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Incidence and severity of medication-related osteonecrosis of the jaw in patients with osteoporosis using data from a Korean nationwide sample cohort in 2002 to 2019: a retrospective study

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Background: Medication-related osteonecrosis of the jaw (MRONJ) is a significant concern, particularly among patients taking bisphosphonates (BPs), denosumab, and selective estrogen receptor modulators (SERMs) for osteoporosis. Despite the known risks, large-scale cohort studies examining the incidence and severity of MRONJ are lacking. We aimed to ascertain the incidence and risk of MRONJ among these patients, whom we stratified by age groups, medication types, and duration of use.

Methods: We utilized data from the National Health Insurance Service's sample cohort database, focusing on patients aged 40 years and above diagnosed with osteoporosis. The patients were divided into three groups: those prescribed BPs only, those prescribed SERMs only, and those prescribed both.

Results: The overall incidence rate of MRONJ was 0.17%. A significantly higher incidence rate was observed among those taking osteoporosis medications, particularly among females with a relative risk of 4.99 (95% confidence interval, 3.21–7.74). The SERM group also had an incidence rate comparable to that of the BP group. Severity was assessed based on the invasiveness of the treatment methods, with 71.3% undergoing invasive treatment in the medication group.

Conclusion: This study provides valuable insights into the incidence and severity of MRONJ among a large cohort of patients with osteoporosis. It underscores the need for comprehensive guidance on MRONJ risks across different medication groups and sets the stage for future research focusing on specific populations and treatment outcomes.

Keywords: Bisphosphonate; Osteonecrosis of jaw; Osteoporosis; Selective estrogen receptor modulators

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a debilitating oral condition characterized by the exposure of necrotic jawbone, typically occurring in patient on certain medications, such as bisphosphonates (BPs) [1]. It is precipitated by dental surgery but occasionally manifests spontaneously. While this disorder has multiple etiologies, its association with BP medication is of particular

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concern, especially given the widespread use of BPs for managing osteoporosis and cancer-related conditions like metastasis to the bone [2]. In the management of osteoporosis, BPs, selective estrogen receptor modulators (SERMs), and denosumab are commonly utilized as first-line pharmacological agents. These medications are frequently cited in multiple clinical guidelines pertaining to the treatment of osteoporosis [3].

One of the most significant adverse effects associated with BPs is osteonecrosis of the jaw (ONJ). Notably, ONJ related to surgical dental procedures, such as tooth extraction, periodontal treatment, and implantation, is a well-documented complication [4]. Additionally, individual comorbidities and lifestyle factors, such as steroid use, cancer, diabetes, and smoking, elevate the risk of ONJ occurrence [5].

As the aging population continues to grow, the prevalence of osteoporosis is also on the rise, leading to an increase in the number of individuals prescribed BPs. The incidence of ONJ among those taking BPs has been reported to range from 0.05% to 0.21% [6]; however, large-scale cohort studies to accurately determine this incidence rate have been lacking. In an aging population where the demand for dental treatments such as implantation is increasing, the potential for complications like ONJ poses a risk of diminished quality of life [7].

In particular, some epidemiological evidence exists regarding the increased risk of ONJ among BP users based on the duration of medication use, sex, and age. However, studies specifically examining the severity of ONJ related to medication use have been lacking. Therefore, we aimed to ascertain the incidence and risk of ONJ among patients with osteoporosis prescribed with BPs and SERMs. We provided data on the incidence rate and risk of these patients stratified by age groups, medication types, and duration of use. Additionally, we presented data on the severity outcomes of MRONJ based on dental treatments.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: YU 2021-12-007), and the requirement for informed consent was waived.

1. Study population and cohort data

The National Health Insurance Service's (NHIS) sample cohort database is a standardized dataset for academic research. The database provides health insurance data from 2002 to 2019 for one million individuals and is organized into tables for eligibility and premiums, birth and death records, medical treatment, health examinations, healthcare facilities, and long-term care. We aimed to analyze data from at least a 10-year period, considering adverse effects that could occur over several years; thus, we set the enrollment year at 2006.

The 2006 data comes from one million individuals who maintained eligibility as health insurance enrollees or medical aid beneficiaries for that year, representing 2% of the entire South Korean population. For the purpose of this study, we excluded 886,082 individuals who were under the age of 40 years and had no diagnosis of osteoporosis from these one million individuals. We also excluded those who were diagnosed with osteoporosis prior to 2006. A total of 113,918 patients aged 40 years and above were identified as having been diagnosed with osteoporosis, among whom 61,183 had been prescribed osteoporosis medications. The data on the prescription of osteoporosis medication was based on the date of the initial prescription.

The definition of an osteoporosis-diagnosed patient in this study was based on the presence of an osteoporosis diagnosis code as either the primary or secondary condition. The criteria for osteoporosis diagnosis were based on the International Classification of Diseases, 10th Revision codes M80 (osteoporosis with pathological fracture), M81 (osteoporosis without pathological fracture), and M82 (osteoporosis in diseases classified elsewhere). The osteoporosis medications were identified based on prior literature and are listed in Table 1. Those prescribed to the study participants consisted of BPs and SERMs, both of which were orally administered.

In this study, we divided the cohort into three groups for analysis: those prescribed only BPs, those prescribed only SERMs, and those prescribed both. Among the 61,183 patients who had been prescribed osteoporosis medications, 195 were diagnosed with ONJ and constituted the final population for analysis.

2. Definition of medication-related osteonecrosis of the jaw

MRONJ is defined as the presence of exposed bone in the maxillofacial area or oral and extraoral fistulas that do not heal within 8 weeks in patients who have been administered bone-modifying agents such as antiresorptive drugs or angiogenesis inhibitors and who have no history of radiation therapy to the head and neck area [8].

To identify MRONJ, the diagnostic codes used were M87.1 (osteonecrosis due to drugs) and K10.2 (inflammatory conditions of jaws). We referred to the dental insurance claim codes used in general hospitals and defined patients with MRONJ based on the following treatment codes, which are listed in Table 2.

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Table 1. List of medications of osteoporosis

Type	Medication	Code
Bisphosphonates	Alendronic acid 10 mg	228301ATB
	Alendronic acid 5 mg	228302ATB
	Alendronic acid 70 mg	228303ALQ
		228303ATB
		228305ATB
	Alendronic acid 5 mg+calcitriol 0.5 μg	468000ATE
	Alendronic acid 70 mg+cholecalciferol (vitamin D3 2.8 kIU)	481100ATB
	Alendronic acid 70 mg+cholecalciferol (vitamin D3 5.6 kIU)	500200ATB
	Disodium etidronate 0.2 g	147401ATB
	Zoledronic acid 5 mg (50 μg/mL)	420732BIJ
	Zoledronic acid 4 mg (40 μg/mL)	420730BIJ
	Zoledronic acid 4 mg (0.8 μg/mL)	420731BIJ
	Risedronate sodium 5 mg	442301ATB
	Risedronate sodium 35 mg	442302ATB
	Risedronate sodium 2.5 hydrate (enteric coated) 35 mg	442302ATE
	Risedronate sodium 75 mg	442303ATB
	Risedronate sodium 0.15 g	442330ATB
	Risedronate sodium 35 mg+ cholecalciferol 5.6 kIU	511200ATB
	Risedronate sodium 0.15 g+ cholecalciferol 30 kIU	518400ATB
	Ibandronic acid 3 mg (1 mg/mL)	480330BIJ
	Ibandronic acid 0.15 g	480304ATB
	Ibandronic acid 0.15 g+cholecalciferol 24 kIU	523900ATB
	Pamidronate 15 mg (15 mg/mL)	207930BIJ
	Pamidronate 0.1 g	207901ACS
SERMs	Raloxifene 55.71 mg	358001ATB
	Raloxifene 55.71 mg+cholecalciferol (as vitamin D3 800 IU)	659200ACH
		659200ATB
	Bazedoxifene 20 mg	617101ATB
	Bazedoxifene 20 mg+cholecalciferol (as vitamin D3 800 IU)	674500ATB
	Toremifene citrate (as toremifene 40 mg)	242101ATB
	Toremifene citrate (as toremifene 20 mg)	234502ATB
	Toremifene citrate (as toremifene 10 mg)	234501ATB
	Clomipramine hydrochloride 25 mg	136302ACH
	Clomipramine hydrochloride 25 mg	136301ACH
	Clomiphene citrate 50 mg	136201ATB

kIU, kilo-international unit; IU, international unit; SERMs, selective estrogen receptor modulators.

3. Data analysis

The data were analyzed using SAS 9.4 and IBM SPSS ver. 27.0 (IBM Corp., Armonk, NY, USA) statistical software, with the statistical significance level set at a p-value of < 0.05. A cross-analysis was conducted to examine the general characteristics of patients with ONJ and the presence or absence of osteoporosis medication. Relative risk (RR) of ONJ occurrence based on the prescription of osteoporosis medication was also analyzed.

Table 2. Treatment codes of osteonecrosis of the jaw

Code	Treatment	Category
U4457	Intraoral antiphlogosis-osteitis of jaw, osteomyelitis of jaw, etc.	Noninvasive treatment
U4467	Extraoral antiphlogosis-osteitis of jaw, osteomyelitis of jaw, etc.	
U4533	Surgery of osteomyelitis of mandible or maxilla-limited alveolar bone	Invasive treatment
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	

Results

Among the 61,183 osteoporosis patients aged 40 years and above who were confirmed to have been prescribed osteoporosis medication, 5,537 were male and 55,646 were female, indicating a female majority. When examined by age group, there were 3,903 individuals aged 40 to 49 years, 14,945 in their 50s, 22,465 in their 60s, and 19,870 aged 70 years and above. There were 52,743 were taking BPs, 3,101 patients taking SERMs, and 5,339 were taking both types of medications (Table 3).

The occurrence of ONJ was examined based on sex, age group, and whether osteoporosis medication was administered (Table 4). The incidence of ONJ was significantly higher in the osteoporosis medication group (RR, 3.81; 95% confidence interval [CI], 2.66–5.48), particularly among females with an RR of 4.99 (95% CI, 3.21–7.74). In the 40s age group, the RR was relatively low at 1.44 and was statistically insignificant (95% CI, 0.26–7.84).

The time from the initial medication administration to the occurrence of ONJ was analyzed during the study period. In both the BP and SERM groups, the majority of cases occurred after 5 years, with 74 cases (51.0%) for the BP group and six cases (42.8%) for the SERM group (Table 5).

In the treatment of ONJ, we examined both invasive and noninvasive surgical treatment methods (Table 6). Among the group that received osteoporosis medication, invasive treatment was more common, accounting for 127 cases (71.3%). In contrast, in the group that did not receive medication, invasive treatment was relatively less common, with 20 cases (55.6%), although this difference was not statistically significant. When examined by medication type, invasive treatment was performed in 69.9% of the BP group, 85.7% of the SERM group, and 75.0% of the group receiving both medications.

Discussion

MRONJ is considered a rare condition due to its low incidence

Table 3. Medications of osteoporosis with regards to sex and age

Variable	Total	Osteoporosis medication			*p*-value
		Bisphosphonates	SERMs	Both	
Sex					
Male	5,537 (9.0)	5,432 (98.1)	58 (1.0)	47 (0.8)	<0.001
Female	55,646 (91.0)	47,311 (85.0)	3,043 (5.5)	5,292 (9.5)	
Age (yr)					
40–49	3,903 (6.4)	2,839 (72.7)	733 (18.8)	331 (8.5)	<0.001
50–59	14,945 (24.4)	12,353 (82.7)	1,125 (7.5)	1,467 (9.8)	
60–69	22,465 (36.7)	19,468 (86.7)	759 (3.4)	2,238 (10.0)	
≥70	19,870 (32.5)	18,083 (91.0)	484 (2.4)	1,303 (6.6)	
Total	61,183 (100)	52,743 (86.2)	3,101 (5.1)	5,339 (8.7)	

Values are presented as number (%).
SERMs, selective estrogen receptor modulators.

Table 4. Numbers of cases of osteonecrosis of the jaws (ONJs)

Variable	Cases of osteoporosis	Cases of ONJ			RR (95% CI)
		Total	Osteoporosis medication		
			Yes	No	
Sex					
Male	14,934 (13.1)	25 (0.17)	12 (48.0)	13 (52.0)	1.57 (0.72–3.44)
Female	98,984 (86.9)	170 (0.17)	147 (86.5)	23 (13.5)	4.99 (3.21–7.74)
Age (yr)					
40–49	15,105 (13.3)	6 (0.04)	2 (33.3)	4 (66.7)	1.44 (0.26–7.84)
50–59	33,063 (29.0)	26 (0.08)	20 (76.9)	6 (23.1)	4.05 (1.62–10.08)
60–69	34,150 (30.0)	92 (0.27)	77 (83.7)	15 (16.3)	2.68 (1.54–4.66)
≥70	31,600 (27.7)	71 (0.22)	60 (84.5)	11 (15.5)	3.23 (1.70–6.14)
Total	113,918 (100)	195 (0.17)	159 (81.5)	36 (18.5)	3.81 (2.66–5.48)

Values are presented as number (%).
RR, relative risk; CI, confidence interval.

Table 5. Time to occurrence of osteonecrosis of the jaw with regard to osteonecrosis medication

Time to incident (yr)	Osteoporosis medication			*p*-value
	Bisphosphonates	SERMs	Total	
<1	10 (6.9)	3 (21.4)	13 (8.2)	
≥1, <2	10 (6.9)	1 (7.2)	11 (6.9)	
≥2, <3	13 (9.0)	3 (21.4)	16 (10.1)	
≥3, <4	16 (11.0)	1 (7.2)	17 (10.7)	
≥4, <5	22 (15.2)	0 (0)	22 (13.8)	
≥5	74 (51.0)	6 (42.9)	80 (50.3)	
Total	145 (91.2)	14 (8.8)	159 (100)	0.171

Values are presented as number (%).
SERMs, selective estrogen receptor modulators.

Table 6. The number of invasive or noninvasive treatments of osteonecrosis of the jaw according to medication

Medication	Total	Noninvasive surgery	Invasive surgery	*p*-value
Yes	178 (83.8)	51 (28.7)	127 (71.3)	0.062
Bisphosphonates	143 (80.3)	43 (30.1)	100 (69.9)	0.650
SERMs	7 (4.0)	1 (14.3)	6 (85.7)	
Both	28 (15.7)	7 (25.0)	21 (75.0)	
No	36 (16.2)	16 (44.4)	20 (55.6)	
Total	214 (100)	67 (31.3)	147 (68.7)	

Values are presented as number (%).
SERMs, selective estrogen receptor modulators.

rate, and its treatment and prognosis are often poor, necessitating prevention and caution. The condition involves complex prescriptions and treatments across multiple specialties, including internal medicine, orthopedics, dentistry, oral and maxillofacial surgery, and plastic surgery. While it is challenging to manage solely within one specialty, there is room for prevention if healthcare providers from any specialty take the risk of MRONJ into account and communicate appropriately with colleagues from other departments. Through this study, we confirmed the incidence rate of MRONJ among patients with osteoporosis who were taking BPs and assessed its severity based on the invasiveness of the treatment methods. While epidemiological studies on the relationship between

BP use and MRONJ are somewhat known, this is the first study, to the best of our knowledge, that evaluates the severity of MRONJ based on medication use in a large-scale cohort.

The prevalence of osteoporosis is increasing and is currently known to be 18.3% worldwide [9]. Elderly women are specifically at risk. Over 90% of patients with osteoporosis are women, particularly those older than 50 years. The demand for dental treatment also increases with age. Consequently, it was hypothesized that the incidence of MRONJ would also increase with age among those taking osteoporosis medications. This study confirmed epidemiological evidence to support this. Given that over 90% of patients with osteoporosis are women and that BP prescriptions are also more common among female patients, it was observed that the incidence of MRONJ is higher in women. Specifically, when examined by sex, it was confirmed that women are more vulnerable to MRONJ while on medication than men, which contrasts with previous studies that suggested a higher incidence of MRONJ among men taking BP compared to women [10,11].

A significantly higher incidence of MRONJ was observed in the group taking osteoporosis medications compared to those who were not. The incidence rate of MRONJ was found to be 0.17%. The incidence rate of MRONJ among patients with osteoporosis varies from study to study; for instance, a study in Japan reported an incidence rate of 0.06% [12]. This finding is consistent with previously known incidence rates, lending credibility to the reliability of this sample cohort.

We aimed to examine the differences between the BP group and the SERM group as a control. Interestingly, the incidence rate of MRONJ in the SERM group was found to be at the same level as that in the BP group. While MRONJ is generally not well-known to occur in patients taking SERMs, it has been reported to occur even in those receiving SERMs alone [13,14]. However, the association between MRONJ and SERMs should be carefully interpreted. The number of MRONJ cases should be considered as it is a relatively small number compared to that of the BP group. In addition, we observed MRONJ cases only in patients with osteoporosis. This may have resulted in increased cases in the SERMs group, not in breast cancer or other SERM users. Although the results could be interpreted as an effect of past BP use in the SERM group, it suggests the need for comprehensive guidance on the risks of MRONJ for patients with osteoporosis undergoing drug treatment, including those in the SERM group.

There are several limitations in this study. First, the representativeness of the data extracted from the sample cohort was limited as it was secondary data. Although the data from the NHIS claims to cover the entire population, the 2% of the allegedly entire population uniformly extracted may still have lacked representativeness. Second, securing statistical significance was challenging due to the rarity of MRONJ. Lastly, while it would have been ideal to evaluate the severity of MRONJ through staging in actual clinical settings, this was not feasible due to poor staging and limitations in accessing medical records. Therefore, we utilized a research method based on treatment method names.

The evaluation concerning the severity and stage of MRONJ in clinical setting was as follows [15]. Stage 1 patients had exposed bone and were asymptomatic with no localized soft tissue infection. Stage 2 patients had exposed bone, pain, and regional soft tissue inflammation or infection. Stage 3 patients had exposed bone with associated pain, localized soft tissue inflammation (or secondary infection), pathological fracture, and extraoral or oral-antral fistulas. Radiographically, the bone showed osteolysis extending to the inferior mandibular border or maxillary sinus floor. However, those staging systems rarely applied to the patient, and the stage information was not available in NHIS.

Despite these limitations, we were able to utilize nationwide data accumulated over a long period in this study. Particularly, we evaluated the severity of MRONJ by using treatment methods as variables. Future research should focus on specific populations such as patients with osteoporosis and cancer and further explore the relationship between medication use and the location and severity of MRONJ.

Article information

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: all authors; Data curation, Formal analysis: SYK, TYH; Funding acquisition, Methodology, Validation: TYH, KB, CP; Resources, Software: SYK; Supervision: TYH; Writing-original draft: SYK; Writing-review & editing: KB, CP

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References

1. AlDhalaan NA, BaQais A, Al-Omar A. Medication-related osteonecrosis of the jaw: a review. Cureus 2020;12:e6944.
2. Campisi G, Fedele S, Fusco V, Pizzo G, Di Fede O, Bedogni A. Epidemiology, clinical manifestations, risk reduction and treatment strategies of jaw osteonecrosis in cancer patients exposed to antiresorptive agents. Future Oncol 2014;10:257–75.
3. Jeon Y, Kim IJ. Pharmacological treatment of osteoporosis: 2022 update. J Korean Med Assoc 2022;65:241–8.
4. Di Fede O, Panzarella V, Mauceri R, Fusco V, Bedogni A, Lo Muzio L, et al. The dental management of patients at risk of medication-related osteonecrosis of the jaw: new paradigm of primary prevention. Biomed Res Int 2018;2018:2684924.
5. Barasch A, Cunha-Cruz J, Curro FA, Hujoel P, Sung AH, Vena D, et al. Risk factors for osteonecrosis of the jaws: a case-control study from the CONDOR dental PBRN. J Dent Res 2011;90:439–44.
6. Lo JC, O'Ryan FS, Gordon NP, Yang J, Hui RL, Martin D, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. J Oral Maxillofac Surg 2010;68:243–53.
7. Miksad RA, Lai KC, Dodson TB, Woo SB, Treister NS, Akinyemi O, et al. Quality of life implications of bisphosphonate-associated osteonecrosis of the jaw. Oncologist 2011;16:121–32.
8. Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' position paper on medication-related osteonecrosis of the jaws: 2022 update. J Oral Maxillofac Surg 2022;80:920–43.
9. Salari N, Ghasemi H, Mohammadi L, Behzadi MH, Rabieenia E, Shohaimi S, et al. The global prevalence of osteoporosis in the world: a comprehensive systematic review and meta-analysis. J Orthop Surg Res 2021;16:609.
10. Yamazaki T, Yamori M, Ishizaki T, Asai K, Goto K, Takahashi K, 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;41:1397–403.
11. Dioguardi M, Spirito F, Alovisi M, Aiuto R, Garcovich D, Crincoli V, et al. Location and gender differences in osteonecrosis of the jaws in patients treated with antiresorptive and antineoplastic drugs undergoing dentoalveolar surgical, systematic review with meta-analysis and trial sequential analysis. J Clin Med 2023;12:3299.
12. Ishimaru M, Ono S, Morita K, Matsui H, Hagiwara Y, Yasunaga H. Prevalence, incidence rate, and risk factors of medication-related osteonecrosis of the jaw in patients with osteoporosis and cancer: a nationwide population-based study in Japan. J Oral Maxillofac Surg 2022;80:714–27.
13. Baur DA, Altay MA, Teich S, Schmitt Oswald M, Quereshy FA. Osteonecrosis of the jaw in a patient on raloxifene: a case report. Quintessence Int 2015;46:423–8.
14. Bindakhil M, Shanti RM, Mupparapu M. Raloxifene-induced osteonecrosis of the jaw (MRONJ) with no exposure to bisphosphonates: clinical and radiographic findings. Quintessence Int 2021;52:258–63.
15. Gupta M, Gupta N. Bisphosphonate related jaw osteonecrosis. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Oct 5]. https://www.ncbi.nlm.nih.gov/books/NBK534771/