J Periodontal Implant Sci. 2024 Apr;54(2):65-74
https://doi.org/10.5051/jpis.2300120006
pISSN 2093-2278·eISSN 2093-2286

JPIS
Journal of Periodontal & Implant Science

Research Article
Periodontal Science

Check for updates

Pulp and periapical disease as a risk factor for osteonecrosis of the jaw: a national cohort-based study in Korea

Hyeong-Jin Baek [1], **Hyejin Lee** [2], **Jae-Ryun Lee** [2], **Jung-Hyun Park** [3], **Keun-Suh Kim** [1], **Min-Jeong Kwoen** [1], **Tae-Yeon Lee** [4], **Jin-Woo Kim** [3,*], **Hyo-Jung Lee** [1,*]

[1]Department of Periodontology, Section of Dentistry, Seoul National University Bundang Hospital, Seongnam, Korea
[2]Department of Family Medicine, Seoul National University Bundang Hospital, Seongnam, Korea
[3]Department of Oral and Maxillofacial Surgery, Research Institute for Intractable Osteonecrosis of the Jaw, College of Medicine, Ewha Womans University, Seoul, Korea
[4]Department of Conservative Dentistry, Yeouido ST. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

OPEN ACCESS

Received: Jun 17, 2022
Revised: Mar 6, 2023
Accepted: Apr 3, 2023
Published online: Jun 16, 2023

***Correspondence:**
Jin-Woo Kim
Department of Oral and Maxillofacial Surgery, Research Institute for Intractable Osteonecrosis of the Jaw, College of Medicine, Ewha Womans University, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Korea.
Email: jinu600@gmail.com
Tel: +82-2-2650-2720
Fax: +82-2-2650-2754

Hyo-Jung Lee
Department of Periodontology, Section of Dentistry, Seoul National University Bundang Hospital, 82 Gumi-ro, 173beon-gil, Bundang-gu, Seongnam 13620, Korea.
Email: periolee@gmail.com
Tel: +82-31-787-7547, 2780
Fax: +82-31-787-4068

ORCID iDs
Hyeong-Jin Baek
https://orcid.org/0000-0002-5378-9784
Hyejin Lee
https://orcid.org/0000-0001-5279-340X
Jae-Ryun Lee
https://orcid.org/0000-0001-6776-3406
Jung-Hyun Park
https://orcid.org/0000-0002-5297-5059

ABSTRACT

Purpose: This longitudinal cohort study aimed to evaluate the relationship between osteonecrosis of the jaw and pulp and periapical disease in patients who were administered bisphosphonates.
Methods: Using data from a nationwide cohort, we examined the association among dental caries, pulp and periapical disease, and osteonecrosis of the jaw in women aged >50 years who received bisphosphonates for more than 1 year between 2002 and 2015. Because of ambiguities in the diagnosis of osteonecrosis of the jaw in population-based data, we operationally defined and categorized the condition into established and potential osteonecrosis of the jaw.
Results: Pulp and periapical disease significantly increased the development of both established and potential osteonecrosis of the jaw (hazard ratio, 2.21; 95% confidence interval, 1.40–3.48; and hazard ratio, 2.22; 95% confidence interval, 1.65–2.98, respectively). Root canal treatment did not have any influence on the development of osteonecrosis of the jaw.
Conclusions: Pulp and periapical disease may be a major risk factor for osteonecrosis of the jaw. The study findings suggest that patients should undergo regular dental examinations to detect pulp and periapical disease before or during the administration of bisphosphonates and that root canal treatment should be considered to decrease the risk of osteonecrosis of the jaw.

Keywords: Bisphosphonates; Bisphosphonate-associated osteonecrosis of the jaw; Inflammation; Periapical disease; Pulpitis; Root canal therapy

INTRODUCTION

Bisphosphonates (BPs), which are analogs of pyrophosphate, are inhibitors of osteoclast-mediated bone resorption that are used to treat metabolic and pathologic bone diseases such as osteoporosis, Paget's disease, and metastatic malignant disease [1]. Despite being beneficial in the treatment of cancer and metabolic bone disease, the use of BPs can result in osteonecrosis of the jaw (ONJ) [2,3]. Even though ONJ is uncommon, its severe consequences

Keun-Suh Kim
https://orcid.org/0000-0002-5986-4810
Min-Jeong Kwoen
https://orcid.org/0000-0002-0246-4090
Tae-Yeon Lee
https://orcid.org/0000-0002-2659-739X
Jin-Woo Kim
https://orcid.org/0000-0002-1672-5730
Hyo-Jung Lee
https://orcid.org/0000-0002-0439-7389

Funding

This work was supported by Seoul National University Bundang Hospital (grant numbers 02-2018-042 and 06-2020-020) and the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (grant number 2020R1A2C4001842).

Conflict of Interest

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

Availability of Data

All data used in this study are publicly available upon request from the National Health Insurance Service of Korea (https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do).

Author Contributions

Conceptualization: Hyeong-Jin Baek, Hyo-Jung Lee, Jin-Woo Kim; Data Curation: Hyeong-Jin Baek, Hyejin Lee, Jae-Ryun Lee, Jung-Hyun Park, Keun-Suh Kim, Min-Jeong Kwoen, Tae-Yeon Lee; Formal Analysis: Hyeong-Jin Baek, Hyejin Lee, Jae-Ryun Lee; Investigation: Hyejin Lee, Jae-Ryun Lee, Jung-Hyun Park; Methodology: Hyeong-Jin Baek, Hyejin Lee, Jung-Hyun Park, Keun-Suh Kim, Tae-Yeon Lee; Software: Jae-Ryun Lee; Validation: Hyo-Jung Lee, Jin-Woo Kim; Project Administration: Hyo-Jung Lee, Jin-Woo Kim; Writing - original draft: Hyeong-Jin Baek; Writing - review & editing: Hyejin Lee, Jae-Ryun Lee, Jung-Hyun Park, Keun-Suh Kim, Min-Jeong Kwoen, Tae-Yeon Lee, Hyo-Jung Lee, Jin-Woo Kim.

can have a negative impact on patients' quality of life [4]. Inhibition of angiogenesis, suppression of bone turnover, infection/inflammation, soft tissue toxicity, and immune-related mechanisms are among the possible pathophysiological aspects of ONJ that have received attention from researchers [5].

Dental procedures can cause ONJ, with tooth extraction inducing almost 50% of ONJ cases [6-9]. Therefore, most studies on ONJ have concentrated on tooth extraction, while ignoring the implications of other dental risks. Pathologic disorders are affected by delayed local wound healing or infection, which may have an impact on ONJ [10-16]. Dental caries and pulp and periapical disease, which are prevalent infectious dental illnesses, can lead to jaw bone inflammation and local catabolic consequences [17]. Inflammation plays an important role in the pathophysiology of ONJ related to osteoimmunology and is a key risk factor for ONJ [18,19]. Pulp and periapical disease may lead to tooth extraction or periodontitis, which are considered risk factors for ONJ. Therefore, pulp and periapical disease-induced inflammation may have a direct or indirect impact on the development of ONJ. However, its role in ONJ remains to be clarified.

Root canal treatment is performed to disinfect the pulp, resolve pulpal inflammation and periapical disease, and prevent further microbial invasion of periapical tissue. According to Vahtsevanos et al., [20] root canal treatment does not increase the risk of ONJ; nonetheless, the relationship between root canal treatment and ONJ remains unclear.

Previous research has shown associations among BP use, ONJ, and pulp and periapical disease [18,19]. However, those investigations using ONJ animal models were unable to establish a relationship between pulp and periapical disease and ONJ. Using a nationally representative cohort database in Korea, this study aimed to confirm the association between ONJ and pulp and periapical disease in patients receiving BPs.

MATERIALS AND METHODS

Data source

The National Health Insurance Service (NHIS) is the sole insurance provider in Korea; it is managed and supported by the Korean government, and it covers almost 97% of the Korean population. Health screening of the entire population is conducted by the NHIS every year or every other year depending on the age and occupation of those covered by insurance, and the results are released to the public [21]. We conducted a longitudinal cohort study using the general health screening database of the NHIS. The cohort comprised random samples representing approximately 510,000 individuals (aged 40–79 years), equivalent to 10% of the total population who were offered health examinations [21]. Data were extracted by sampling high-demand information from the national health insurance database. We used the health examination cohort database to analyze the medication use and examination results. Data from January 1, 2002 to December 31, 2015 were extracted.

Ethical approval of studies and informed consent

This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB No. X-2004/606-905) and conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because this retrospective study used anonymized data.

Study population

We extracted diagnosis codes from the NHIS database using Korean Standard Classification of Diseases and Causes of Death-7 (KCD-7) codes, a modified version of the 10th edition of the International Classification of Diseases and Related Health Problems. The treatment codes were based on the treatment and surgery fee codes in Korea.

Women who fulfilled the following inclusion criteria were included in the study: i) aged >50 years, ii) taking BPs for at least a year, and iii) medication adherence of >0% during the year (or a medication possession ratio >80%). Both oral and injectable methods were covered. Alendronate, ibandronate, risedronate, pamidronate, and zoledronate were the BPs examined. The index date was set as January 1, 2009.

The onset of ONJ could be affected by underlying disorders or some other contributing elements, and the frequency of ONJ is expected to be significantly higher in patients who have cancer or other bone diseases that require BP therapy. Therefore, patients taking high doses of BPs for cancer treatment were not included. Additionally, patients who died prior to the index date were not included in the study.

Definitions of ONJ, pulp and periapical disease, and dental caries

ONJ was diagnosed using a combination of KCD-7 and therapy codes. First, we divided ONJ into established ONJ and potential ONJ. Established ONJ was defined as individuals with 1 of the following criteria: osteonecrosis due to drugs, multiple sites (M87.1); inflammatory conditions of jaws (K10.2) as a diagnosis; 1 of the treatments was also registered; or both diagnoses were registered after the index date (**Supplementary Table 1**).

Potential ONJ is a broad concept encompassing all aspects of suspected ONJ, such as diagnosis and treatment. The following diagnosis and treatment codes were considered as potential ONJ: osteonecrosis due to drugs, multiple sites (M87.1, 87.3, 87.8, and 87.9); inflammatory conditions of jaws (K10.2, 10.3 10.8); acute hematogenous osteomyelitis, multiple sites (M86); and disorders of teeth and supporting structures, unspecified (K08.9) (**Supplementary Table 2**).

Pulp and periapical disease and dental caries were defined as the presence of the diagnosis code after the index date (**Supplementary Table 3**). Root canal treatment was defined as the existence of a root canal treatment code recorded after the diagnosis of pulp and periapical disease, dental caries, or ONJ (**Supplementary Table 4**).

Data collection

Patient variables such as the baseline year, age, income level, and disability were included. The National Statistical Office uses the income quintile to classify all families in Korea into 10 levels, with each level reflecting a 10% division based on the quarterly income level. The first quintile has the lowest income levels. The income increases as the quintile rises. There were 5 stages in the analysis. Disability was categorized as present or absent (**Table 1**). The prevalence of diseases was defined according to the presence of hypertension (I10, I15), diabetes (E10, E118, E119, E13, E149), hyperlipidemia (E78), myocardial infarction (I21, I22), stroke (I60–63), or anemia (D46, D50-53, D55-64, D74) (**Table 1**).

https://doi.org/10.5051/jpis.2300120006

Table 1. Characteristics of the patients with pulp and periapical disease and dental caries

Characteristics	Pulp and periapical disease (–) (n=22,963)	Pulp and periapical disease (+) (n=4,205)	*P* value	Dental caries (–) (n=23,755)	Dental caries (+) (n=3,413)	*P* value
Established ONJ	69 (0.30)	26 (0.62)	0.002	80 (0.34)	15 (0.44)	0.426
Potential ONJ	158 (0.69)	62 (1.47)	<0.001	190 (0.80)	30 (0.88)	0.704
Baseline year			0.656			0.273
2009	4,373 (19.04)	828 (19.69)		4,593 (19.33)	608 (17.81)	
2010	2,230 (9.71)	427 (10.15)		2,333 (9.82)	324 (9.49)	
2011	4,190 (18.25)	757 (18.00)		4,322 (18.19)	625 (18.31)	
2012	4,204 (18.31)	750 (17.84)		4,324 (18.20)	630 (18.46)	
2013	4,337 (18.89)	764 (18.17)		4,426 (18.63)	675 (19.78)	
2014				3,757 (15.82)	551 (16.14)	
Age at baseline	67.7±7.9	67.1±7.3	<0.001	67.7±7.8	66.4±7.5	<0.001
Distribution			<0.001			<0.001
50–59	3,999 (17.41)	708 (16.84)		4,017 (16.91)	690 (20.22)	
60–69	9,196 (40.05)	1,872 (44.52)		9,553 (40.21)	1,515 (44.39)	
70–79	8,279 (36.05)	1,446 (34.39)		8,658 (36.45)	1,067 (31.26)	
≥80	1,489 (6.48)	179 (4.26)		1,527 (6.43)	141 (4.13)	
Comorbidities						
Hypertension	11,289 (49.16)	2,052 (48.80)	0.678	11,735 (49.40)	1,606 (47.06)	0.011
Diabetes mellitus	5,386 (23.46)	1,015 (24.14)	0.348	5,608 (23.61)	793 (23.23)	0.647
Dyslipidemia	11,390 (49.60)	2,100 (49.94)	0.698	11,763 (49.52)	1,727 (50.60)	0.244
Anemia	2,826 (12.31)	546 (12.98)	0.230	2,949 (12.41)	423 (12.39)	0.995
Myocardial infarction	82 (0.36)	17 (0.40)	0.743	85 (0.36)	14 (0.41)	0.747
Stroke	1,345 (5.86)	196 (4.66)	0.002	1,369 (5.76)	172 (5.04)	0.095
Household income			0.900			0.527
Medicaid	1,034 (4.50)	188 (4.47)		1,071 (4.51)	151 (4.42)	
1st, 2nd	3,484 (15.17)	612 (14.55)		3,593 (15.13)	503 (14.74)	
3rd, 4th	2,670 (11.63)	480 (11.41)		2,769 (11.66)	381 (11.16)	
5th, 6th	3,224 (14.04)	595 (14.15)		3,351 (14.11)	468 (13.71)	
7th, 8th	4,679 (20.38)	879 (20.90)		4,818 (20.28)	740 (21.68)	
9th, 10th	7,872 (34.28)	1,451 (34.51)		8,153 (34.32)	1,170 (34.28)	
Disability			0.772			0.285
Yes	622 (2.71)	110 (2.62)		650 (2.74)	82 (2.40)	
Type of bisphosphonate						
Alendronate	11,083 (48.26)	1,995 (47.44)	0.336	11,468 (48.28)	1,610 (47.17)	0.235
Risedronate	11,478 (49.98)	2,069 (49.20)	0.360	11,853 (49.90)	1,694 (49.63)	0.788
Pamidronate	770 (3.35)	154 (3.66)	0.332	807 (3.40)	117 (3.43)	0.966
Ibandronate	5,006 (21.80)	969 (23.04)	0.077	5,184 (21.82)	791 (23.18)	0.078
Zoledronate	144 (0.63)	14 (0.33)	0.028	144 (0.61)	14 (0.41)	0.198
Bisphosphonate use history						
Cumulative bisphosphonate PDC	93.3±6.2	93.3±6.2	0.659	93.3±6.2	93.3±6.2	0.436
Distribution of cumulative bisphosphonate PDC			0.855			0.990
>90%	16,457 (71.67)	3,020 (71.82)		17,031 (71.69)	2,446 (71.67)	
80–90%	6,506 (28.33)	1,185 (28.18)		6,724 (28.31)	967 (28.33)	

Values are presented as number (%) or mean ± standard deviation. Pulp and periapical disease and dental caries were defined using the diagnosis codes in **Supplementary Table 3**. Established ONJ and potential ONJ were defined using the diagnosis codes described in the manuscript and the treatment codes in **Supplementary Tables 1** and **2**, respectively.
ONJ: osteonecrosis of the jaw, PDC: proportion of days covered.

Statistical analyses

Baseline characteristics are presented as numbers (%) for categorical variables and as mean ± standard deviations. We conducted the χ^2 test (median with interquartile range) for continuous variables, as well as the *t*-test or analysis of variance. Moreover, we adjusted the 14 years of cohort data for baseline year, age, comorbidities, income disability, type of BP administered, and cumulative proportion of days to analyze the hazard ratio (HR) of ONJ based on the prevalence of pulp and periapical disease and dental caries. Cox proportional-hazards models were used to evaluate the associations between independent variables and the occurrence of ONJ events. In addition, we calculated HRs and 95% confidence intervals

https://doi.org/10.5051/jpis.2300120006

JPIS Journal of Periodontal & Implant Science

(CIs) to evaluate these associations. Statistical significance was defined as a 2-tailed *P*-value <0.05. All statistical analyses were conducted using the R programming language (version 3.3.3; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

After excluding patients with cancer or ONJ and those who died before the index date, this study included 27,168 patients (**Figure 1**). Among them, 4,205 (15.48%) and 3,413 (12.56) patients were diagnosed with pulp and periapical disease and dental caries, respectively.

Among patients with and without pulp and periapical disease, established ONJ was diagnosed in 26 (0.62%) and 69 (0.30%), while potential ONJ was diagnosed in 62 (1.47%) and 158 (0.69%) patients, respectively. Moreover, established ONJ was present in 15 (0.44%) and 80 (0.34%) patients with and without dental caries, and potential ONJ was present in 30 (0.88%) and 190 (0.80%) patients, respectively. The significance of the difference varied depending on the diagnostic criteria. Nonetheless, pulp and periapical disease was associated with the development of both established and potential ONJ. Contrarily, the proportion of patients with established and potential ONJ was higher in the dental caries group, but no significant difference was noted (**Table 1**).

The presence of pulp and periapical disease significantly increased the risk of ONJ development compared with the absence of this disease (HR, 2.21; 95% CI, 1.40–3.48 and HR, 2.22; 95% CI, 1.65–2.98 for established and potential ONJ, respectively). However, the presence of dental caries was not significant (HR, 1.52; 95% CI, 0.87–2.64 and HR, 1.22; 95% CI, 0.83–1.79 for established and potential ONJ, respectively) (**Table 2**). We analyzed the HR of root canal treatment for ONJ development among patients with pulp and periapical disease and dental caries and did not find statistically significant results (**Table 3**).

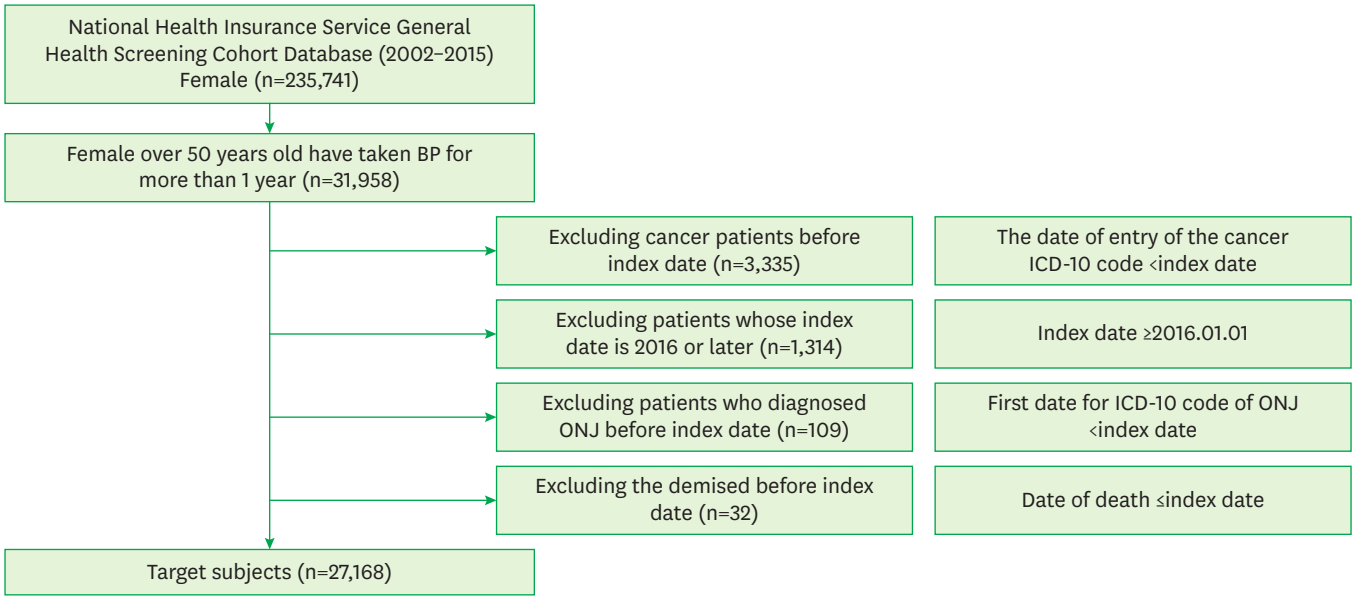

Figure 1. Flow diagram of study participant selection.
BP: bisphosphonate, ICD-10: International Classification of Diseases 10th Revision, ONJ: osteonecrosis of the jaw.

https://doi.org/10.5051/jpis.2300120006

JPIS
Journal of Periodontal & Implant Science

Table 2. Hazard ratios for ONJ development according to pulp and periapical disease and dental caries

Variables	Pulp and periapical disease	Dental caries
Established ONJ	2.21 (1.40–3.48)	1.52 (0.87–2.64)
Potential ONJ	2.22 (1.65–2.98)	1.22 (0.83–1.79)

Adjusted for baseline year, age, comorbidities, income, disability, type of bisphosphonate, and cumulative proportion of days covered.
ONJ: osteonecrosis of the jaw.

Table 3. Hazard ratios for ONJ development according to root canal treatment

Variables	Root canal treatment	
	Pulp and periapical disease	Dental caries
Established ONJ	1.38 (0.47–4.08)	2.76 (0.35–21.68)
Potential ONJ	2.28 (0.98–5.32)	1.95 (0.58–6.50)

Adjusted for baseline year, age, comorbidities, income, disability, type of bisphosphonate, and cumulative proportion of days covered. Root canal treatment was defined using the diagnosis codes in **Supplementary Table 4**.
ONJ: osteonecrosis of the jaw.

DISCUSSION

Even though tooth extraction is a significant risk factor for ONJ, the chronic inflammation induced by pulp and periapical disease, which can lead to tooth extraction, has received less attention in ONJ. BPs depress osteoclast activity, causing decreased bone remodeling. As a result, periapical radiolucent lesions in the alveolar bone are concealed in individuals using BPs. Furthermore, the morbidity of pulp and periapical disease is frequently overlooked in patients taking BPs. Therefore, research on the relationship between pulp and periapical disease and ONJ is sparse. Nevertheless, the few studies conducted on this issue—including the one by Cheong et al. [18]—have reported that the uptake of BPs increases in patients with pulp and periapical disease. Kang et al. [19] demonstrated that pulp and periapical disease with BP administration caused ONJ in mice. Those studies have limitations because they were based on ONJ animal models, but they nonetheless suggested an association between pulp and periapical disease and ONJ. We found that patients with pulp and periapical disease who received BPs for more than 1 year showed increased morbidity due to established and potential ONJ. We hypothesized that pulp and periapical disease increases the inflammation in the alveolar bone close to the root is induced. According to research using animal models, this inflammation results in an overabundance of BPs, subsequently leading to the development of ONJ [18,19].

In addition, lesions that produce inflammation, including periodontitis and pulp and periapical disease, increase the susceptibility of sites to ONJ development, although tooth extraction is undoubtedly also a risk factor for ONJ. Difficulties in analyzing or studying ONJ have led to a focus on consequent interventions. To understand the causes of ONJ and the approach to treatment, it is vital to understand how inflammation affects ONJ. Because the jaw bone changes more frequently than other peripheral bones, an increased concentration of BPs is noted in that location [15]. According to Gong et al., [22] the bone-marrow stroma of the jaw bone is more vulnerable to BPs than that of the iliac and tibial bones. Moreover, Lim et al. [23] reported that the osseous healing mechanism differs based on the site. These traits would be very important in ONJ. Therefore, it would be beneficial to comprehend the association between osteoimmunology and inflammation to treat ONJ.

We focused on the progression of dental caries, even though the development of pulp and periapical disease may be attributable to different factors, including the periapical status and pathosis [24-26]. Despite being a pulp-limited disease, dental caries causes pulp and

https://doi.org/10.5051/jpis.2300120006

periapical disease that results in chronic inflammation of the jaw bone. Inflammation is a definitive risk factor for the development of ONJ. The morbidity of ONJ in patients with dental caries was also investigated, and we found that, contrastingly, dental caries did not substantially increase the risk of ONJ. Therefore, we contend that ONJ cannot be caused by tooth pulp tissue inflammation alone.

Furthermore, untreated pulp and periapical disease can cause inflammation to extend to the adjacent periodontal tissue. This can lead to retrograde periodontitis with subsequent bone destruction, which is another risk factor for ONJ, and can exacerbate the severity of periodontal disease [27,28]. Retrograde peri-implantitis can also arise from untreated pulp and periapical disease [29-31]. For these reasons, it is necessary to treat pulp and periapical disease.

We also examined the effect of endodontic treatment for pulp and periapical disease on the risk of ONJ. Similar to the findings of Vahtsevanos et al., [20] we found that root canal therapy did not affect the risk of ONJ in cases of BP treatment. Therefore, BP deposition in pulp and periapical disease is unaffected by endodontic treatment. However, as the analysis only covered a very small number of events, this finding is difficult to interpret conclusively. Furthermore, root canal therapy may have been used to treat pulpal lesions alone or prior to the emergence of an osteolytic lesion. Our research indicates that preventive root canal therapy would be required before BP use. Additionally, a BP drug holiday would be necessary for those who need root canal therapy while taking a BP. This finding supports studies, including articles and reviews published by the American Association of Oral and Maxillofacial Surgeons, which recommend that patients be administered an anti-resorptive drug to treat or control dental disease prior to starting therapy. Moreover, individuals should continue practicing good oral hygiene even after receiving medication to lower the probability of developing ONJ [32-36].

The results of this study indicate that pulp and periapical disease is a risk factor for ONJ. In addition to osteoporosis, BPs are typically used to treat bone conditions such as Paget's disease, multiple myeloma, and tumors (e.g., breast cancer) that may metastasize to the bones. Despite excluding the aforementioned diseases in this study, the results indicate that patients should undergo routine dental examinations to detect dental caries and pulp and periapical disease, either before or while using BPs.

Other drugs that cause ONJ, such anti-angiogenic agents, are another issue [37,38]. The relationship between anti-angiogenic drugs and periapical disease in ONJ needs to be further investigated.

The study has some limitations. First, the study covered a small number of cases because it was limited to the NHIS cohort database, which only included women aged >50 years. Second, it was challenging to assess the grade and stage of ONJ because the disease was not verified by medical records or direct oral examinations. Third, the analysis would have been more accurate if it had accounted for periodontitis and tooth extraction. Due to the specific characteristics of the data set, whether the cases of pulp and periapical illness included in this study were induced by dental caries was also unknown. In addition, it is difficult to be sure whether pulp and periapical disease had been diagnosed, and whether the diagnosis and treatment codes were assigned accurately. Moreover, caution in interpreting the results for specific conditions is needed, especially for reversible pulpitis and pulp degeneration. Reversible pulpitis can return to a normal state if the cause is removed, and

https://doi.org/10.5051/jpis.2300120006

JPIS
Journal of Periodontal & Implant Science

pulp degeneration results from the aging process. Therefore, further research is needed to establish the relationship between pulp and periapical disease and ONJ.

In conclusion, our research on a nationally representative database showed that pulp and periapical disease substantially increased the risk of ONJ. Consequently, pulp and periapical disease needs to be considered as a risk factor for ONJ. Future research should explain how low-grade inflammation affects the development of ONJ.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Treatment codes related to established osteonecrosis of the jaw

Supplementary Table 2
Treatment codes related to potential osteonecrosis of the jaw

Supplementary Table 3
Diagnosis codes for pulp and periapical disease and dental caries

Supplementary Table 4
Treatment codes for root canal treatment

REFERENCES

1. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc 2008;83:1032-45. PUBMED | CROSSREF
2. Migliorati CA, Hupp WS, Migliorati EK. Treatment of bisphosphonates-associated osteonecrosis. Clin Cases Miner Bone Metab 2007;4:62-8. PUBMED
3. Christodoulou C, Pervena A, Klouvas G, Galani E, Falagas ME, Tsakalos G, et al. Combination of bisphosphonates and antiangiogenic factors induces osteonecrosis of the jaw more frequently than bisphosphonates alone. Oncology 2009;76:209-11. PUBMED | CROSSREF
4. Capocci M, Romeo U, Guerra F, Mannocci A, Tenore G, Annibali S, et al. Medication-related osteonecrosis of the jaws (MRONJ) and quality of life evaluation: a pilot study. Clin Ter 2017;168:e253-7. PUBMED
5. Kim KM, Rhee Y, Kwon YD, Kwon TG, Lee JK, Kim DY. medication related osteonecrosis of the jaw: 2015 Position Statement of the Korean Society for Bone and Mineral Research and the Korean Association of Oral and Maxillofacial Surgeons. J Bone Metab 2015;22:151-65. PUBMED | CROSSREF
6. Jeong HG, Hwang JJ, Lee JH, Kim YH, Na JY, Han SS. Risk factors of osteonecrosis of the jaw after tooth extraction in osteoporotic patients on oral bisphosphonates. Imaging Sci Dent 2017;47:45-50. PUBMED | CROSSREF
7. Soundia A, Hadaya D, Esfandi N, de Molon RS, Bezouglaia O, Dry SM, et al. Osteonecrosis of the jaws (ONJ) in mice after extraction of teeth with periradicular disease. Bone 2016;90:133-41. PUBMED | CROSSREF
8. Chiu WY, Yang WS, Chien JY, Lee JJ, Tsai KS. The influence of alendronate and tooth extraction on the incidence of osteonecrosis of the jaw among osteoporotic subjects. PLoS One 2018;13:e0196419. PUBMED | CROSSREF
9. 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 Implants 2012;41:1397-403. PUBMED | CROSSREF
10. Khan AA, Morrison A, Kendler DL, Rizzoli R, Hanley DA, Felsenberg D, et al. Case-based review of osteonecrosis of the jaw (ONJ) and application of the international recommendations for management from the International Task Force on ONJ. J Clin Densitom 2017;20:8-24. PUBMED | CROSSREF

https://doi.org/10.5051/jpis.2300120006

11. Jadu F, Lee L, Pharoah M, Reece D, Wang L. A retrospective study assessing the incidence, risk factors and comorbidities of pamidronate-related necrosis of the jaws in multiple myeloma patients. Ann Oncol 2007;18:2015-9. PUBMED | CROSSREF
12. Badros A, Weikel D, Salama A, Goloubeva O, Schneider A, Rapoport A, et al. Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. J Clin Oncol 2006;24:945-52. PUBMED | CROSSREF
13. 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. Tex Dent J 2013;130:299-307. PUBMED | CROSSREF
14. Utreja A, Almas K, Javed F. Dental extraction as a risk factor for bisphosphonate related osteonecrosis of the jaw in cancer patients: an update. Odontostomatol Trop 2013;36:38-46. PUBMED
15. He L, Sun X, Liu Z, Qiu Y, Niu Y. Pathogenesis and multidisciplinary management of medication-related osteonecrosis of the jaw. Int J Oral Sci 2020;12:30. PUBMED | CROSSREF
16. Kobayashi Y, Hiraga T, Ueda A, Wang L, Matsumoto-Nakano M, Hata K, et al. Zoledronic acid delays wound healing of the tooth extraction socket, inhibits oral epithelial cell migration, and promotes proliferation and adhesion to hydroxyapatite of oral bacteria, without causing osteonecrosis of the jaw, in mice. J Bone Miner Metab 2010;28:165-75. PUBMED | CROSSREF
17. Song M, Alshaikh A, Kim T, Kim S, Dang M, Mehrazarin S, et al. Preexisting periapical inflammatory condition exacerbates tooth extraction-induced bisphosphonate-related osteonecrosis of the jaw lesions in mice. J Endod 2016;42:1641-6. PUBMED | CROSSREF
18. Cheong S, Sun S, Kang B, Bezouglaia O, Elashoff D, McKenna CE, et al. Bisphosphonate uptake in areas of tooth extraction or periapical disease. J Oral Maxillofac Surg 2014;72:2461-8. PUBMED | CROSSREF
19. Kang B, Cheong S, Chaichanasakul T, Bezouglaia O, Atti E, Dry SM, et al. Periapical disease and bisphosphonates induce osteonecrosis of the jaws in mice. J Bone Miner Res 2013;28:1631-40. PUBMED | CROSSREF
20. Vahtsevanos K, Kyrgidis A, Verrou E, Katodritou E, Triaridis S, Andreadis CG, et al. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. J Clin Oncol 2009;27:5356-62. PUBMED | CROSSREF
21. Seong SC, Kim YY, Park SK, Khang YH, Kim HC, Park JH, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. BMJ Open 2017;7:e016640. PUBMED | CROSSREF
22. Gong X, Yu W, Zhao H, Su J, Sheng Q. Skeletal site-specific effects of zoledronate on in vivo bone remodeling and in vitro BMSCs osteogenic activity. Sci Rep 2017;7:36129. PUBMED | CROSSREF
23. Lim SS, Lee B, Kim IS, Hwang SJ. Differential modulation of zoledronate and etidronate in osseous healing of an extracted socket and tibia defect. Oral Surg Oral Med Oral Pathol Oral Radiol 2017;123:8-19. PUBMED | CROSSREF
24. Kamberi B, Hoxha V, Stavileci M, Dragusha E, Kuçi A, Kqiku L. Prevalence of apical periodontitis and endodontic treatment in a Kosovar adult population. BMC Oral Health 2011;11:32. PUBMED | CROSSREF
25. Chala S, Abouqal R, Abdallaoui F. Prevalence of apical periodontitis and factors associated with the periradicular status. Acta Odontol Scand 2011;69:355-9. PUBMED | CROSSREF
26. Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of untreated caries: a systematic review and metaregression. J Dent Res 2015;94:650-8. PUBMED | CROSSREF
27. Jansson L, Ehnevid H, Lindskog S, Blomlöf L. The influence of endodontic infection on progression of marginal bone loss in periodontitis. J Clin Periodontol 1995;22:729-34. PUBMED | CROSSREF
28. Seltzer S, Bender IB, Nazimov H, Sinai I. Pulpitis-induced interradicular periodontal changes in experimental animals. J Periodontol 1967;38:124-9. PUBMED | CROSSREF
29. Ayangco L, Sheridan PJ. Development and treatment of retrograde peri-implantitis involving a site with a history of failed endodontic and apicoectomy procedures: a series of reports. Int J Oral Maxillofac Implants 2001;16:412-7. PUBMED
30. Sussman HI, Moss SS. Localized osteomyelitis secondary to endodontic-implant pathosis. A case report. J Periodontol 1993;64:306-10. PUBMED | CROSSREF
31. Zhou W, Han C, Li D, Li Y, Song Y, Zhao Y. Endodontic treatment of teeth induces retrograde peri-implantitis. Clin Oral Implants Res 2009;20:1326-32. PUBMED | CROSSREF
32. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg 2014;72:1938-56. PUBMED | CROSSREF

33. Rupel K, Ottaviani G, Gobbo M, Contardo L, Tirelli G, Vescovi P, et al. A systematic review of therapeutical approaches in bisphosphonates-related osteonecrosis of the jaw (BRONJ). Oral Oncol 2014;50:1049-57. PUBMED | CROSSREF

34. Lee SH, Chan RC, Chang SS, Tan YL, Chang KH, Lee MC, et al. Use of bisphosphonates and the risk of osteonecrosis among cancer patients: a systemic review and meta-analysis of the observational studies. Support Care Cancer 2014;22:553-60. PUBMED | CROSSREF

35. Bonacina R, Mariani U, Villa F, Villa A. Preventive strategies and clinical implications for bisphosphonate-related osteonecrosis of the jaw: a review of 282 patients. J Can Dent Assoc 2011;77:b147. PUBMED

36. Dimopoulos MA, Kastritis E, Bamia C, Melakopoulos I, Gika D, Roussou M, et al. Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. Ann Oncol 2009;20:117-20. PUBMED | CROSSREF

37. Migliorati CA, Brennan MT, Peterson DE. Medication-related osteonecrosis of the jaws. J Natl Cancer Inst Monogr 2019;2019:lgz009. PUBMED | CROSSREF

38. Aghaloo TL, Cheong S, Bezouglaia O, Kostenuik P, Atti E, Dry SM, et al. RANKL inhibitors induce osteonecrosis of the jaw in mice with periapical disease. J Bone Miner Res 2014;29:843-54. PUBMED | CROSSREF

https://doi.org/10.5051/jpis.2300120006