Clinical Oral Investigations (2025) 29:368
https://doi.org/10.1007/s00784-025-06430-1

RESEARCH

Risk of bisphosphonate-related osteonecrosis of the jaw in implants vs. extractions: a nationwide population-based study

Jin-Joo Yoo[1] · Jaeyeon Kim[2] · Min Jin Kang[3] · Wonse Park[2,4,5] · Joon-Ho Yoon[1]

Received: 14 April 2025 / Accepted: 19 June 2025 / Published online: 2 July 2025

Abstract

Objectives This study aimed to investigate the incidence of and factors associated with bisphosphonate-related osteonecrosis of the jaw (BRONJ) after dental procedures in South Korean patients with osteoporosis who use bisphosphonates, using a nationwide population-based approach.

Materials and methods The study utilised the National Health Insurance Service– National Health Information Database (NHIS-NHID), which covers the entire South Korean population. Patients diagnosed with osteoporosis between 2010 and 2018 were included, excluding those with malignant neoplasms, Paget's disease, or multiple myeloma. BRONJ cases were identified based on diagnostic codes, multiple outpatient visits or hospitalisation, and ONJ-specific treatments. Variables included age, sex, medications, and dental-related clinical information. Multiple logistic regression was used to determine the odds ratios for BRONJ incidence after dental treatment.

Results Among 57,572 patients, 250 developed BRONJ after dental treatment. The overall BRONJ incidence was 0.43%, with an incidence of 0.85% in extraction, 0.27% in periodontal treatment, and 0.13% in implant surgery. Implant surgeries (odds ratio = 0.15) and periodontal treatments (odds ratio = 0.32) had a significantly lower association with BRONJ compared to tooth extraction. Increasing age and longer duration of bisphosphonate use were associated with a higher incidence of BRONJ, but longer drug holidays were associated with a lower incidence of BRONJ.

Conclusion Implant surgeries and periodontal treatments had a lower association with BRONJ compared to extraction. A longer bisphosphonate medication duration showed a higher association with possible BRONJ.

Clinical relevance This study suggests that tooth extraction is more strongly associated with BRONJ compared to implant surgery or periodontal treatment. To minimise the incidence of BRONJ, it is important to consider patient age and duration of bisphosphonate treatment.

Keywords Bisphosphonate-associated osteonecrosis of the jaw · Osteronecrosis of the jaw, Bisphosphonate-associated · Osteoporosis · Diphosphonates · Health surveys

JJY and JK contributed equally as first authors.

WP and JHY contributed equally as corresponding authors.

✉ Wonse Park
wonse@yuhs.ac

✉ Joon-Ho Yoon
yoonjuno@nhimc.or.kr

[1] Department of Prosthodontics, National Health Insurance Service– Ilsan Hospital, Goyang, South Korea

[2] Department of Advanced General Dentistry, Yonsei University College of Dentistry, Seoul, South Korea

[3] Department of Research and Analysis, National Health Insurance Service– Ilsan Hospital, Goyang, South Korea

[4] Institute for Innovation in Digital Healthcare, Yonsei University, Seoul, South Korea

[5] Human Identification Research Institute and Oral Science Research Center, Yonsei University College of Dentistry, Seoul, South Korea

Introduction

Bisphosphonates (BP), including alendronate, ibandronate, risedronate, and zoledronic acid, and denosumab (Dmab) (an antibody against RANKL), are frontline medications used to treat osteoporosis. Both BPs and Dmab are anti-resorptive drugs (ARDs), which are the most commonly used treatments for osteoporosis [1, 2]. At low cumulative annual absorbed doses, both ARDs inhibit bone resorption, reduce bone turnover, and increase bone density, thereby reducing the risk of hip and spine fracture. BPs inhibit bone resorption primarily by reducing osteoclast activity by inhibiting farnesyl diphosphate synthase [3]. Dmab reduces bone resorption primarily by inhibiting the formation and differentiation of osteoclasts, with only minor effects on osteoclast activity [4–6]. At high cumulative annual absorbed doses, about ten-fold greater than those used to treat osteoporosis, zoledronic acid, ibandronate, and Dmab are also used to reduce the risk of skeletal-related events (SREs; bone metastases and hypercalcemia of malignancy) in patients with breast cancer, prostate cancer, or multiple myeloma [7].

Treatment of patients with osteoporosis using ARDs reduces the risk of hip fracture by 50% and spine fracture by 70% [5–7]. However, the use of ARDs for osteoporosis is encumbered by side effects such as oesophageal irritation and acute phase reaction for BPs and hypocalcaemia for Dmab; and two adverse events—atypical femoral fracture and medication-related osteonecrosis of the jaw (MRONJ) [8, 9]. MRONJ is defined based on three criteria: (1) current or previous therapy with only antiresorptive therapy or combined with immune modulators or antiangiogenic medications; (2) no history of radiation therapy or metastatic disease to the jaws; and (3) exposed bone or bone that can be probed using an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for > 8 weeks [2].

MRONJ requires the coexistence of systemic and local oral risk factors [2, 10–14]. The most frequent MRONJ systemic risk factor for patients with osteoporosis is using an ARD. The most frequent local oral risk factor is tooth-related inflammatory dental disease, such as periapical or periodontal infection [11, 14–19]. Some have reasoned that the inflammatory process accompanying the local response to tooth-related dental infection kills the alveolar bone. That necrotic bone tissue, which would have been promptly removed by osteoclasts in the absence of ARDs, lingers owing to the influence of an ARD, accumulating in sufficient quantity to be recognised as MRONJ [13, 14]. Other systemic risk factors include smoking, glucocorticoid use, and diabetes [2, 10]. Although tooth extraction is often cited as an inciting event for MRONJ, most extracted teeth are infected at the time of their removal. There is good reason to believe that it is the infection rather than the trauma of the surgery associated with the tooth extraction procedure that gives rise to MRONJ [19, 20]. The prevalence of MRONJ in patients with cancer or multiple myeloma is 1.8–5%, while that in patients with osteoporosis is 0.01–0.03% [2, 10]21– [23].

A nationwide population-based study is a type of retrospective study performed using data obtained from medical insurance companies regarding citizens of a country. An advantage of this type of study is its ability to do a large-scale analysis. Citizens and healthcare providers must enrol in the National Health Insurance Service (NHIS) in South Korea. Most treatments are covered by the NHIS, excluding specific treatments such as cosmetic and unproven therapies. As a result, the NHIS database includes information on various treatments and diagnoses according to the Korean Standard Classification of Disease and Cause of Death 7th edition (KCD-7), a modified version of the 10th edition of the International Classification of Disease and Related Health Problems (ICD-10), and socioeconomic data for over 97% of the population [24]. Recently, population-based studies using the NHIS database have been published on the incidence and risk of ONJ in patients with osteoporosis. However, these studies utilised data from a health screening cohort of approximately 500,000 individuals [25] or a sample cohort of only 1 million individuals, representing approximately 2.2% of the entire population [26]. Because the incidence of ONJ in patients with osteoporosis is very low, ranging from 0.01 to 0.03% [10], large-scale population-based studies with larger sample sizes are needed.

This study used data from the National Health Insurance Service– National Health Information Database (NHIS-NHID), encompassing the entire Korean population. Changes in ARD prescription patterns from 2008 to 2020 were examined, and the incidence of bisphosphonate-related osteonecrosis of the jaw (BRONJ) associated with dental implants and extractions was assessed. Furthermore, the incidence of BRONJ and associated factors was analysed using large-scale data, providing potentially valuable information for clinicians.

This study aimed to investigate the incidence and associated factors of BRONJ associated with dental procedures in South Korean patients with osteoporosis who use BPs, using a nationwide population-based approach.

Materials & methods

This study was reviewed and approved by the Institutional Review Board of NHIS-Ilsan Hospital (IRB number: NHIMC-2023-04-008) and was performed in accordance with the STROBE guidelines [27]. To identify newly

diagnosed osteoporosis cases, we screened patients diagnosed with osteoporosis who were prescribed anti-osteoporotic medications between 2008 and 2018 using the NHIS-NHID, which includes diagnostic and treatment information for the entire population of South Korea (Fig. 1). Patients diagnosed between 2008 and 2009 were excluded to establish a 2-year washout period, ensuring only newly diagnosed osteoporosis cases were included. Therefore, 1 January 2010 was set as the baseline for the study. Patients aged < 50 years who died within one year of baseline, those diagnosed with ONJ within six months of baseline, and those who did not use BPs were excluded. To exclude those who received BPs for reasons other than osteoporosis, individuals with a history of malignant neoplasms, Paget's disease, or multiple myeloma were excluded.

The KCD-7 diagnostic codes were used. Prescription and treatment codes were based on the NHIS Treatment Procedure Codes, which identify and classify medical procedures, services, and treatments provided to patients covered by the NHIS. In this study, patients with osteoporosis were defined as those with diagnostic codes of M80 (osteoporosis with current pathological fracture), M81 (osteoporosis without current pathological fracture), or M82 (osteoporosis in diseases classified elsewhere) recorded during the study period according to the primary diagnosis code. Diagnosis codes related to ONJ and treatment codes of dental procedures

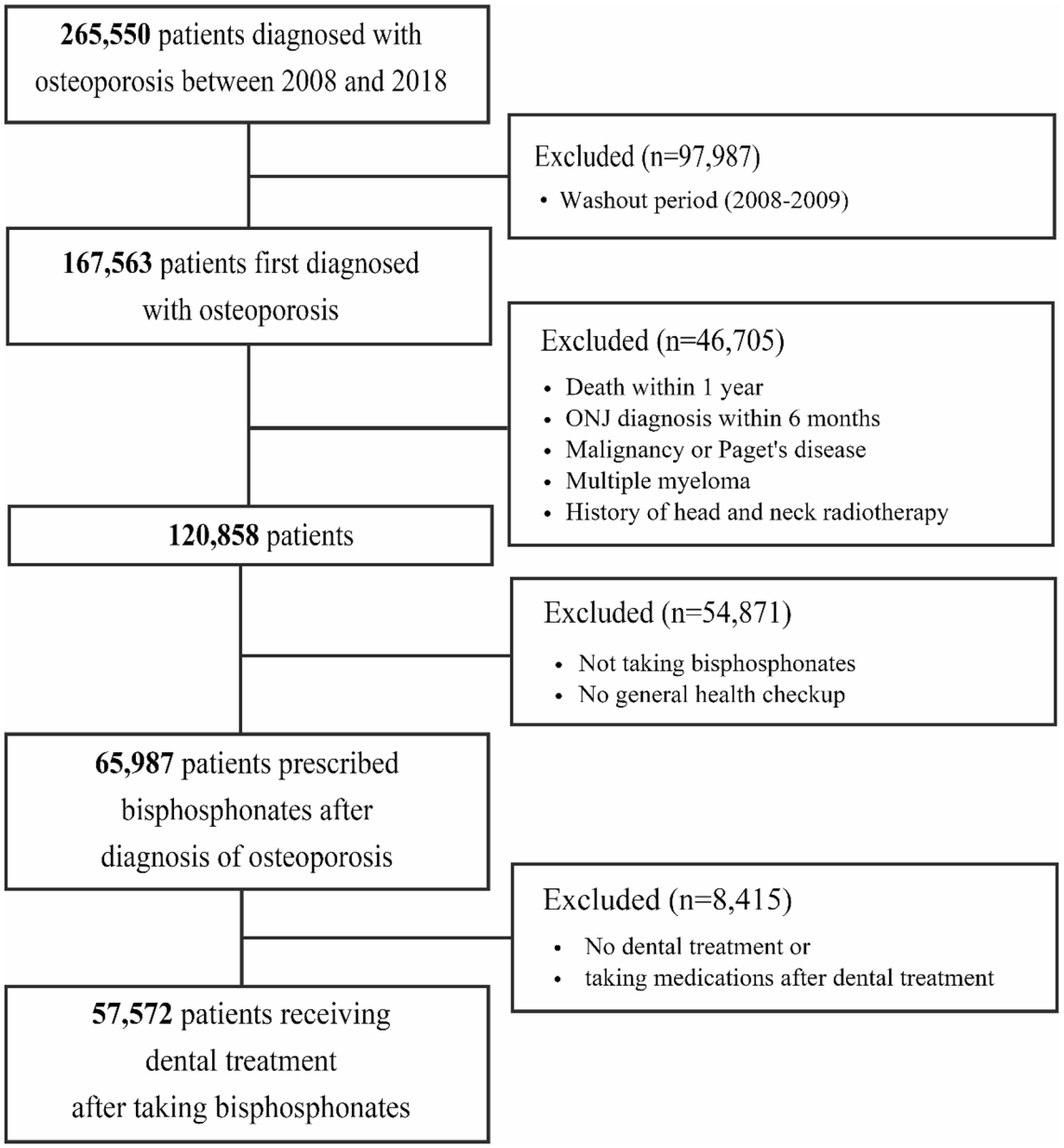

Fig. 1 Flow chart of the inclusion and exclusion criteria of this study. Individuals were excluded if they met even one of the exclusion criteria

associated with ONJ are also presented (Table 1). Only patients diagnosed between 2010 and 2018 were selected to assess the incidence of ONJ after dental treatment.

Patients with ONJ were defined as those with a diagnostic code related to ONJ who had visited an outpatient clinic at least twice within three months or received inpatient treatment and who had received dental treatment for ONJ management and antibiotic treatment at least twice.

To provide an overview of ARD use patterns in South Korea, we analysed the trends in BPs and Dmab prescriptions and the number of MRONJ cases from 2010 to 2020. For the subsequent analysis of BRONJ incidence after dental treatment and the associated risk factors, we included only patients who received BPs for osteoporosis treatment. The names and main ingredient codes of the BPs prescribed are listed in Supplemental Table (1) Dental treatment experience was defined as a patient having a dental procedure known to be associated with BRONJ within the 12 weeks preceding its onset. The duration of medication use was calculated by dividing the total dose before BRONJ onset by the defined daily dose (DDD) of each drug. Drug holidays were defined as the number of days the medication was discontinued before performing dental treatment known to be associated with BRONJ. Dental treatments were categorised as tooth extractions, periodontal treatment, implants, and other oral and maxillofacial surgeries. Treatment codes assessed in this study are presented in Supplemental Table (2) Lastly, age groups were divided into 50s (50–59 years), 60s (60–69 years), 70s (70–79 years), and > 80 based on the age at diagnosis of osteoporosis.

Table 1 Codes and names of diagnosis or treatment procedure

	Code	Name of Diagnosis OR Treatment Procedure
Diagnosis-related to osteoporosis	M80	Osteoporosis with current pathological fracture
	M81	Osteoporosis without current pathological fracture
	M82	Osteoporosis in diseases classified elsewhere
Diagnosis-related to ONJ	M87.0	Idiopathic aseptic necrosis of bone
	M87.1	Osteonecrosis due to drugs
	M87.2	Osteonecrosis due to previous trauma
	M87.3	Other secondary osteonecrosis
	M87.8	Other osteonecrosis
	M87.9	Osteonecrosis, unspecified
Dental procedures possibly related to ONJ	U4533	Surgery of Osteomyelitis of Mandible or Maxilla-Limited Alveolar Bone
	U4534	Surgery of Osteomyelitis of Mandible or Maxilla-One Side Mandible 1/3 Below
	U4535	Surgery of Osteomyelitis of Mandible or Maxilla-One Side Mandible 1/3 Over
	U4454	Incision of Gingival Abscess, Pericoronal Abscess
	U4455	Incision of Alveolar Abscess or Palatal Abscess
	U4456	Intraoral Antiphlogosis-Abscess of Tongue or Mouth of Floor
	U4457	Intraoral Antiphlogosis-Osteitis of Jaw, Osteomyelitis of Jaw, etc.
	U4464	Extraoral Antiphlogosis-Superficial Layer
	U4465	Extraoral Antiphlogosis-Deep Layer
	U4467	Extraoral Antiphlogosis-Osteitis of Jaw, Osteomyelitis of Jaw etc.
	U4520	Incision of Peritonsillar Abscess
	U4610	Orofacial Fistula Closure
	U4621	Oroantral Fistula Closure with Advancement Flap
	U4622	Oroantral Fistula Closure with Pedicled Flap
	U4791	Partial Maxillectomy
	U4792	Total Maxillectomy
	U4861	Partial Mandibulectomy
	U4862	Hemimandibulectomy

The descriptive statistics of patient numbers and proportions of each variable of interest according to the presence of BRONJ among patients on osteoporosis medications who received dental treatment were analysed. Multivariate analysis adjusted for age, sex, duration of medication use, drug holidays, and type of dental treatment was conducted to calculate the odds ratio (OR) for BRONJ. Multiple logistic regression was used to analyse the association between BRONJ incidence and each potential risk factor. The estimated OR with 95% confidence intervals and corresponding p-values were calculated to assess statistical significance. SAS Enterprise guide version 8.8 (SAS Institute, Cary, NC, USA) was used for the statistical analysis.

Results

Between 2010 and 2020, the annual numbers of patients with osteoporosis who were administered BPs, Dmab, or both and with MRONJ are shown in Fig. 2. The annual number of MRONJ cases increased gradually from 55 in 2010 to 130 in 2014, after which the yearly number plateaued around 125 until 2018. Signs of a new uptrend may be apparent in 2019 and 2020, as the number of annual cases reached its highest level at 159 in 2020, the final year of this study.

The incidence of BRONJ in patients who received dental treatment was 0.43% (Table 2). The highest incidence of BRONJ was in patients aged 70–79 years (0.70%), followed by those aged ≥ 80 years (0.69%). The incidence of BRONJ was similar between male (0.44%) and female (0.43%) patients. The incidence of BRONJ was the highest in patients with a medication duration of over 180 days (0.61%) and in patients with less than 60 days of drug holidays (0.91%).

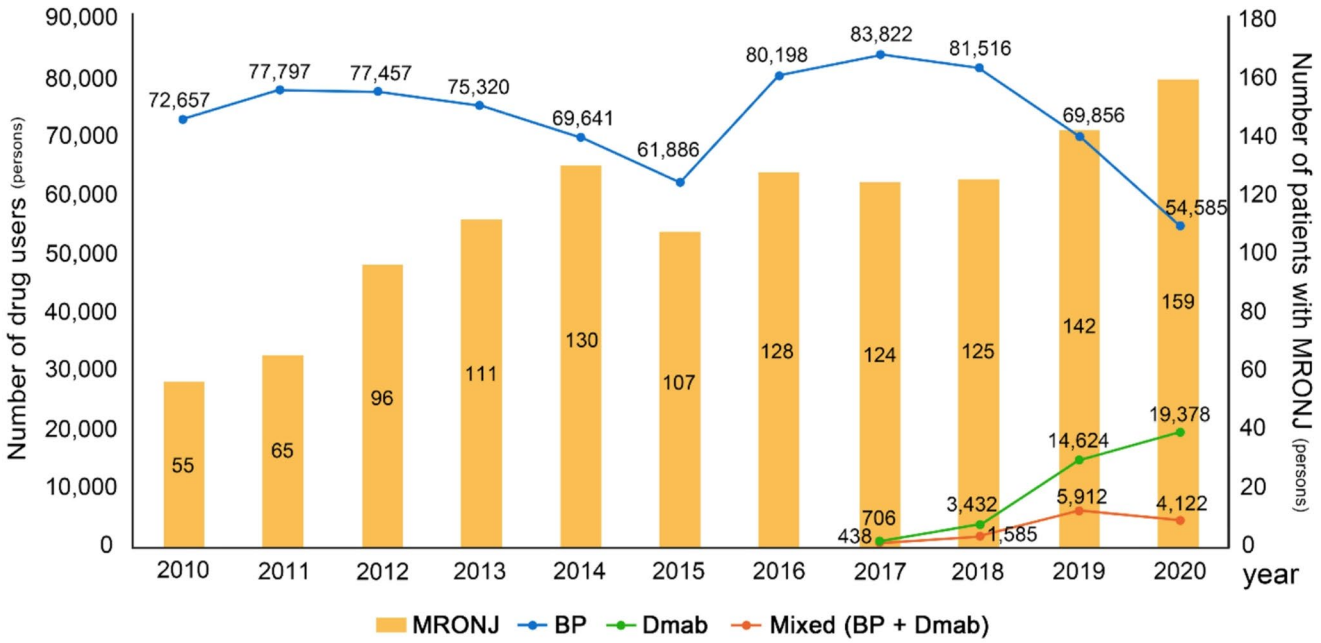

Fig. 2 Trends of prescribed ARD (BPs, Dmab, and mixed users) and number of MRONJ from 2010 to 2020. This figure shows all MRONJ cases identified in the database regardless of dental treatment history. Mixed users refer to cases where the medication has been changed, not simultaneous prescriptions

Table 2 The number and rate of patients based on the presence or absence of BRONJ after dental treatment

	BRONJ			
	(-)		(+)	
	N	%	*N*	%
All	57,322	99.57	250	0.43
Age (years)				
<60	11,960	99.86	17	0.14
60~69	22,818	99.68	74	0.32
70~79	18,683	99.30	132	0.70
>= 80	3,861	99.31	27	0.69
Sex				
Male	5,249	99.56	23	0.44
Female	52,073	99.57	227	0.43
Duration of medication				
<= 90 days	18,669	99.80	38	0.20
91~180 days	7,737	99.72	22	0.28
>180 days	30,916	99.39	190	0.61
Drug Holidays				
<60 days	13,209	99.09	121	0.91
61~180 days	8,127	99.44	46	0.56
181~365 days	5,864	99.59	24	0.41
>365 days	30,122	99.80	59	0.20
Type of dental treatment				
Extraction	17,020	99.15	146	0.85
Periodontal treatment	33,823	99.73	92	0.27
Implant surgery	5,513	99.87	7	0.13
Other surgery	966	99.49	5	0.51

The incidence of BRONJ was 0.85% in tooth extraction, 0.27% in periodontal treatment, 0.13% in implant surgery, and 0.51% in other dental surgery. The incidence of BRONJ was highest in individuals who underwent tooth extractions.

In multiple logistic regression analysis, the incidence of BRONJ in those in their 60s, 70s, and >80s showed a significantly higher association compared to those in their <60, with odds ratios of 2.28, 4.97, and 4.92, respectively ($p<0.05$) (Table 3). Those who received medication for more than 180 days had a 2.8-fold higher association with BRONJ compared to those under 90 days ($p<0.001$). A drug holiday of 60 to 180 days (OR=0.67, $p=0.0211$) was associated with a lower incidence of BRONJ compared to a drug holiday of 60 days. Drug holidays of 181 to 365 days (OR=0.50, $p=0.0015$) and >365 days (OR=0.26, $p<0.0001$) were also associated with a lower incidence. In addition, compared to extraction, periodontal treatment (OR=0.32, $p<0.0001$) and implant surgery (OR=0.15, $p<0.0001$) were associated with a lower incidence of BRONJ.

Discussion

Changes in the prescription patterns of ARDs in South Korea would reflect the changes in insurance coverage criteria for osteoporosis, which occurred several times during the study period. A precise quantitative standard was established and applied in November 2012, which was if

Table 3 Correlation between the incidence of BRONJ after dental treatment and variables of interests

Odds Ratio Estimates and Wald Confidence Intervals				
Effect	Estimate	95% Confidence Limits		Pr > ChiSq
Age (Ref: < 60 years)				
60 ~ 69	2.282	1.346	3.867	0.0022
70 ~ 79	4.971	2.998	8.241	< 0.0001
>= 80	4.920	2.679	9.036	< 0.0001
Sex (Ref: Male)				
Female	0.934	0.547	1.595	0.8037
Duration of medication (Ref: <=90 days)				
91 ~ 180 days	1.382	0.816	2.340	0.2286
> 180 days	2.754	1.937	3.917	< 0.0001
Drug holidays (Ref: <60 days)				
60 ~ 180 days	0.669	0.475	0.941	0.0211
181 ~ 365 days	0.491	0.316	0.762	0.0015
> 365 days	0.260	0.189	0.356	< 0.0001
Type of dental treatment (Ref: Extraction)				
Periodontal treatment	0.317	0.244	0.412	< 0.0001
Implant surgery	0.148	0.069	0.316	< 0.0001
Other surgery	0.603	0.247	1.475	0.2679

the T-score was −2.5 or less on dual-energy X-ray absorptiometry of the lumbar spine or femur except for Ward's triangle or calculated bone mineral density from quantitative CT (QCT) was less than 80 mg/cm^3, BP prescription was covered by insurance for a year. If the T-score was −3.0 or less on peripheral bone densitometry, BP prescription was covered by insurance only for six months. Previously, many patients had received BPs under insurance because the criteria were ambiguous; however, after the criteria were clarified, BP prescriptions seemed to decrease. In May 2015, BP insurance coverage was extended to three years for confirmed osteoporotic fractures, leading to a rapid increase in BP use. Dmab prescription was first covered by insurance in October 2017 but only under restrictive conditions. In 2019, when these restrictions were removed, the number of Dmab prescriptions increased rapidly, replacing some BP prescriptions. During the study period, the incidence of BRONJ was 0.43% in patients diagnosed with osteoporosis who had been administered BPs and received dental treatment. In this study, we excluded patients treated with Dmab (Prolia® and Xgeva®) because of the short follow-up period following its insurance approval in Korea.

In claims data-based research, patients who develop the condition but do not visit a dental clinic are inherently omitted from patient counts. Therefore, we limited our study population to those who received dental treatment to exclude individuals who had never visited a dental clinic from the denominator. The incidence was higher than the value reported in previous studies despite the exclusion of cancers that are treated with high-dose BPs and steroids [28, 29]. Owing to the nature of this study using claims data, among the diagnostic criteria for ONJ, bone exposure lasting longer than eight weeks or bone probing through an oral or extraoral fistula, which reflects the clinical situation, could not be implemented as an operational definition [2, 30, 31]. In other words, MRONJ was defined broadly compared to the definition in other studies that clinically confirmed MRONJ according to the American Association of Oral and Maxillofacial Surgeons (AAOMS) criteria [2]. The patients considered as per the former criteria might have been in a mild inflammatory state, as evidenced by the bone exposure being resolved within eight weeks. To compensate for this issue, a previous study defined MRONJ as a diagnosis code for ONJ persisting for more than eight weeks, even with broad-spectrum antibiotics [32].

As the duration of BPs administration increased, the incidence of BRONJ increased; conversely, as the drug holidays increased, the incidence of BRONJ decreased. However, studies have suggested different durations for a critical increase in BRONJ risk after BP administration [28, 31]. The present study analysed this duration by dividing the duration of medication use into shorter periods than in previous studies. The OR of BRONJ incidence increased to 2.7 times when BPs were administered for >180 days compared to when administered for <90 days. In particular, the OR of BRONJ incidence was reduced by 0.36 times after one year of medication cessation. Additionally, patients with drug holiday periods of less than 60 days exhibited a notably high BRONJ incidence rate exceeding 1%. However, many studies have questioned the effectiveness of drug holidays in BP administration [23, 33–35]. Claims-based datasets are unreliable in tracking actual medication adherence, discontinuation, or short-term discontinuation, potentially leading to misclassification bias. Further studies should comprehensively evaluate the role of medication holidays using data sets that provide more accurate adherence tracking, such as electronic medical records or pharmacy refill data.

Among all oral and maxillofacial procedures, tooth extraction has an increased risk of ONJ [36]. However, few studies have investigated the effects of various dental treatments on BRONJ risk [26]. Previous studies have investigated the risk of ONJ in osteoporotic patients undergoing implant surgery [26, 37], but this study provides a broader perspective on BRONJ risk factors by assessing the risks of specific dental treatments in osteoporotic patients treated with BP. Compared to BRONJ incidence after tooth extraction, that after periodontal treatment was 0.4 times, and after implant surgeries was 0.3 times lower. Notably, the incidence of BRONJ in osteoporotic patients who did not undergo dental procedures was approximately one-fourth of that observed in patients who received

dental treatments. Among various dental procedures, implant surgery demonstrated the lowest BRONJ incidence rate, comparable to that of patients with osteoporosis who received no dental treatment. This observation can be attributed to several factors: while tooth extractions and periodontal treatments are often preceded by inflammation or infection, and other dental surgeries typically involve extensive invasive procedures with tissue or bone resection, implant surgery sites are generally clean and free from pre-existing infection or inflammation. Additionally, implant procedures are generally less invasive compared to other surgical interventions. All periodontal treatments are covered by health insurance; however, only up to two implants are covered by national insurance for patients aged≥65 years in South Korea, which could cause bias. In patients with a history of ARDs, 0.5–15% experience MRONJ after extraction. However, the role of BPs in implant failure in patients taking ARDs for osteoporosis remains unclear [38, 39]. MRONJ occurs due to factors unrelated to the implant surgery, such as peri-implantitis and the characteristics of the implant prosthesis, rather than the implant surgery procedures. It has been reported that implant failure occurred in only 5% of patients who had received oral BPs before implant placement [40], which is consistent with the results of the present study.

This study had several limitations. As mentioned above, insurance coverage was not applied to patients who did not meet the specific criteria for the disease. Throughout the study period, the criteria for insurance coverage for patients with osteoporosis changed, and some cases were excluded because of age limitations and the number of implants covered by insurance. Only insurance-covered implants were included in this study, which is a common limitation in Korean population-based studies using NHIS data [26, 41]. Several previous studies investigating implant-related complications and adverse events in Korea have successfully utilised this database with similar methodological approaches [26, 41]. Similar to these studies, there is no evidence of a difference in the risk of BRONJ because insurance and non-insurance implants use similar materials and surgical techniques. Given these similarities, further studies incorporating non-insurance cases would be needed for validation. Similar to other studies that used claims information, the possibility that incorrect diagnostic codes were used could not be excluded. As a database study inherently limited in its ability to assess actual clinical scenarios, our research encountered challenges in operationally defining MRONJ cases that strictly adhere to the AAOMS criteria. Therefore, considering the AAOMS diagnostic criteria of MRONJ, multi-centre research or a study that merges NHIS claims data with hospital clinical data reflecting actual patient examinations should be conducted to identify specific cases that meet al.l clinical criteria for MRONJ. In this study, the number of patients who were administered Dmab was small, and the follow-up period for these patients was short; therefore, the effect of Dmab on MRONJ could not be analysed. Given the timing of when insurance coverage began for Dmab in South Korea, further studies are needed.

Conclusion

This population-based study investigated the incidence and factors associated with possible BRONJ in South Korean patients with osteoporosis. Compared to tooth extraction, implant surgery and periodontal treatment showed a lower association with BRONJ. In-depth consideration from a risk/benefit perspective is needed regarding whether to interrupt osteoporosis medication for treatments with a relatively lower BRONJ risk, such as implant surgeries, or for patients with high severity of osteoporosis who may experience complications with higher mortality, such as hip or vertebral fractures when the medication is discontinued.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00784-025-06430-1.

Acknowledgements This study used the National Health Insurance Service-National Health Information Database (REQ202301367-001), made by the National Health Insurance Service (NHIS). The authors alone are responsible for the content and writing of the paper.

Author contributions JK, MJK, WP, and JHY substantially contributed to the conception and design. MJK and JHY contributed to data acquisition. JJY, WP, and JHY contributed to the analysis and interpretation of data. JJY, JK, WP, and JHY contributed to drafting the manuscript and drawing the figures. All authors reviewed and approved the final manuscript.

Funding This study was supported by the National Health Insurance Ilsan Hospital Grant (NHIMC-2022-PR-023).

Data availability No datasets were generated or analysed during the current study.

Declarations

Compliance with ethical standards Disclosure of potential conflicts of interest.

Research involving human participants and/or animals This study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The use of anonymised data from the National Health Insurance Service (NHIS) database was approved by the Institutional Review Board (IRB) of NHIS-Ilsan Hospital (IRB number: NHIMC-2023-04-008).

Informed consent Since the data were fully anonymised and de-identified, the requirement for informed consent was waived.

Competing interests The authors declare no competing interests.

References

1. Yarom N, Shapiro CL, Peterson DE et al (2019) Medication-Related osteonecrosis of the jaw: MASCC/ISOO/ASCO clinical practice guideline. J Clin Oncol 37:2270–2290
2. Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D (2022) American association of oral and maxillofacial surgeons' position paper on medication-related osteonecrosis of the Jaws—2022 update. J Oral Maxillofac Surg 80:920–943
3. Kavanagh KL, Guo K, Dunford JE, Wu X, Knapp S, Ebetino FH, Rogers MJ, Russell RGG, Oppermann U (2006) The molecular mechanism of nitrogen-containing bisphosphonates as antiosteoporosis drugs. Proceedings of the National Academy of Sciences 103:7829–7834
4. Fleisch H, Reszka A, Rodan G, Rogers M (2002) Bisphosphonates: mechanisms of action. Principles of bone biology:1361-XLIII
5. Reginster J-Y, Minne H, Sorensen O, Hooper M, Roux C, Brandi ML, Lund B, Ethgen D, Pack S, Roumagnac I (2000) Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Osteoporos Int 11:83–91
6. Cummings SR, Martin JS, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A (2009) Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 361:756–765
7. Lorange J-P, Luna JRG, Grou-Boileau F, Rosenzweig D, Weber MH, Akoury E (2023) Management of bone metastasis with Zoledronic acid: A systematic review and bayesian network meta-analysis. J Bone Oncol 39:100470
8. Barrette L-X, Suresh N, Salmon MK, De Ravin E, Harris J, Kamdar R, Moreira AG, Rajasekaran K (2022) Assessment of clinical guidelines for medication-related osteonecrosis of the jaw: current status and future directions. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology
9. Marx RE (2003) Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 61:1115–1117
10. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S (2015) Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 30:3–23
11. Katsarelis H, Shah N, Dhariwal D, Pazianas M (2015) Infection and medication-related osteonecrosis of the jaw. J Dent Res 94:534–539
12. Messer J, Calle JM, Jiron J, Castillo E, Van Poznak C, Bhattacharyya N, Kimmel D, Aguirre J (2018) Zoledronic acid increases the prevalence of medication-related osteonecrosis of the jaw in a dose dependent manner in rice rats (Oryzomys palustris) with localized periodontitis. Bone 108:79–88
13. Aguirre J, Castillo E, Kimmel D (2021) Preclinical models of medication-related osteonecrosis of the jaw (MRONJ). Bone 153:116184
14. Tetradis S, Allen MR, Ruggiero SL (2023) Pathophysiology of Medication-Related osteonecrosis of the Jaw—A minireview. J Bone Mineral Res Plus 7:e10785
15. Aghaloo TL, Kang B, Sung EC, Shoff M, Ronconi M, Gotcher JE, Bezouglaia O, Dry SM, Tetradis S (2011) Periodontal disease and bisphosphonates induce osteonecrosis of the jaws in the rat. J Bone Miner Res 26:1871–1882
16. Vandone A, Donadio M, Mozzati M, Ardine M, Polimeni M, Beatrice S, Ciuffreda L, Scoletta M (2012) Impact of dental care in the prevention of bisphosphonate-associated osteonecrosis of the jaw: a single-center clinical experience. Ann Oncol 23:193–200
17. Aghaloo T, Hazboun R, Tetradis S (2015) Pathophysiology of osteonecrosis of the jaws. Oral Maxillofacial Surg Clin 27:489–496
18. Castillo E, Messer J, Abraham A, Jiron J, Alekseyenko A, Israel R, Thomas S, Gonzalez-Perez G, Croft S, Gohel A (2021) Preventing or controlling periodontitis reduces the occurrence of osteonecrosis of the jaw (ONJ) in rice rats (Oryzomys palustris). Bone 145:115866
19. Kim HY (2021) Review and update of the risk factors and prevention of antiresorptive-related osteonecrosis of the jaw. Endocrinol Metabolism 36:917–927
20. Bolette A, Lecloux G, Rompen E, Albert A, Kerckhofs G, Lambert F (2019) Influence of induced infection in medication-related osteonecrosis of the jaw development after tooth extraction: A study in rats. J Cranio-Maxillofacial Surg 47:349–356
21. jaws Atfob-root (2007) American association of oral and maxillofacial surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofacial Surgery: Official J Am Association Oral Maxillofacial Surg 65:369–376
22. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O'Ryan F (2014) American association of oral and maxillofacial surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg 72:1938–1956
23. Adler RA, El-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA, Compston JE, Drake MT, Edwards BJ, Favus MJ (2016) Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American society for bone and mineral research. J Bone Miner Res 31:16–35
24. Jung CH, Seo GH, Suh S, Bae JC, Kim MK, Hwang Y-C, Kim JH, Lee B-W (2015) The population-based risk of need for coronary revascularization according to the presence of type 2 diabetes mellitus and history of coronary heart disease in the Korean population. PLoS ONE 10:e0128627
25. Kim SH, Lee Y-K, Kim T-Y, Ha Y-C, Jang S, Kim HY (2021) Incidence of and risk for osteonecrosis of the jaw in Korean osteoporosis patients treated with bisphosphonates: A nationwide cohort-study. Bone 143:115650
26. Ryu JI, Kim HY, Kwon YD (2021) 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 32:437–447
27. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, Initiative S (2014) The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg 12:1495–1499
28. Lo JC, O'Ryan FS, Gordon NP, Yang J, Hui RL, Martin D, Hutchinson M, Lathon PV, Sanchez G, Silver P (2010) Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. J Oral Maxillofac Surg 68:243–253
29. Hallmer F, Andersson G, Götrick B, Warfvinge G, Anderud J, Bjørnland T (2018) 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 126:477–485
30. Vestergaard P, Schwartz K, Rejnmark L, Mosekilde L, Pinholt EM (2012) Oral bisphosphonate use increases the risk for inflammatory jaw disease: a cohort study. J Oral Maxillofac Surg 70:821–829
31. Kwon J-W, Park E-J, Jung S-Y, Sohn H, Ryu H, Suh H (2015) A large National cohort study of the association between bisphosphonates and osteonecrosis of the jaw in patients with osteoporosis: a nested case-control study. J Dent Res 94:212S–219S

32. Lin T-C, Yang C-Y, Kao Yang Y-H, Lin S-J (2014) Incidence and risk of osteonecrosis of the jaw among the Taiwan osteoporosis population. Osteoporos Int 25:1503–1511
33. Nazrun AS, Tzar MN, Mokhtar SA, Mohamed IN (2014) A systematic review of the outcomes of osteoporotic fracture patients after hospital discharge: morbidity, subsequent fractures, and mortality. Therapeutics and clinical risk management:937–948
34. Kang SH, Park SJ, Kim MK (2020) The effect of bisphosphonate discontinuation on the incidence of postoperative medication-related osteonecrosis of the jaw after tooth extraction. J Korean Assoc Oral Maxillofac Surg 46:78–83
35. Aboalela AA, Farook FF, Alqahtani AS, Almousa MA, Alanazi RT, Almohammadi DS, Aboalela A, Alqahtani AS, Almousa M, AlMohammadi D (2022) The effect of antiresorptive drug holidays on medication-related osteonecrosis of the Jaw: A systematic review and meta-analysis. Cureus 14
36. Mavrokokki T, Cheng A, Stein B, Goss A (2007) Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. J Oral Maxillofac Surg 65:415–423
37. Park J-H, Lee J-R, Lee H, Lee H-J, Kim J-W (2024) No increased risk of osteonecrosis of the jaw in osteoporotic patients with dental implants: a nationwide cohort study. Clin Oral Invest 28:83
38. Diniz-Freitas M, Limeres J (2016) Prevention of medication-related osteonecrosis of the jaws secondary to tooth extractions. A systematic review. Med Oral Patol Oral Cir Bucal 21:e250–259
39. Yamazaki T, Yamori M, Ishizaki T, Asai K, Goto K, Takahashi K, Nakayama T, Bessho K (2012) Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: a cohort study. Int J Oral Maxillofac Surg 41:1397–1403
40. Stavropoulos A, Bertl K, Pietschmann P, Pandis N, Schiødt M, Klinge B (2018) The effect of antiresorptive drugs on implant therapy: systematic review and meta-analysis. Clin Oral Implants Res 29:54–92
41. Park JH, Lee JR, Lee H, Lee HJ, Kim JW (2024) No increased risk of osteonecrosis of the jaw in osteoporotic patients with dental implants: a nationwide cohort study. Clin Oral Investig 28:83