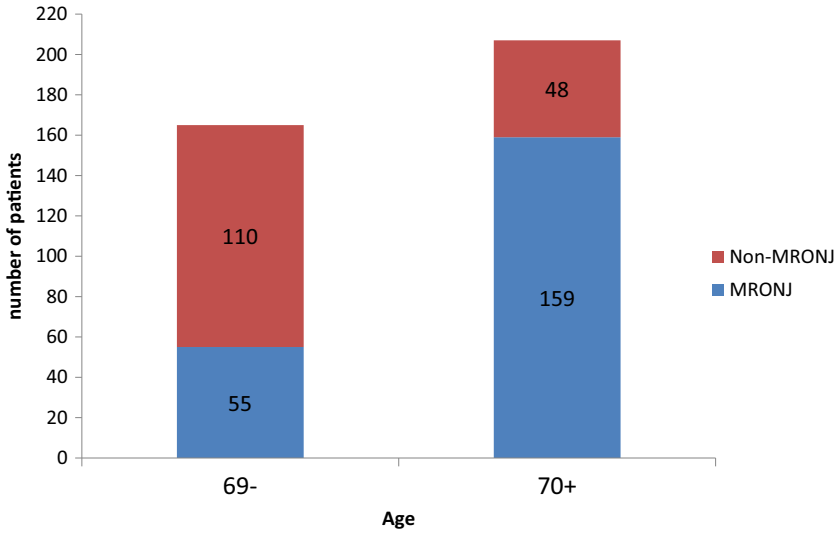

Fig. 3 Number of cases of inflammatory jawbone diseases related to the age group. Non-MRONJ was more common in the under 70-year-old patients, and MRONJ was significantly more common in patients 70 years old and over ($p < 0.05$, paired *t* test)

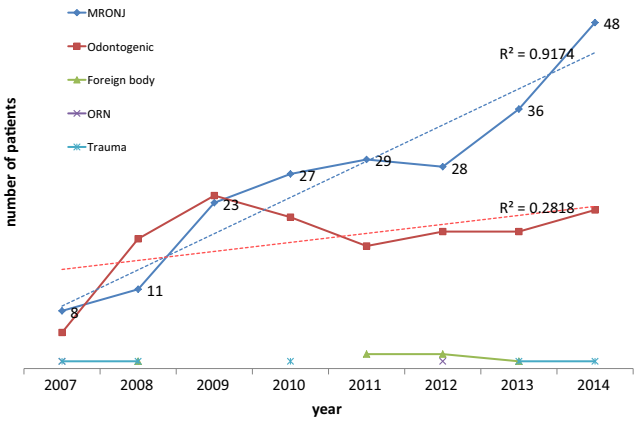

Fig. 4 The R^2 values for the linear regression analysis from 2007 to 2014 depicting five etiologic factors: MRONJ (R^2 = 0.9174), odontogenic (R^2 = 0.2818), trauma, ORN, and foreign body. The number of MRONJ cases has been linearly increasing showing statistical reliability ($R^2 > 0.7$)

stage 3 MRONJ (Fig. 2). 92.1 % (197 patients) was taking oral bisphosphonates, 5.1 % (11 patients) was receiving IV injections, and 2.8 % (6 patients) had of combination of oral and IV bisphosphonates as the mode of application. The exact type of bisphosphonates was ambiguous in 27 patients. Out of the 187 patients, 118 patients (63.1 %) were taking solely alendronate; 30 patients (16 %) were taking solely risedronate; 26 patients (13.9 %) were taking solely ibandronate; 3 patients (1.6 %) were taking solely zolendronate; 1 patient (0.5 %) was taking solely pamidronate; 6 patients (3.2 %) were taking a combination of risedronate and alendronate; 1 patient (0.5 %) was taking a combination of alendronate and ibandronate; 1 patient (0.5 %) was taking a combination of ibandronate and zolendronate; and 1 patient (0.5 %) was taking a cocktail of ibandronate, risedronate, and alendronate. In 51 out of the 214 patients, the exact starting point of bisphosphonate treatment is unknown, so the average duration for bisphosphonate treatment was 4.42 ± 3.14 years (range 0.5–15 years) for 163 patients. Eighty-four patients had been administering bisphosphonates for under 4 years and 79 patients for 4 years and more. Triggering factors were extraction in 127 patients, implant origin in 26 patients, endodontic or periodontal origin in 18 patients, denture and other origin in 18 patients, and unknown in 25 patients. The s-CTX values were available for 187 patients. The average s-CTX value was 0.17 ± 0.15 and ranged from 0.01 to 1.44. The average s-CTX value for patients younger than 70 years old (n = 45) was 0.133 and 0.182 for 70 years and older (n = 142).

Non-MRONJ patients Out of the 158 patients (86 female, 72 male) with an average age of 58.42 ± 16.78 years ranging from 12 to 89 years, osteomyelitis was due to ORN in 2 patients (2 male), trauma in 5 patients (1 female, 4 male), foreign body in 6 patients (5 female, 1 male), and odontogenic in 145 patients (80 female, 65 male). One hundred twenty-six patients had the lesion in the mandible (118 patients with one and 8 patients with two or more lesions), 28 patients had the lesion in the maxilla (27 patients with one and 1 patient with two or more lesions), and 4 patients had lesions in both jaws.

Differences between MRONJ and non-MRONJ groups

Gender, age, site prevalence

There was a significant prevalence of female patients in the MRONJ group compared to the non-MRONJ group (94.4 vs. 54.4 %). Prevalence of patients 70 years old and older was also observed in the MRONJ group (74.3 %), while 69 years and younger patients were more often linked to non-MRONJ lesions (69.6 %). More lesions were observed in the mandible in both groups (Fig. 3). The MRONJ group had 76.6 % and the non-MRONJ group had 83.3 % lesions found in the mandible solely or in combination with the maxilla.

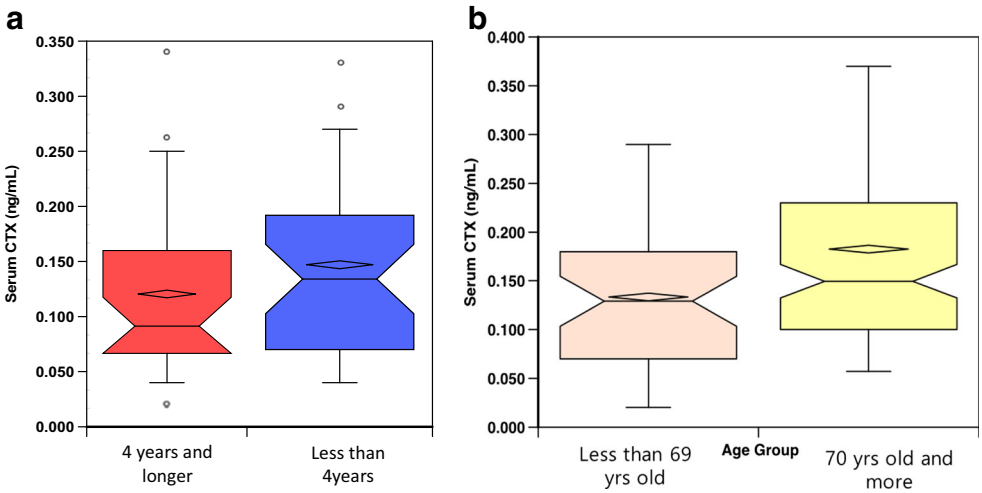

Fig. 5 Comparison of s-CTX values according to the **a.** intake duration (less than 4 vs. 4 years and more). No significant difference was found between the two groups (p = 0.092, t test, whiskers show tenth and 90th percentile with outliers). **b.** Age groups (70 years and older vs. younger than 70 years). Significant differences were found between the two groups ($p < 0.05$, Student's t test, *whiskers* represent fifth and 95th percentile)

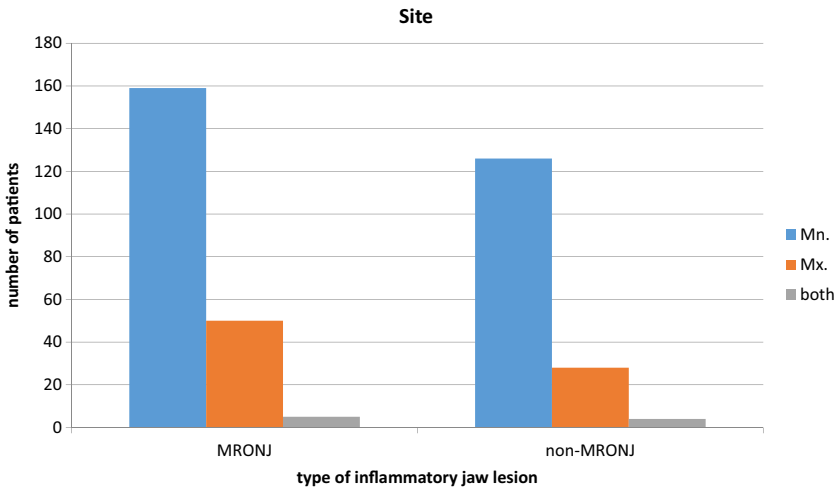

Fig. 6 Distribution of inflammatory jaw lesions. MRONJ: mandible (74.3 %), maxilla (23.4 %), both (2.3 %), $p < 0.05$; Non-MRONJ: mandible (79.8 %), maxilla (17.7 %), both (2.5 %), $p < 0.05$

Annual number of cases

Linear regression graphs showed that up till 2008, odontogenic etiology was the main cause of inflammatory jawbone diseases. While MRONJ cases have been on a steady rise since 2009, odontogenic causes have slightly decreased. The R^2 values for the regression analysis from 2007 to 2014 were $R^2 = 0.9174$ for MRONJ and $R^2 = 0.2818$ for odontogenic etiology (Fig. 4). In conclusion, the annual number of MRONJ cases was constantly increasing whereas the number of non-MRONJ (odontogenic, foreign body, trauma-induced inflammatory bone diseases, ORN) was constant over the 8 years.

Statistical analysis

Further investigation of the MRONJ group was initiated. Comparing s-CTX values between the two age groups (70 years and older vs. younger than 70 years) and according to the duration of BP administration (4 years and more vs. less than 4 years), we were able to find significant difference in the age groups ($p < 0.05$) but not by BP intake duration ($p = 0.092$) (Fig. 5a, b). Further analysis revealed that MRONJ was more frequently seen in the older age group (70 years old and above), and this was statistically significant ($p < 0.05$). Regarding gender and sites, MRONJ was significantly seen in the female gender ($p < 0.05$) and the mandible ($p < 0.05$) (Fig. 6).

Investigation for the non-MRONJ group revealed the younger age group (under 70 years old) to be prevalent, and this was statistically significant ($p < 0.05$). Regarding gender and sites, non-MRONJ showed no statistical significance ($p > 0.05$) in the gender but was prevalent in the mandible ($p < 0.05$) (Fig. 6).

Discussion

In the present study, osteomyelitis is mainly caused by bisphosphonates and due to odontogenic factors, while other factors such as trauma was really rare. Among the patients with MRONJ, most patients received bisphosphonates due to osteoporosis since bisphosphonates lower the vertebral and non-vertebral fractures by 25–70 % [12].

It has been described for many countries such as Japan, the USA, and Germany that the population is aging, and the proportion of patients taking bisphosphonates is increasing and so is the absolute number of patients with MRONJ [11, 14, 18]. Out of 51,671 osteoporosis patients described in the Korean Health Insurance claims database, 50.4 % receive bisphosphonates [22]. In 2014, the percentage of individuals older than 65 years of age was 12.7 % and will be 14.3 % in 2018 [22]. Therefore it is likely that the number of patients with MRONJ will increase in the next years so that preventive strategies have to be implemented to counter this trend. This would include a referral of patients before the bisphosphonate administration or a therapy with other antiresorptive or antiangiogenic agents will start [19, 23] and special dental care during and after the bisphosphonate treatment in order to reduce the incidence [24].

There is lacking evidence for a benefit for a drug holiday if surgical procedures are planned in patients administering bisphosphonates. Preclinical data, however, show the additional negative impact on soft tissue cells [25] that are crucial for wound healing so that a drug holiday may be beneficial for the soft tissue wound healing. In a previous study of 201 postmenopausal female patients on bisphosphonates, it was described that one third of these patients had a low fracture risk and 40 % were eligible for a drug holiday or even cessation [26] so that the outcome regarding MRONJ development in elective oral surgery could be optimized. There is also a negative impact of especially nitrogen-containing BPs such as pamidronate and zoledronate on angiogenesis, which is also a very important aspect in wound healing and soft tissue regeneration and therefore also a possible reason for a perioperative drug holiday [27].

Another option as an adjunct treatment may be rhPTH (1-34) therapy. It is the first and only osteoporosis therapy

approved by the FDA that stimulates bone formation. Although the evidence supporting the utilization of teriparatide as an adjunctive modality may be lacking, still several studies show favorable results in managing MRONJ with this hormone as an adjunct treatment modality [28–30]. Further supportive options are hyperbaric oxygen; platelet rich plasma; LLT applications [31]; and the substitution of geranylgeraniol, the product of the mevalonate pathway that is no longer produced due to the inhibition of an upstream enzyme [32]. But yet, the evidence is very low for all these methods. S-CTX as a marker to predict the development of MRONJ has been discussed for several years [33, 34], but here as well, the evidence is very low. In the present study, there was no statistical significant difference between the CTX values between patients using bisphosphonates for more respectively less than 4 years.

Most of the patients in the present study were stage 2 MRONJ. In stage 1 MRONJ, patients are usually asymptomatic and recognition of the disease may be premature. Therefore, most patients probably had visited the clinic at stage 2 when pain exerts or the inflammatory status is apparent. The comparison between sites showed the mandible to be the most often affected site for MRONJ, corroborating previous reports [35]. A plausible hypothesis might be the decreased vascularity of the relatively compact bone in the mandible. The higher rate of lesions in the mandible has also been described for patients with ORN [36].

Most of the patients had oral bisphosphonates, whereas in most Western countries, multiple myeloma, prostate, and breast cancer play the most important role in MRONJ [37]. A possible explanation for this phenomenon might be that the dosage of bisphosphonates for osteoporosis patients is designed for those who are 70 kg, but the average Korean is usually smaller and therefore a higher concentration may interact more with the bone metabolism. Also, patients and doctors prefer to take and prescribe oral tablets over injections. Thus, an adaption of the daily dosage should be discussed for such patients in future studies.

Basically, a prospective cohort or a case-control study in large scale will be encouraged because this is a retrospective study depending on patients' medical and dental history.

Since 2007, the National Health Insurance Service in Korea has initiated annual bone density tests for females over 65 and males over 70 years. This may contribute to an early detection of patients with depressed bone density levels, but on the other hand, this may generate a potential increase in patients being at risk to develop MRONJ.

Overall, the number of MRONJ has escalated, and most of the patients are elderly people. The current trend of inflammatory conditions of the jaw may have changed since the advent of MRONJ. Therefore, further observation of such trends much be meticulously followed and prevention strategies should be implemented.

Compliance with ethical standards

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

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Ethical approval The study does not include any personal information of patients. This study protocol has been approved by Kyung Hee University Dental Hospital IRB (KHD IRB 1411-2).

Informed consent The patients were informed of the scientific use of their clinical data.

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