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Incidence of and risk for osteonecrosis of the jaw in Korean osteoporosis patients treated with bisphosphonates: A nationwide cohort-study

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ABSTRACT

Purpose: To estimate the incidence of osteonecrosis of the jaw (ONJ) in patients treated with bisphosphonates (BPs) and to identify clinical risk factors that increase the risk for ONJ in Korean osteoporosis patients.
Methods: We used data acquired from the Korean National Health Insurance Service. Among 2,140,149 participants with osteoporosis in 2012, we selected 164,926 new BP users and 164,926 age- and sex-matched control subjects. The control group included only patients with no prescriptions for BPs between January 1, 2011, and December 31, 2016. Participants were followed for 4 years.
Results: Over the 4-year follow-up period, the cumulative incidence rates of ONJ were 20.9 and 6.9 per 100,000 person-years in the BP and control groups, respectively. The BP group had an increased risk for ONJ compared to the control group after adjusting for multiple variables (hazard ratio [HR] 3.72, 95% CI 2.70–5.11). Advanced age (≥70 years), comorbid diseases such as diabetes, hypertension, and rheumatoid arthritis (RA) were independent risk factors for the development of ONJ. In addition, tooth extraction (HR 9.85), gingivitis, and periodontal disease (HR 4.78) were strongly associated with ONJ.
Conclusions: ONJ incidence was 21 per 100,000 person-years in osteoporosis patients receiving bisphosphonates. Clinical factors including advanced age, diabetes, RA, dental disease, as well as BP use were significantly associated with ONJ.

1. Introduction

Bisphosphonates (BPs) decrease bone loss and reduce vertebral and hip fracture risk in patients with osteoporosis [1,2] and thus they are commonly used for the treatment of osteoporosis. However, they suppress bone turnover, resulting in the accumulation of microdamage, raising concerns that long-term BP use may impair bone quality [3,4].

Osteonecrosis of the jaw (ONJ) is a major concern for patients undergoing long-term BP treatment. ONJ is characterized by exposed necrotic bone in the maxillofacial region that does not heal within 8 weeks, with no history of radiation therapy to the craniofacial region [5]. At this time, the majority of ONJ cases have been reported with the use of high-dose intravenous BPs in the cancer patient population. Recently, the International Task Force on Osteonecrosis of the Jaw conducted a systematic literature review and reported that the incidence of ONJ in oncology patients treated with intravenous BP ranges from 0 to 12,222 per 100,000 patient-years [6]. They also estimated the incidence of ONJ in osteoporosis patients prescribed BPs at 1 to 90 per 100,000 patient-years, slightly higher than the frequency observed in the general population [7–13]. However, these estimates are largely based on studies in Western populations; there are few epidemiological studies of ONJ incidence and risk in Asian populations, and the results are inconsistent. One previous study showed that most patients with ONJ were Asian-Americans, which raised concerns about the higher prevalence of ONJ in Asians compared to Western populations receiving oral BPs [14]. A recent study conducted in Taiwan found a

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similar incidence of ONJ between calcitonin/raloxifene and alendronate treatment groups, and the incidence rate of ONJ seemed to be higher than in Western populations (69 to 82 per 100,000 person-years) [15]. Meanwhile, another study found that oral alendronate was associated with a seven-fold increased risk for ONJ in Taiwan [16]. Kwon et al. [17] completed a nested case-control study and noted an association between BPs and ONJ with an odds ratio (OR) of 3.9 (95% CI: 2.4, 6.2). To date, there have been no cohort studies on the incidence of ONJ and clinical risk factors that increase the risk for ONJ in osteoporosis patients treated with BPs in Korea.

In this study, we estimated the incidence rates of ONJ in patients treated with BPs, investigated whether BP treatment increases the risk for ONJ among the Korean osteoporosis population, and examined the potential clinical risk factors for ONJ development.

2. Methods

2.1. Study population and follow-up

We used data acquired from the Korean National Health Insurance Service (KNHIS), which provides obligatory health insurance to all Koreans. The KNHIS database contains all prescription drugs and treatment claim records for nearly all Koreans. We identified subjects who were newly initiating BP treatment among subject with osteoporosis based on the International Classification of Disease, Tenth Revision (ICD-10) codes (M80–82) between January 1 and December 31, 2012. We excluded participants aged < 50 years and those who did not have information on smoking, alcohol, or BMI at baseline. We also excluded participants who died within 1 year of the index date or were diagnosed with ONJ within 6 months of the index date. Participants documented as having malignant neoplasm or Paget's disease or patients prescribed SERM or calcitonin between 2011 and 2016 were excluded. Ultimately, 329,852 participants were selected in the BP user group. The control group was defined as participants who did not have any prescriptions for BPs between January 1, 2011, and December 31, 2016. We included patients prescribed SERM (raloxifene) or calcitonin at baseline or during the follow-up period in the control group. Therefore, the control group included untreated or raloxifene or calcitonin users. Exclusion criteria were the same as in the BP group and 421,898 participants were identified in the control group. After 1:1 matching for age and sex, 164,926 BP users and 164,926 non-BP users were included in this study (Fig. 1). The index date was defined as the first date of BP prescription in the BP group or the first date of osteoporosis diagnosis using ICD-10 codes in the control group. Follow-up lasted from the index date until ONJ occurred, the patient died, or the study ended (December 31, 2016). This study was approved by the Institutional Review Board of Wonkwang University Sanbon Hospital (IRB No. WMCSB 201706–64).

2.2. Medical risk factors

Height and body weight were measured with the subjects wearing light clothing. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2) and stratified into four categories: underweight (BMI < 18.5 kg/m^2), normal (BMI = 18.5–22.9 kg/m^2), overweight (BMI = 23.0–24.9 kg/m^2), and obese (BMI ≥ 25.0 kg/m^2). Smoking was considered positive if the participants had ever smoked tobacco. The consumption of five or more units of alcohol per day for men and three or more units per day for women was considered high alcohol intake. Comorbid chronic diseases were evaluated within 12 months before the index date. Chronic diseases in this study included diabetes, hypertension, dyslipidemia, rheumatoid arthritis, chronic renal failure, myocardial infarction, heart failure, Parkinson's disease, stroke, Alzheimer's disease, liver cirrhosis, pancreatitis, systemic lupus erythematosus, and hypoparathyroidism. Tooth extraction, dental implant, gingivitis, and periodontal disease were assessed using ICD-10 codes from the index date to 2016. Glucocorticoid use was defined as having a prescription for more than 90 days during the baseline and follow-up periods. Use of angiogenesis inhibitors was defined as having a prescription at least one time from the index date to 2016.

2.3. BP subgroup

The BPs included in this study were alendronate, risedronate, ibandronate, and zoledronic acid. A patient who took at least one prescription during the baseline period was considered a BP user. A new user was defined as a subject who had not been prescribed any BPs during the year prior to the index date. We further divided the BP group according to the administered route (oral, intravenous, both), class of

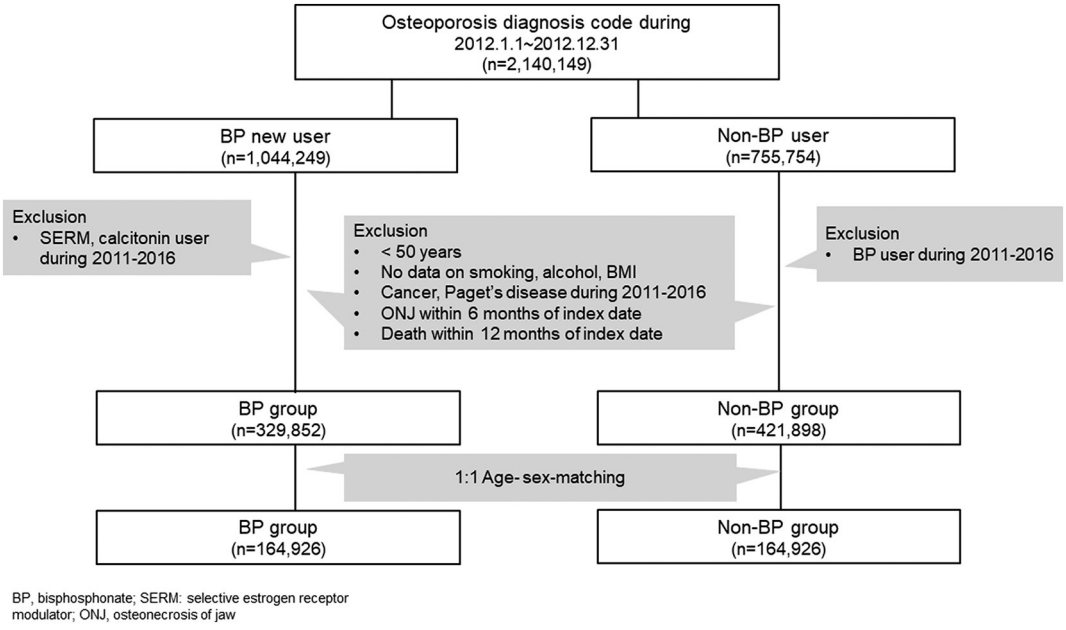

Fig. 1. Flow diagram of study participant selection.

BP (alendronate, risedronate, ibandronate, zoledronic acid, pamidronate only, BP switch), or cumulative dose of BPs (< 365, 365–729,730–1094, ≥1095) using defined daily doses (DDDs) proposed by the WHO. The drug usages in DDDs of bisphosphonates were calculated by multiplying number of items issued with amount of drug per item divided by DDD.

2.4. Study outcomes

ONJ was identified based on selected ICD-10 codes, use of antibiotics, and related-procedure codes. The diagnosis codes of ONJ were K10.2 (inflammatory condition of the jaw) or M87.1 (osteonecrosis due to drugs). Use of broad-spectrum antibiotics was considered as one of factor for possible ONJ cases. Related dental procedure codes included alveolectomy, sequestrectomy, incision and drainage, or partial resection of the maxilla or mandible. Only cases with persistent diagnosis records longer than 8 weeks (at least two visits within 3 months with the diagnosis of ONJ), antibiotic codes (more than two times), and procedure codes (more than one time) were defined as possible ONJ cases.

2.5. Statistical analyses

The baseline characteristics of the BP group and the control group were compared using the chi-square test. The incidence rates of ONJ were calculated for the 4-year follow-up period. The Cox proportional hazards model was used to determine hazard ratios (HRs) and 95% confidence intervals (CIs) after adjusting for confounding variables. Confounders included age, sex, BMI, smoking, osteoporotic fracture, dental disease, glucocorticoid use, use of angiogenesis inhibitors, and co-morbid diseases. Propensity score-matched control groups were used to generate Kaplan-Meier curves to present event rates and time-to-event curves. SAS for Windows version 9.1 (SAS Institute, Inc., Cary, NC, USA) was used to conduct the statistical tests. *P*-values < 0.05 indicated statistical significance.

3. Results

3.1. Baseline characteristics of study participants

Table 1 shows the demographic and clinical characteristics of the participants. The frequencies of the matched variables including age and sex were the same in both groups. There were more obese patients in the control group, whereas the BP group had more patients with low and normal-range BMI. The control group was more likely to have a history of diabetes, hypertension, dyslipidemia, and rheumatoid arthritis. The incidences of use of glucocorticoid and angiogenesis inhibitors were similar between the groups.

3.2. Incidence and risk for ONJ in BP and control groups

We identified 166 cases of ONJ in the BP group and 55 cases in the control group during the 4-year follow-up period. The demographic and clinical characteristics of ONJ patients in the control and BP group were similar (Supp Table 1). The cumulative incidence rates were 20.9 and 6.9 per 100,000 person-years in the BP and control groups, respectively (Table 2). Time to onset of ONJ in the BP and control groups was explored using Kaplan-Meier survival analyses. The survival curves depicted a higher incidence in the BP group than in the control group during the follow-up period (*P*-value for log-rank test < 0.0001) (Fig. 2). BP users had a significantly higher risk for ONJ compared to the controls after adjusting for multiple variables (adjusted HR 3.72; 95% CI, 2.70–5.11, *P* value < 0.0001) (Table 3).

3.3. Clinical risk factors for ONJ occurrence

To identify clinical risk factors for ONJ, Cox proportional hazards regression analyses were performed. Age was a significant risk factor; compared to patients aged 50–59 years, adjusted HRs for ONJ were 2.31 (95% CI 1.44–3.69) for the 70–79 years age group and 2.96 (95% CI, 1.59–5.48) for patients older than 80 years (Table 3). Low BMI (< 18.5) was associated with a higher risk for ONJ compared to the normal or high BMI group. Tooth extraction showed the highest risk factor for ONJ among clinical risk factors (HR 9.85, 95% CI 6.03–16.08). In addition, gingivitis and periodontal disease were significantly associated with increased risk for incident ONJ (HR 4.78, 95% CI 1.71–13.35). Patients with diabetes, hypertension, and rheumatoid arthritis were at higher risk for ONJ compared to those without these comorbidities. Interestingly, angiogenic inhibitors were significantly associated with ONJ (HR 10.11, 95% CI 1.41–72.40) (Table 3).

3.4. Risk for ONJ according to BP subgroup

We further examined ONJ risk according to BP cumulative dose subgroups among only BP users (DDD < 365 vs. 365–729 vs. 730–1094 vs. ≥1095). Compared to BP users with DDD < 365, the adjusted HRs for ONJ were 2.77 (95% CI, 1.79–4.27) for BP users with DDD 365–729, 3.69 (95% CI, 2.35–5.81) for BP users with DDD 729–1094, and 2.21 (95% CI, 1.35–3.63) for BP users with DDD ≥1095 (Table 4). There was no difference in ONJ risk according to the administration route of BP or BP classification (Table 4).

4. Discussion

4.1. Major findings

This cohort study using the nationwide database found a significant association between BP use and the risk for ONJ among the osteoporosis population aged over 50 in Korea (HR 3.72; 95% CI, 2.70–5.11). The incidence of possible ONJ was 21 per 100,000 person-years in bisphosphonate users, which is within the range of previous reports. Moreover, a higher risk for ONJ in patients receiving higher cumulative doses of BP was observed. We also found that old age, diabetes, hypertension, rheumatoid arthritis, and dental factors such as tooth extraction and periodontal disease were independent risk factors for ONJ irrespective of BP use.

4.2. Incidence of ONJ in BP users

Prospective cohort data evaluating the incidence of ONJ in the osteoporosis patient population are limited. Published data evaluating the epidemiology of ONJ have largely been obtained from case series, retrospective observational studies, and retrospective cohort studies such as insurance claims data. Lo et al. [18] provided a reliable example of the incidence of ONJ. They surveyed 13,946 patients who had received chronic oral BP therapy in the Kaiser Permanente of Northern California database and found possible ONJ cases. Then these possible ONJ cases were confirmed by oral medicine specialists or dental records according to the American Association of Oral and Maxillofacial Surgeons (AAOMS) criteria and incidence was estimated at 28 per 100,000 person-years in adults aged older than 21 years. It is not possible to confirm possible ONJ cases in this study using claim data, so incidence rates vary depending on the algorithm identifying possible ONJ across studies. Tennis et al. [9] showed that in the osteoporosis cohort, age- and sex-standardized incidences of ONJ using ICD code was 15 per 100,000 person-years among those who used oral bisphosphonates. Lin et al. [15] investigated the incidence of ONJ (defined by ICD 9, AAOMS criteria duration, and antibiotics use) in patients receiving oral alendronate for osteoporosis treatment from 2003 to 2007 using Taiwan

Table 1
Clinical characteristics of the control and bisphosphonate groups at baseline or follow-up.

Variables	Characteristics	Control group		Bisphosphonate group	
		N = 164,926		N = 164,926	
Sex	Women	150,912	(91.5)	150,912	(91.5)
	Men	14,014	(8.5)	14,014	(8.5)
Age group	50–59 years	35,376	(21.5)	35,376	(21.5)
	60–69 years	63,350	(38.4)	63,350	(38.4)
	70–79 years	55,941	(33.9)	55,941	(33.9)
	≥80 years	10,259	(6.2)	10,259	(6.2)
BMI group	< 18.5 kg/m^2	3792	(2.3)	6206	(3.8)
	18.5–22.9 kg/m^2	53,967	(32.7)	64,455	(39.1)
	23.0–24.9 kg/m^2	42,665	(25.9)	41,935	(25.4)
	≥25.0 kg/m^2	64,502	(39.1)	52,330	(31.7)
Osteoporotic fracture[a]		14,844	(9.0)	26,704	(16.2)
Smoking status	Never smoker	155,658	(94.4)	156,504	(94.9)
	Smoker	9268	(5.6)	8422	(5.1)
High alcohol intake[b]		5711	(5.6)	6358	(3.9)
Dental procedure[c]	Tooth extraction	72,623	(44.0)	68,735	(41.7)
	Dental implant	9438	(5.7)	8538	(5.2)
	Gingivitis & periodontal disease	130,274	(79.0)	124,932	(75.8)
Co-administered agents	Glucocorticoid[d]	15,371	(9.3)	15,694	(9.5)
	Angiogenic inhibitor[e]	130	(0.1)	104	(0.1)
Comorbidity[f]	Diabetes	28,400	(17.2)	22,370	(13.6)
	Hypertension	70,771	(42.9)	62,320	(37.8)
	Dyslipidemia	34,529	(20.9)	30,235	(18.3)
	Rheumatoid arthritis	1981	(1.2)	1220	(0.7)
	Chronic renal failure	1033	(0.6)	556	(0.3)
	Myocardial infarction	406	(0.2)	405	(0.2)
	Heart failure	1770	(1.1)	2072	(1.3)
	Parkinson's disease	1035	(0.6)	1236	(0.7)
	Stroke	6250	(3.8)	6611	(4.0)
	Alzheimer's or other dementia	2862	(1.7)	2811	(1.7)
	Liver cirrhosis	545	(0.3)	527	(0.3)
	Pancreatitis	206	(0.1)	215	(0.1)
	Systematic lupus erythematosus	111	(0.1)	87	(0.1)
	hypoparathyroidism	111	(0.1)	36	(0.0)
Administered route of BP	Oral BP			126,293	(76.6)
	Intravenous BP			8601	(5.2)
	Both			30,032	(18.2)
Duration of BP	< 365 days			86,271	(52.3)
	365–729 days			32,538	(19.7)
	730–1094 days			21,064	(12.8)
	≥1095 days			25,053	(15.2)
Classification of BP	Alendronate only			40,250	(24.4)
	Risedronate only			38,189	(23.1)
	Ibandronate oral only			3983	(2.4)
	Ibandronate intravenous only			4978	(3.0)
	Zoledronic acid intravenous only			274	(0.2)
	Pamidronate intravenous only			1776	(1.1)
	BP switch[g]			75,476	(45.8)

Values given are number (%) unless indicated otherwise. BP, bisphosphonate; BMI, body mass index.
[a] Subjects with osteoporotic fracture after the baseline and follow-up period.
[b] Men who drink more than five units or women who drink more than three units per day.
[c] Subjects with dental procedure after the baseline and follow-up period.
[d] Subjects who had 90 or more days of clinical care with 5 mg or more oral steroid prescription after the baseline and follow-up period.
[e] Subjects who visited the clinic at least once with angiogenesis inhibitor prescription after the baseline and follow-up period.
[f] Subjects with known comorbidities at baseline assessment.
[g] Subjects who treated with one class of BP and then switched to another class of BP during follow-up.

claim data. They found 25 potential ONJ cases in 18,030 alendronate users during a 6-year follow-up period and estimated an incidence of 82 per 100,000 person-years. This incidence rate in a Taiwanese population is much higher than that in our study (82 vs. 25) per 100,000 person-years. In our study, the procedure code was added to the operational definition of ONJ; therefore, it is difficult to directly compare the results. Because there is no specific ICD code for ONJ and no verified claim-based algorithms, the definition of our study with the addition of dental procedure codes seems to be more suitable for estimating the clinically significant occurrence of ONJ. Although we could not confirm the cases due to lack of examination data, we adopted the AAOMS criteria and found that the incidence rate of possible ONJ cases in Korean BP users was similar to that of Lo et al. [18].

4.3. Association between BP and ONJ in osteoporosis participants

With regard to the association between BP and ONJ among the osteoporosis population, most studies have reported a positive association. Barasch et al. [19] showed that BP use was strongly associated with ONJ occurrence in participants without cancer (OR 7.2; 95% CI 2.1–24.7) in a case-control study based on large networks of dental practices. They also noted that the risk for ONJ increased after 5 years of BP treatment in non-cancer patients, although they had a recall bias for BP duration. An Italian study [20] also found an adjusted odds ratio

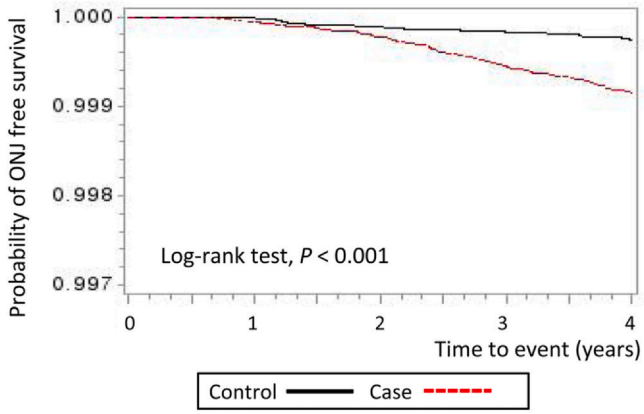

Fig. 2. Kaplan-Meier curves comparing time to osteonecrosis of the jaw (ONJ) in the bisphosphonate (BP) and control groups.

of 2.8 for ONJ in current BP users compared to never BP users. In their analyses, a longer exposure to oral BPs showed a trend toward an increased risk for ONJ (OR, 4.2; 95% CI, 0.5–41.4), although, due to the small sample size, it did not reach statistical significance. A case-control study in Korea [17] noted the association between BP exposure and ONJ in patients with osteoporosis. They assessed bisphosphonate exposure over 2 years prior to ONJ (defined as the index date) using cumulative drug exposure (CDE). The odds of ONJ was five times higher in patients with 1.5 years < CDE ≤ 2 years compared to those with 0 < CDE ≤ 0.5 years. Consistent with these studies, we found a significant association between BP use and the risk for ONJ among the osteoporosis population (HR 3.72; 95% CI, 2.70–5.11) and higher risk for ONJ in patients receiving higher cumulative doses of bisphosphonate. The risk for ONJ was 2.8-fold and 3.0-fold higher in BP users with DDD 365–729 and DDD ≥ 730 compared to BP users with DDD < 365. In our study, we used DDD to assess the duration of treatment. Considering the persistence of bisphosphonates, the actual duration of drug exposure could be longer than their estimated DDD.

4.4. Other risk factors for ONJ in osteoporosis patients

Previously described risk factors for ONJ, such as intravenous BP (both dose of BP and duration), advanced age [21–23], glucocorticoid therapy [21], periodontal disease [24], diabetes [25], denture use [26–28], and renal dialysis [21], are based on studies in oncology populations. Few studies have reported risk factors such as dental extraction or diabetes for ONJ development in osteoporosis patients [16,19]. Therefore, it is important to assess whether the risk factors for ONJ among cancer patients also increase the risk in osteoporosis populations receiving low-dose BPs. Age was an independent risk factor for ONJ development in our study. Patients older than 80 years of age had a three-fold higher risk for ONJ compared to relatively younger patients aged 50–59 years. Local dental factors including tooth extraction (HR 9.85) and periodontal disease (HR 4.78) significantly increased the risk for ONJ in patients with osteoporosis. This is consistent with Barasch et al. [19]. Among co-morbid diseases, rheumatoid arthritis (HR 7.39), diabetes (HR 1.42), and hypertension (HR 1.43) were independent risk factors for ONJ. On the other hand, steroid use did not have a significant effect on the development of ONJ in our study. We believe that many of the chronic steroid users may be rheumatoid arthritis patients, and the effects of steroid use could be attenuated in Cox proportional hazards regression analyses. It remains unclear whether rheumatoid arthritis itself is a risk factor for ONJ development or whether medications such as steroids or immunosuppressive agents for rheumatoid arthritis management play a role in the development of ONJ in patients with osteoporosis [29–31]. Similarly, some previous studies have found that diabetes and hypertension are potentially correlated with ONJ [16,32]. In addition, a well-known risk factor, angiogenesis inhibitors, increased the risk for ONJ in all participants (HR 10.12), and poses a greater risk than bisphosphonates (HR 3.72). However, the number of angiogenesis inhibitor users was very small, so the HR for ONJ in angiogenesis inhibitor users had a wide confidence interval, although with a significant range. Therefore, further study on a large number of patients is needed to clarify the association between angiogenesis inhibitors and ONJ.

4.5. Strengths and limitations

This study had several strengths and weaknesses. We used the KNHIS database, which covers nearly the entire Korean population. Therefore, we captured nearly all subjects who were newly initiating BP among osteoporosis participants in 2012 and were followed-up over 4 years. Thus, this is the first large-scale study determining the incidence of possible ONJ in Korea. The main limitation was that we could not confirm cases of ONJ due to our study design using medical claims data. However, we defined ONJ using ICD-10 codes (osteonecrosis due to drugs, M87.1, or inflammatory conditions of the jaw, K10.2) based on definitions used in a Swedish study [33]. The authors validated potential cases of ONJ by reviewing medical records and found that osteonecrosis due to drugs (M87.1) had the highest positive predictive value (PPV) (83%; 95% CI, 36–100%). Inflammatory conditions of the jaw (K10.2) also had a low PPV (16%). Other possible ONJ codes such as periapical abscess with sinus and alveolitis of the jaws had a PPV of 0. Because conservative broad-spectrum antibiotics are the main therapy for ONJ, we considered ONJ cases to only be those that received antibiotics treatment. A study conducted in Korea also noted that all validated ONJ cases had been prescribed antibiotics [34]. However, some patients with stage 1 ONJ who do not need antibiotics could be excluded in our study. We further restricted possible ONJ to those with a persistent diagnosis record longer than 8 weeks, and reported dental procedure codes such as alveolectomy or sequestrectomy for the treatment of ONJ. Therefore, the incidence of ONJ in our study included mostly stage 2 and 3 cases and may be lower than the actual incidence. Second, according to the KSBMR osteoporosis fact sheet, more than 50% of patients discontinue treatment medication within a year in Korea. Thus, we could not select continuous BP users and we subdivided patients according to the cumulative dose of BPs. Lastly, due to relatively low numbers of SERM or calcitonin users and probable

Table 2
Incidence rate of ONJ over a 4-year follow-up period in the bisphosphonate and control group.

Variables	Group	Event	Patient number	Followed person-years	Incidence rate per 100,000 person-years	95% confidence interval
Control vs. BP	Control	55	164,926	791,921	6.94	6.93–6.95
	BP group	166	164,926	796,311	20.85	20.83–20.86
Sex	Male	15	28,028	125,664	11.94	11.92–11.96
	Female	206	301,824	1,462,617	14.08	14.07–14.09
Age group	50–59 years	23	70,752	351,659	6.54	6.53–6.55
	60–69 years	65	126,700	624,208	10.41	10.41–10.42
	70–79 years	112	111,882	529,593	16.58	16.54–16.61
	≥80 years	21	20,518	82,821	26.39	26.30–26.49

Table 3
Association between hazard ratio and risk factors based in multivariate Cox model.

Variables	Subgroup	Number of ONJ case/number of subgroup patients	aHR[a]	95% CI	*P*-value
Control/BP group	Control	55/164,871	1.0 (Ref)		
	BP group	166/164,871	3.72	2.70–5.11	< 0.001
Sex	Male	16/28,028	1.0 (Ref)		
	Female	205/301,824	1.48	0.86–2.56	0.156
Age group	50–59 years	23/70,752	1.0 (Ref)		
	60–69 years	65/126,700	1.28	0.79–2.07	0.315
	70–79 years	112/111,882	2.31	1.44–3.69	< 0.001
	≥80 years	21/20,518	2.96	1.59–5.48	< 0.001
BMI	< 18.5 kg/m^2	11/9998	1.0 (Ref)		
	18.5–22.9 kg/m^2	84/118,422	0.67	0.35–1.26	0.221
	23.0–24.9 kg/m^2	59/84,660	0.63	0.33–1.21	0.170
	≥25.0 kg/m^2	67/116,832	0.48	0.25–0.93	0.029
Smoking	Smoking	6/12,069	0.75	0.31–1.76	0.508
Osteoporotic fracture		53/41,548	1.56	1.13–2.14	0.005
Dental disease	Tooth extraction	202/141,358	9.85	6.03–16.08	< 0.001
	Dental implant	16/17,976	0.59	0.35–0.98	0.042
	Gingivitis & periodontal disease	217/255,206	4.78	1.71–13.35	0.002
Co-administered agents	Glucocorticoid	31/31,065	1.01	0.66–1.55	0.946
	Angiogenesis inhibitors	1/234	10.11	1.41–72.40	0.021
Co-morbid disease	Diabetes	51/50,770	1.42	1.02–1.95	0.033
	Hypertension	115/133,091	1.43	1.07–1.88	0.012
	Rheumatoid arthritis	13/3201	7.39	3.90–14.00	< 0.001
	Renal failure	2/1589	1.92	0.47–7.78	0.359
	Heart failure	3/3842	0.87	0.27–2.72	0.809
	Stroke	8/12,861	0.70	0.34–1.43	0.337
	Parkinson's disease	2/2271	0.91	0.22–3.71	0.903

aHR, adjusted hazard ratio; BP, bisphosphonate; CI, confidence interval; BMI, body mass index.
The aHR (95% CI) and *P*-values were obtained using a Cox proportional hazards regression analysis.
[a] Adjusted for age, sex, BMI, smoking, osteoporotic fracture, dental disease, glucocorticoid use, use of angiogenesis inhibitors, and co-morbid diseases.

selection bias, the age and sex-matched control group was not limited to SERM or calcitonin users only but selected from all non-BP treated patients. Presumably the control group participants, including untreated participants, have less severe osteoporosis than those in the BP group. Although we have no information on bone mineral density (BMD), it may have an impact on the risk of ONJ in both groups.

5. Conclusions

To the best of our knowledge, this was the first study to evaluate the incidence of ONJ among osteoporosis populations using a nationwide cohort in Korea. Our study confirmed previous findings in which ONJ incidence was extremely low in osteoporosis patients receiving BPs. However, our results suggest that an increased cumulative dose of BPs could increase the risk for ONJ in Asian populations with osteoporosis. Moreover, age > 70 years, dental extraction, and rheumatoid arthritis were significant clinical risk factors for ONJ, as well as bisphosphonate use. Future studies using prospectively collected patient medical records may provide more accurate information on the risk and prognosis of ONJ.

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Table 4
Multivariate-adjusted hazard ratios (HRs) for ONJ in the bisphosphonate group.

Variables	Subgroup	Number of ONJ case/number of subgroup patients	aHR	95% CI	*P*-value
Cumulative dose of BP	< 365	42/86,271	1.0 (Ref)		
	365–729	49/32,538	2.77	1.79–4.27	< 0.001
	730–1094	44/21,064	3.69	2.35–5.81	< 0.001
	≥1095	31/25,053	2.21	1.35–3.63	0.002
Administration type of BP	Oral	114/126,293	1.0 (Ref)		
	Intravenous	7/8601	1.39	0.51–3.80	0.519
	Both	45/30,032	0.98	0.59–1.30	0.516
Classification of BP	Alendronate only	31/40,250	1.0 (Ref)		
	Risedronate only	20/38,189	0.62	0.36–1.10	0.101
	Ibandronate oral only	3/3983	0.93	0.28–3.06	0.908
	Ibandronate intravenous only	2/4978	0.30	0.05–1.73	0.178
	Zoledronate intravenous only	0/274			
	Pamidronate intravenous only	1/1776	0.42	0.05–3.85	0.445
	BP switch[a]	109/75,476	1.92	0.69–1.72	0.705

aHR, adjusted hazard ratio; BP, bisphosphonate; CI, confidence interval.
The aHR (95% CI) and *P*-values were obtained using a Cox proportional hazards regression analysis.
[a] Subjects who treated with one class of BP and then switched to another class of BP during follow-up.

administration. **Tae-Young Kim:** Methodology, Data curation. **Yong-Chan Ha:** Resources, Methodology. **Sunmee Jang:** Formal analysis, Software, Data curation. **Ha Young Kim:** Conceptualization, Methodology, Writing - review & editing.

Declaration of competing interest

The author(s) declare no conflict of interest with NHIS.

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