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ORIGINAL ARTICLE

Association between periodontal disease, tooth extraction, and medication-related osteonecrosis of the jaw in women receiving bisphosphonates: A national cohort-based study

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Abstract

Background: We investigated whether periodontal diseases contribute to the development of medication-related osteonecrosis of the jaw (MRONJ) in addition to tooth extraction, which is a major risk factor for MRONJ occurrence.

Methods: This retrospective, nationwide cohort study was performed using South Korea's National Health Insurance Service database on women aged > 50 years who took bisphosphonates for at least 1 year between 2010 and 2015. MRONJ, periodontal disease, and tooth extraction were defined using the claims data.

Results: Among the 27,168 patients analyzed, the incidence of confirmed MRONJ was significantly higher in the periodontal disease group (0.58%) than in the nonperiodontal disease group (0.31%). While extraction alone showed an increased risk of MRONJ development (hazard ratio [HR] = 1.61, 95% confidence interval [CI]: 0.74–3.52), periodontal disease without tooth extraction also indicated a similar risk (HR = 1.68, 95% CI: 0.86–3.28); when a history of both periodontal disease and tooth extraction was present, the HR significantly increased to 2.55 (95% CI: 1.41–4.64).

Conclusions: The risk of MRONJ increased significantly when tooth extraction was performed in patients diagnosed with periodontal disease; therefore, periodontal diseases should be proactively managed in patients taking bisphosphonates.

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KEYWORDS
bisphosphonate-related osteonecrosis of the jaw, osteonecrosis, periodontal diseases, tooth extraction

1 | INTRODUCTION

Bisphosphonates are a common drug group used to prevent and treat osteoporosis in postmenopausal women,[1] and although medication-related osteonecrosis of the jaw (MRONJ) due to bisphosphonate administration is rare, this severe side effect can affect a patient's quality of life.[2]

The pathophysiology of MRONJ has not been established yet; however, several dental and medical comorbidities—such as tooth extraction, periodontal diseases, and long-term steroid use—have been suggested.[3,4] Over half of the MRONJ cases develop after surgical extraction.[5] To date, the most common immediate facilitating risk factors are invasive oral procedures that directly affect the jawbone, followed by periodontal diseases.[6] Based on these findings, the American Association of Oral and Maxillofacial Surgeons(AAOMS) recommended that patients who begin treatment with an antiresorptive agent should undergo dental screening before initiating treatment, as well as maintain good oral hygiene—even during treatment—to reduce the risk of MRONJ.[5] Nevertheless, there is insufficient evidence to determine which dental diseases should be managed.

Periodontal diseases are defined as chronic inflammatory conditions of the attachment apparatus that supports the teeth, which has a direct catabolic effect on the jawbone.[7] MRONJ is caused by a high accumulation of bisphosphonates in the jawbone, which has a high turnover rate[7]; therefore, a reasonable question has been raised regarding whether periodontal disease—which affects the jawbone—could also affect the occurrence of MRONJ. Since periodontal disease is the most common (>60%) cause of tooth extraction in patients aged ≥45 years,[8–10] it may be an undervalued key factor for MRONJ occurrence.

Existing evidence regarding the association between periodontal disease and MRONJ is scarce. A low incidence of MRONJ did not allow adequate statistical analyses in previous studies,[11] and the cause of tooth extraction in patients with MRONJ has not yet been appropriately investigated.[6] Furthermore, the focus on establishing MRONJ treatment strategies has limited the evaluation of coexisting diseases.[12]

Tooth extraction is still considered a major risk factor for the occurrence of MRONJ. Thus, the present study aimed to evaluate the role of periodontal disease and tooth extraction in the development of MRONJ in patients receiving bisphosphonates; a nationally representative database of South Korea was used.

2 | MATERIALS AND METHODS

This study was approved by the institutional review board (IRB No. X-2004/606-905, Seoul National University Bundang Hospital). This database was provided anonymously by the National Health Insurance Service (NHIS) for research purposes and was analyzed securely through the NHIS servers. The data were open to the public and anonymous; therefore, informed consent was not required.

2.1 | Data source

We used the NHIS-Health Screening Cohort (NHIS-HEALS) database—created using the public health screening and claims database of the NHIS—which contains information regarding the diagnosis, medical examination results, and medical use during the follow-up period, based on insurance benefit claims.

As the exclusive insurance provider of South Korea, the NHIS manages the claims data of all citizens,[13] and conducts general health screening for adults every 1–2 years. Approximately 510,000 individuals (aged 40–79 years), who received general health screening in 2002 and 2003, were eligible for this study. The construction period was from January 1, 2002 to December 31, 2015, including 14 years of data. The basic composition of the general health screen consists of preparing a questionnaire for medical history, including lifestyle, physical examination, urine test, blood test, chest radiography, and oral examination; additional testing occurs depending on sex and age. The oral examination included a self-reported survey of dental visits, dental symptoms, oral hygiene care, and a dentist's evaluation of periodontal status, decay, missing teeth, and fillings.

Diagnosis of all individuals registered in the NHIS database follows the Korean standard classification of disease and cause of death-7 (KCD-7) code, a modified version of the International Classification of Diseases and Related Health Problems, 10th edition. Procedures were identified using the claims codes.

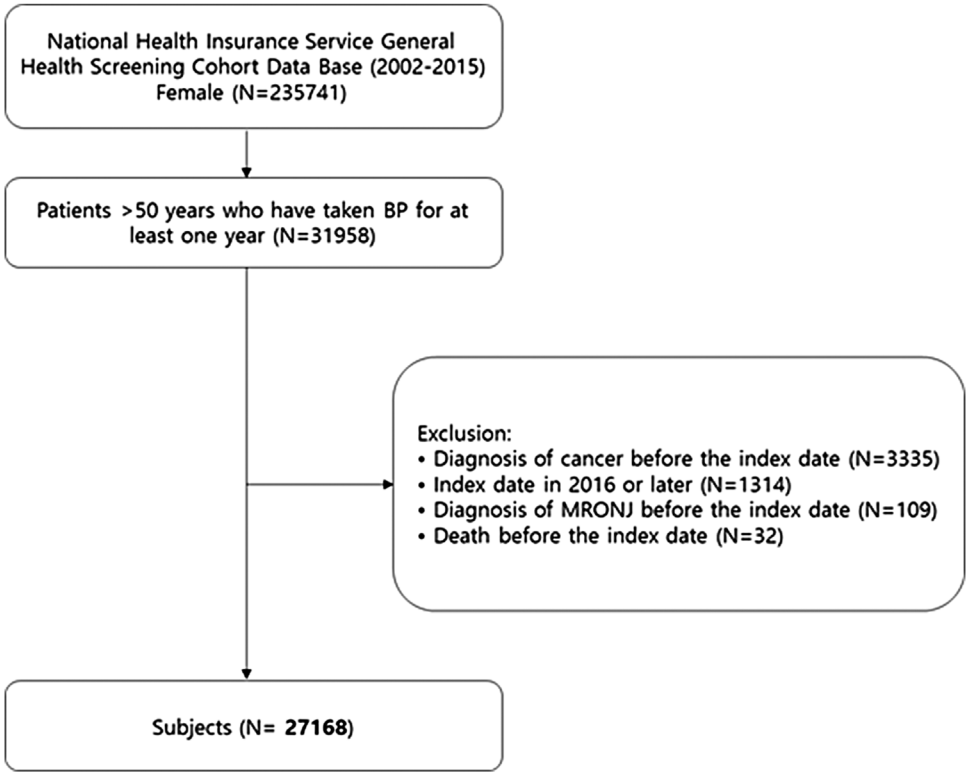


FIGURE 1 Flow diagram of study participant selection. BP, bisphosphonates; MRONJ, medication-related osteonecrosis of the jaw

2.2 | Study population

Women aged ≥50 years who used bisphosphonates for at least 1 year and showed a medication possession ratio (MPR) of ≥80% between 2010 and 2015 were included in the study. The index date was set as 365 days after the first prescription of bisphosphonates that satisfied the dosage standard. Both oral and injectable bisphosphonates were included in the analysis, which ultimately included those who used alendronate, ibandronate, risedronate, pamidronate, and zoledronate. The exclusion criteria were as follows: intake of bisphosphonates beyond the prescribed dose for osteoporosis treatment; diagnosis of cancer; development of MRONJ within 1 year of initiating bisphosphonates; and death before follow-up (Figure 1).

2.3 | Definition of MRONJ

For a more accurate diagnosis of MRONJ, we used both the KCD-7 code and procedure code. MRONJ was analyzed by classifying it as either confirmed MRONJ, with both diagnosis and treatment corresponding to MRONJ, or as possible MRONJ, with suspected cases (see Table S1 in online *Journal of Periodontology*).

Confirmed MRONJ was defined as when one specific KCD-7 code (M87.1: osteonecrosis due to drugs and multiple sites, and K10.2: inflammatory conditions of jaws) and procedure codes (U4533-4535, U4454-4457, U4464, U4465, U4467, U4520, U4610, U4621-4622, U4791-4792, and U4861-4862) were entered, or when both KCD-7 codes were entered after the index date. This criterion was based on the results of a previous study.[14]

2.4 | Definition of periodontal diseases and tooth extraction

Periodontal disease was defined as acute periodontitis (K05.2), chronic periodontitis (K05.3), periodontosis (K05.4), other periodontal diseases (K05.5), or unspecified periodontal disease (K05.6) if they were entered more than once within a year before the index date. This criterion was based on the results of a previous study.[15]

If the tooth extraction procedure code was entered at least once within a year before the index date, it was determined that the tooth was extracted (U4591, U4592, U4630, U4731, U4732, U4430, U4412, U4413, U4414, U4415, U4416, U4417, U4420, U4430, U4591, U4592, U4630, U4731, and U4732). Details of each code are included in Table S2 in online *Journal of Periodontology*.

2.5 | Other variables

Patient demographics from the baseline year, including data on patients' age, income level, comorbidities, dental status, household income, type of bisphosphonate, and distribution of cumulative bisphosphonate MPR, were included. The income level in the first quintile is the lowest, and the higher the quintile, the higher the income. Disability was categorized as either present or absent based on disability registration.

Hypertension, diabetes, hyperlipidemia, myocardial infarction, stroke, and anemia were defined by the presence of claims for hypertension (I10 and I15), diabetes (E10, E118, E119, E13, and E149), hyperlipidemia (E78), myocardial infarction (I21 and I22), stroke (I60-63), and anemia (D46, D50-53, D55-64, and D74).

2.6 | Statistical analyses

Baseline characteristics are reported using numbers for categorical variables and mean ± standard deviations. The χ^2 test and *t*-test or analysis of variance test were performed. Cox proportional hazard models were used to evaluate the associations between the independent variables and the occurrence of MRONJ events. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Multivariable regression models were constructed with adjustment for baseline year, age, income, disability, comorbidities, type of bisphosphonate, and cumulative proportion of days covered. Proportional hazard assumptions were confirmed using graphical methods. Statistical significance was defined as a two-tailed p-value < 0.05. Statistical analyses were conducted using R programming (version 3.3.3; The R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Baseline characteristics of patients

A total of 27,168 people were included in this study. Among the subjects, 3997 (14.7%) were diagnosed with periodontal disease. Tooth extraction was performed in 39.9% of the periodontal disease group subjects and 5.9% of the non-periodontal disease group subjects. The extraction rate of the periodontal disease group was significantly higher ($p < 0.001$). Confirmed MRONJ accounted for 0.3% and 0.6% of patients with periodontal disease and non-periodontal disease, respectively (Table 1).

3.2 | HRs for osteonecrosis of the jaw by having periodontal diseases or tooth extraction in the confirmed MRONJ group

Regarding the presence of periodontal diseases, the HR was 2.01 (95% CI: 1.25–3.22). When analyzing HR according to tooth extraction, the value obtained was 2.01 (95% CI: 1.23–3.29) (Figure 2 and Tables S3, S4 in online *Journal of Periodontology*). When we analyzed the risk of possible MRONJ, the results were similar with confirmed MRONJ (see Figure S1 and Tables S5 and S6 in online *Journal of Periodontology*).

3.3 | HRs for osteonecrosis of the jaw according to periodontal diseases, tooth extraction, or both in the confirmed MRONJ group

The HR of MRONJ was 1.61 (95% CI: 0.74–3.52) for patients who underwent tooth extraction but had no periodontal disease. The HR was 1.68 (95% CI: 0.86–3.28) for patients with periodontal disease who did not undergo tooth extraction. The HR increased to 2.55 (95% CI: 1.41–4.64) for patients with a history of both periodontal disease and tooth extraction (Figure 3 and Table S7 in online *Journal of Periodontology*). When we analyzed the risk of possible MRONJ, the results were similar with confirmed MRONJ (see Figure S2 and Table S8 in online *Journal of Periodontology*).

3.4 | Case of tooth extraction

When analyzing the diagnosis at the time of extraction in confirmed MRONJ patients, there were 16 cases (61.5%) associated with periodontal disease, three cases (11.5%) of tooth decay and diseases of pulpal origin, six cases (23.1%) with unknown reasons for extraction, and one case (3.8%) related to prosthetic problems. This revealed that in patients with confirmed MRONJ, the majority of tooth extractions were performed after the diagnosis of periodontal disease (see Table S9 in online *Journal of Periodontology*).

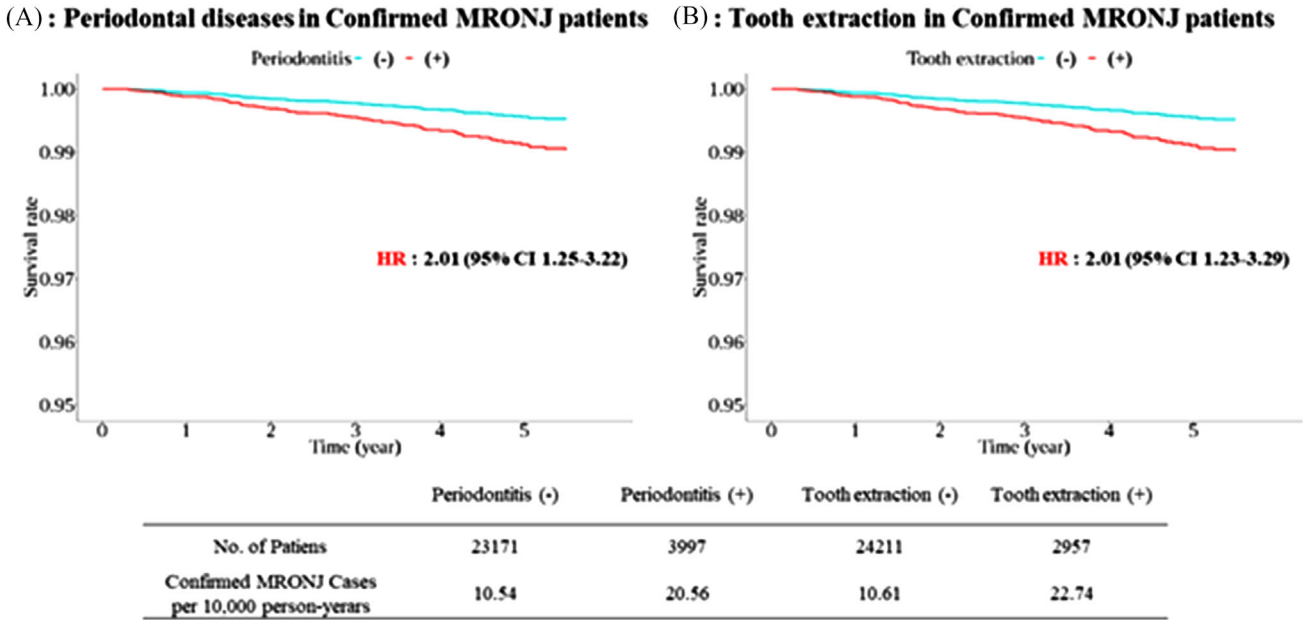
4 | DISCUSSION

In this study, we found that periodontal disease and tooth extraction were independent risk factors for MRONJ in women aged ≥50 years who used bisphosphonates. Considering both risk factors together, the risk of confirmed

TABLE 1 Characteristics of the patients

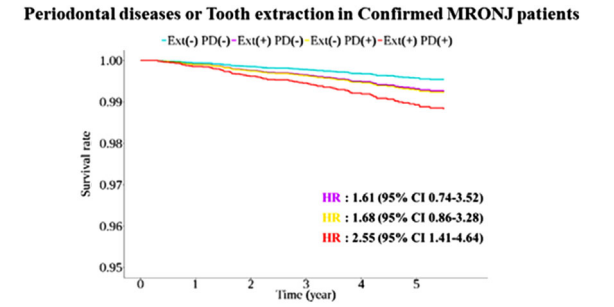
Characteristic	(*N* = 23,171) Periodontitis (−)	(*N* = 3997) Periodontitis (+)	*p*-Value
Baseline year			<0.001
2009	4514 (19.5%)	687 (17.2%)	
2010	2315 (10.0%)	342 (8.6%)	
2011	4216 (18.2%)	731 (18.3%)	
2012	4234 (18.3%)	720 (18.0%)	
2013	4306 (18.6%)	795 (19.9%)	
2014	3586 (15.5%)	722 (18.1%)	
Age at baseline			
Mean (SD) – year	67.77 (7.8)	66.53 (7.6)	<0.001
Comorbidities – no. (%)			
Hypertension	11,453 (49.4%)	1888 (47.2%)	0.011
Diabetes mellitus	5407 (23.3%)	994 (24.9%)	0.037
Dyslipidemia	11,373 (49.1%)	2117 (53.0%)	<0.001
Anemia	2878 (12.4%)	494 (12.4%)	0.934
Myocardial infarction	83 (0.4%)	16 (0.4%)	0.790
Stroke	1330 (5.7%)	211 (5.3%)	0.260
Dental status – no. (%)			
Tooth extraction	1362 (5.9%)	1595 (39.9%)	<0.001
Household income – no. (%)			0.032
Medicaid	1050 (4.5%)	172 (4.3%)	
First, second	3532 (15.2%)	564 (14.1%)	
Third, fourth	2728 (11.8%)	422 (10.6%)	
Fifth, sixth	3261 (14.1%)	558 (14.0%)	
Seventh, eighth	4701 (20.3%)	857 (21.4%)	
Ninth, tenth	7899 (34.4%)	1424 (35.6%)	
Disability – no. (%)			
Yes	614 (2.7%)	118 (3.0%)	0.300
Type of bisphosphonate – no. (%)			
Alendronate	11,171 (48.2%)	1907 (47.7%)	0.570
Risedronate	11,621 (50.2%)	1926 (48.2%)	0.023
Pamidronate	804 (3.5%)	120 (3.0%)	0.145
Ibandronate	5007 (21.6%)	968 (24.2%)	<0.001
Zoledronate	144 (0.6%)	14 (0.4%)	0.049
Bisphosphonate use history			
Cumulative bisphosphonate PDC – mean (SD)	93.23 (6.2)	93.48 (6.1)	0.023
Distribution of cumulative bisphosphonate MPR – no. (%)			0.004
>90%	16,536 (71.4%)	2941 (73.6%)	
80–90%	6635 (28.6%)	1056 (26.4%)	
Confirmed MRONJ	72 (0.3%)	23 (0.6%)	0.013
Possible MRONJ	168 (0.7%)	52 (1.3%)	<0.001

Abbreviations: PDC, proportion of days covered; MPR, medication possession ratio; MRONJ, medication-related osteonecrosis of the jaw.



	Periodontitis (-)	Periodontitis (+)	Tooth extraction (-)	Tooth extraction (+)
No. of Patiens	23171	3997	24211	2957
Confirmed MRONJ Cases per 10,000 person-yerars	10.54	20.56	10.61	22.74

FIGURE 2 Multivariable-adjusted survival curve for cox proportional hazards regression model. Hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for baseline year, age, comorbidities, income, disability, type of bisphosphonate, and cumulative proportion of days covered. (**A**) Comparison of subjects with or without periodontal diseases in patients with confirmed MRONJ. (**B**) Comparison of subjects with or without tooth extraction in patients with confirmed MRONJ. MRONJ, medication-related osteonecrosis of the jaw



	Ext(-) PD(-)	Ext(+) PD(-)	Ext(-) PD(+)	Ext(+) PD(+)
No. of Patiens	21809	1362	2402	1595
Confirmed MRONJ Cases per 10,000 person-yerars	10.12	17.15	15.44	27.58

FIGURE 3 Multivariable-adjusted survival curve for cox proportional hazards regression model. Hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for baseline year, age, comorbidities, income, disability, type of bisphosphonate, and cumulative proportion of days covered. Patients with periodontal disease alone, tooth extraction alone, and both periodontal disease and tooth extraction were compared with patients without both diseases in patients with confirmed MRONJ. The hazard ratio (HR) was 1.61 in the case of tooth extraction only, and 1.68 in the case of periodontal diseases only. HR increased to 2.55 when periodontal disease and tooth extraction were present at the same time. Ext, tooth extraction; PD, periodontal diseases. MRONJ, medication-related osteonecrosis of the jaw. HR, hazard ratio

MRONJ increased, but not significantly, when one of the two risk factors alone was present; however, the risk was greater for patients undergoing tooth extraction due to periodontal disease. It was found that in patients taking oral bisphosphonates, chronic inflammation of the periodontium, which leads to tooth extraction, plays a vital role in MRONJ development. This is the first study to analyze the effect of periodontal disease on the occurrence of MRONJ using extensive nationwide claims data.

Chronic inflammation associated with periodontal diseases and tooth extraction have been reported as risk factors for MRONJ. A Japanese cohort study showed that regarding tooth extraction in patients taking bisphosphonates, the risk ratio for MRONJ was 122.6, indicating that the risk of developing MRONJ was remarkably high. In this study, the incidence of MRONJ was significantly associated with the bone loss score, and the prevalence of severe periodontitis was significantly high in patients with MRONJ (MRONJ 20.0% vs. non-MRONJ 7.4%).[16] In a systematic review that analyzed patients diagnosed with MRONJ, tooth extraction corresponded to 45%, and periodontal diseases corresponded to 10% of the dental and medical risk factors for MRONJ development.[4] Based on these results, the authors mentioned that severe periodontitis could be a risk factor for MRONJ due to the high possibility that periodontal diseases already exist before tooth extraction.[16]

Periodontal diseases may act as a factor that initiates MRONJ development as an event preceding extraction. Chronic inflammation can act as a trigger or the damage to the bones caused by tooth extraction may contribute to the spread of inflammation caused by periodontal diseases to the deep areas of the jaw and mucosa. In a prospective study that analyzed 55 patients diagnosed with medication-related MRONJ, 39 patients underwent tooth extraction and 10 patients were diagnosed with marginal periodontitis. Evaluation of the panoramic radiographs taken before the procedure confirmed that 91% of the patients had severe marginal periodontitis.[17] This emphasis on the role of periodontal disease is consistent with our findings. Histological analysis of the extracted teeth from patients who took bisphosphonates also supports the importance of periodontal disease in the development of MRONJ. In all cases, chronic inflammation was the cause of tooth extraction, 78% of which were associated with periodontal disease. In the biopsy samples, osteonecrosis was found in 6% of patients, even without exposure of the necrotic bone.[18] They reported the possibility that bone necrosis existed before extraction and may have appeared in the form of inflammation.[19]

The results of animal experiments reporting that the treatment of periodontal disease has a significant effect on the alleviation of MRONJ are noteworthy. They showed that the medication-related MRONJ lesion improved on removing the pre-existing periodontal inflammatory condition before tooth extraction in mice who were administered bisphosphonates.[19,20] Based on this, they proved through preclinical studies that an already existing inflammatory environment creates sufficient risk for the onset of MRONJ and that resolving this inflammation interrupts the chain of events involved in the development of MRONJ.

The impact of periodontal diseases can be confirmed again through the results of other cohort studies using the NHIS database. They reported that tooth extraction and periodontal disease were local dental factors that significantly increased the incidence of MRONJ. Although none of the previous cohort studies have focused exclusively on periodontal disease, they have reported it as a risk factor for MRONJ, with results similar to ours.[21] recent study analyzed the effects of tooth extraction and dental implant placement, which are invasive dental procedures, on MRONJ in patients taking bisphosphonates using the same NHIS database. Compared with the high HR of extraction, the HR of implant surgery was significantly lower, indicating that it was not a risk factor for MRONJ development.[22] The difference is that an extraction is performed when there is a functional and structural problem, and implant surgery is conducted on healthy tissues. In other words, the environment that leads to tooth extraction can play a more significant role in the development of MRONJ than trauma inflicted on the jaw bones by invasive dental procedures.

Since this study used claims data, there is concern regarding the accuracy of diagnosis. In South Korea, dentists tend to habitually apply KCD-7 codes associated with periodontal diseases when the diagnosis is ambiguous. Therefore, using only a single KCD-7 code to ascertain the presence of periodontal diseases can lead to serious errors. For the sake of increasing the accuracy of diagnosis, only cases in which the periodontal disease-related KCD-7 codes were entered more than once were included. To ensure high reliability regarding the diagnosis of the patients with MRONJ, we combined the KCD-7 codes and procedure codes. In addition, we determined confirmed MRONJ and possible MRONJ inconsideration of the characteristics of the disease, which are not well established. For this reason, some patients with MRONJ could have been excluded from the statistical analysis, and the number of research subjects decreased. However, it can be said that the reliability of the data is greater on setting strict criteria for patients with MRONJ and periodontal diseases.

Risk factors for periodontal diseases are diverse, and some aspects are not easily controlled. If not treated appropriately, it can lead to tooth extraction. However, periodontal diseases are preventable, treatable, and manageable.[23,24] In other words, the incidence of tooth extraction can be reduced by preventing or treating periodontal diseases. Furthermore, even if there is an indication for tooth extraction, the risk of MRONJ can be reduced by resolving pre-existing inflammatory conditions. Based on this logic, MRONJ can also be considered preventable, which has significant clinical meaning in medicine and dentistry. This logic corresponds with the results of a randomized controlled trial in which Sim et al. found that improvement in dental hygiene decreased MRONJ incidence in cancer patients.[25] It is also consistent with the AAOMS position-paper and several studies that recommend the maintenance of optimal oral health before initiating treatment with anti-resorptive or anti-angiogenic agents.[5,26,27] Although this study could not analyze the effect of periodontal treatment on the occurrence of MRONJ, additional studies to investigate the causal relationship between periodontal treatment and MRONJ are required.

There were some limitations to our study. First, although we used extensive nationwide data, the number of patients with confirmed MRONJ was <100, as MRONJ is a rare disease with a low incidence rate. The second limitation is due to the nature of the NHIS-HEALS; as this study used claims data, we could not determine the number of untreated patients with MRONJ, nor the clinical course and severity

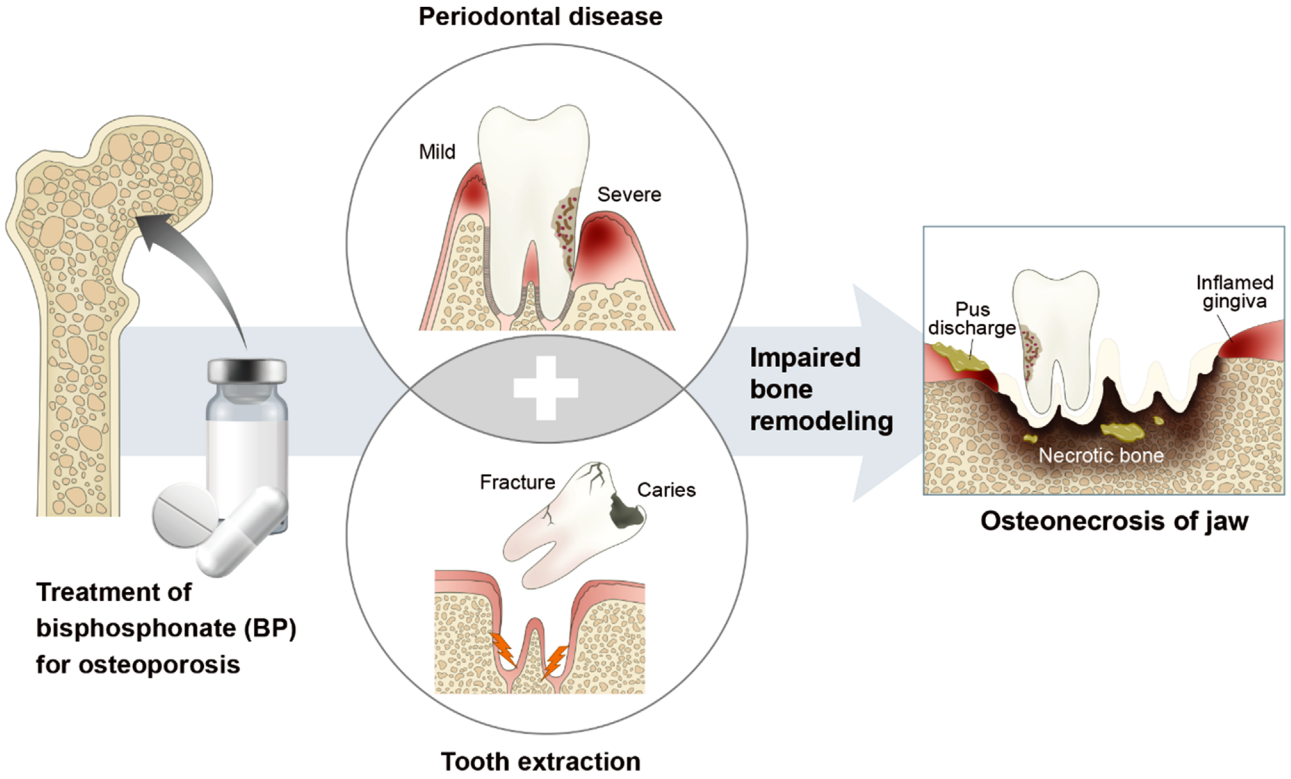


FIGURE 4 Proposed dental risk factors for medication-related osteonecrosis of the jaw (MRONJ). For patients receiving bisphosphonates for osteoporosis, periodontal disease and tooth extraction cause similar risk for the development of MRONJ. When both events are present at the same time, the likelihood of an MRONJ outbreak increases significantly

of the diseases. Further research on the dose-response relationship by analyzing the severity of periodontal disease or the extent/number of tooth extraction together will be beneficial. Due to the nature of dental disease—which is not life-threatening—patients who did not go to the dentist, even if they had dental problems, were excluded from the study. Third, diagnosis for periodontal disease may have inconsistency because different dentists have different diagnostic criteria for periodontal disease, and the diagnosis was not made through objective measures such as radiographs.[28,29] In addition, as a limitation of the retrospective cohort study, the consideration of socio-epidemiologic and behavioral features, such as smoking, was insufficient.

Nevertheless, this study has several advantages in that we used nationally representative data that has been monitored for a considerably long time. The reliability of the results was improved by applying strict criteria for the determination of MRONJ and periodontal diseases using claim data, and only patients with sufficient exposure to oral bisphosphonates were included.

In conclusion, the results of this study using a nationally representative database showed that periodontal disease and tooth extraction were independently associated with the onset of MRONJ. Furthermore, the risk of MRONJ tended to increase when tooth extraction was performed in patients diagnosed with periodontal disease (Figure 4). Periodontal disease, a low-grade inflammatory condition that necessitates tooth extraction, can be considered an underestimated risk factor for the onset of MRONJ. This finding highlights the need to manage periodontal disease in patients taking bisphosphonates.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare. All authors had access to all the study data, took responsibility for the accuracy of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication.

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REFERENCES

1. Black DM, Rosen CJ. Clinical practice. Postmenopausal osteoporosis. *N Engl J Med*. 2016;374:254-262.
2. Capocci M, Romeo U, Guerra F, et al. Medication-related osteonecrosis of the jaws (MRONJ) and quality of life evaluation: a pilot study. *Clin Ter*. 2017;168:e253-e257.
3. Chang J, Hakam AE, McCauley LK. Current understanding of the pathophysiology of osteonecrosis of the jaw. *Curr Osteoporos Rep*. 2018;16:584-595.
4. McGowan K, McGowan T, Ivanovski S. Risk factors for medication-related osteonecrosis of the jaws: A systematic review. *Oral Dis*. 2018;24:527-536.
5. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw –2014 update. *J Oral Maxillofac Surg*. 2014;72:1938-1956.
6. Huang YF, Chang CT, Muo CH, Tsai CH, Shen YF, Wu CZ, Impact of bisphosphonate-related osteonecrosis of the jaw on osteoporotic patients after dental extraction: a population-based cohort study. *PLoS ONE*. 2015;10:e0120756.
7. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. *Nat Rev Dis Primers*. 2017;3:17038.
8. Hull PS, Worthington HV, Clerehugh V, Tsirba R, Davies RM, Clarkson JE. The reasons for tooth extractions in adults and their validation. *J Dent*. 1997;25:233-237.
9. Quteish Taani DSM. Periodontal reasons for tooth extraction in an adult population in Jordan. *J Oral Rehabil*. 2003;30:110-112.
10. Noman NA, Aladimi AA, Alkadasi BA, et al. Social habits and other risk factors that cause tooth loss: an associative study conducted in Taiz governorate. *Yemen J Contemp Dent Pract*. 2019;20:428-433.
11. Antonuzzo L, Lunghi A, Petreni P, et al. Osteonecrosis of the Jaw and angiogenesis inhibitors: A Revival of a Rare but Serous Side Effect. *Curr Med Chem*. 2017;24:3068-3076.
12. Khan AA, Morrison A, Hanley DA, et al. International Task Force on Osteonecrosis of the Jaw. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res*. 2015;30:3-23.
13. Seong SC, Kim YY, Park SK, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. *BMJ Open*. 2017;7:e016640.
14. Kim HY, Kim JW, Kim SJ, Lee SH, Lee HS, Uncertainty of current algorithm for bisphosphonate-related osteonecrosis of the jaw in population-based studies: a systematic review. *J Bone Miner Res*. 2017;32:584-591.
15. Park SY, Kim SH, Kang SH, et al. Improved oral hygiene care attenuates the cardiovascular risk of oral health disease: a population-based study from Korea. *Eur Heart J*. 2019;40:1138-1145.
16. Yamazaki T, Yamori M, Ishizaki T, et al. Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: a cohort study. *Int J Oral Maxillofac Surg*. 2012;41:1397-1403.
17. Hallmer F, Andersson G, Götrick B, Warfvinge G, Anderud J, Bjornland T. Prevalence, initiating factor, and treatment outcome of medication-related osteonecrosis of the jaw-a 4-year prospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2018;126:477-485.
18. Topaloglu G, Koseoglu OT, Karaca C, Kosemehmetoglu K. The effect of chronic dental inflammation on development of Stage 0 medication-related osteonecrosis of the jaw. *J Craniomaxillofac Surg*. 2017;45:1158-1164.
19. Castillo EJ, Messer JG, Abraham AM, et al. Preventing or controlling periodontitis reduces the occurrence of osteonecrosis of the jaw (ONJ) in rice rats (Oryzomys palustris). *Bone*. 2021;145:115866.
20. Kim T, Kim S, Song M, et al. Removal of pre-existing periodontal inflammatory condition before tooth extraction ameliorates medication-related osteonecrosis of the jaw-like lesion in mice. *Am J Pathol*. 2018;188:2318-2327.
21. Kim SH, Lee YK, Kim TY, Ha YC, Jang S, Kim HY. Incidence of and risk for osteonecrosis of the jaw in Korean osteoporosis patients treated with bisphosphonates: A nationwide cohort-study. *Bone*. 2021;143:115650.
22. Ryu JI, Kim HY, Kwon YD. Is implant surgery a risk factor for osteonecrosis of the jaw in older adult patients with osteoporosis? A national cohort propensity score-matched study. *Clin Oral Implants Res*. 2021;32:437-447.
23. Tonetti MS, Eickholz P, Loos BG, et al. Principles in prevention of periodontal diseases: consensus report of group 1 of the 11th European Workshop on Periodontology on effective prevention of periodontal and peri-implant diseases. *J Clin Periodontol*. 2015; 42: S5-S11. d.
24. Heitz-Mayfield LJA, Lang NP, Surgical and nonsurgical periodontal therapy. Learned and unlearned concepts. *Periodontol 2000*. 2013;62:218-231.
25. Sim IW, Sanders KM, Borromeo GL, Seymour JF, Ebeling PR. Declining Incidence of Medication-Related Osteonecrosis of the Jaw in Patients With Cancer. *J Clin Endocrinol Metab*. 2015;100:3887-3993.
26. Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O. Interventions for managing medication-related osteonecrosis of the jaw. *Cochrane Database Syst Rev*. 2017;10(10):CD012432.
27. Nicolatou-Galitis O, Schiødt M, Mendes RA, et al. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2019;127(2):117-135.
28. Chapple ILC, Mealey BL, Van Dyke TE, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Clin Periodontol*. 2018;45(Suppl 20):S68-S77.

JOURNAL OF Periodontology

29. Tonetti MS, Greenwell H, Kornman KS, Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *J Periodontol*. 2018;89(Suppl 1):S159-S172.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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