Underestimated Risk Factor of Osteonecrosis of the Jaw, Pulp and Periapical Disease: A National Cohort-Based Study in Korea

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Abstract

Background: Osteonecrosis of the jaw (ONJ) is one of the complication of bisphosphonate (BP). Despite being a major risk factor for ONJ, tooth extraction cannot explain all cases of ONJ. However, disease that induce inflammation in the jawbone, such as pulp and periapical disease is underestimated, and studies suggesting relationship are arising. This necessitates the determination of the relationship between ONJ and inflammatory disease, which would contribute to the understanding and treatment of ONJ.

Methods: We analyzed the relationship between ONJ and pulp and periapical disease, and caries in women aged over 50 years who were administered BP for over 1 year from 2010 to 2015, based on a nationwide cohort study. ONJ, pulp and periapical disease, and caries were defined according to the Korean Standard Classification of Diseases and Causes of Death-7 and claims data. ONJ was operationally defined into definite ONJ and possible ONJ because of the ambiguity of population-based ONJ diagnosis.

Results: Pulp and periapical disease significantly increased ONJ development [hazard ratio 2.21 (95% CI 1.40-3.48) and 2.22 (95% CI 1.65-2.98) in definite ONJ and possible ONJ, respectively]. Additionally, the risk of ONJ development increased when caries addition to pulp and periapical disease [hazard ratio 2.28 (95% 1.50-3.47) and 2.05 (95% 1.55-2.70) in definite ONJ and possible ONJ, respectively]. Nonetheless, those in the caries were not significant. Root canal treatment in most cases did not increase ONJ development significantly, but the pulp and periapical disease or caries significantly increased possible ONJ development [hazard ratio 2.17 (95% CI 1.04-4.52)].

Conclusions: It is necessary to focus on pulp and periapical disease resulting in inflammation as a major risk factor for ONJ. Future studies should determine the role of low-grade inflammation for ONJ on other ONJ-inducing drugs as anti-resorptive agents.

Background

Bisphosphonate (BP), an analog of pyrophosphate, is used as an inhibitor of osteoclast-mediated bone resorption for the treatment of metabolic and pathologic bone disease including osteoporosis, Paget's disease, and metastatic malignant disease [1]. Despite being beneficial for cancer and metabolic bone disease treatment, BP use results in osteonecrosis of the jaw (ONJ) [2, 3]. While the incidence of the condition is rare, serious complications can affect the quality of life [4]. There are various hypotheses, including the suppression of bone turnover, infection/inflammation, angiogenesis inhibition, soft tissue toxicity, and immune-related theory because the pathophysiology of ONJ is still controversial [5].

ONJ occurs most frequently following dental interventions, particularly tooth extraction accounting for half of ONJ [6–9]. Therefore, most studies on ONJ have focused on tooth extraction, overlooking the effects of other dental risks. Local wound healing or infection affects pathologic conditions, which would have a possible impact on ONJ [10–13]. Pulp and periapical disease, and caries, the two common infectious dental diseases, can cause chronic inflammation in the jawbone. This in turn induces catabolic

effects within the jawbone and is considered one of the risk factors for ONJ [14, 15]. Inflammation is a major risk factor for ONJ as one of important role of ONJ pathophysiology relating to osteoimmunology. Pulp and periapical disease is another risk factor for tooth extraction, which is considered one of the risk factors for ONJ. However, its role in ONJ has not yet been elucidated. Thus, inflammation caused by pulp and periapical disease would exert a direct or indirect effect on ONJ development.

Root canal treatment is used to disinfect the pulp, resolve inflammation in the pulp and periapical disease, and protect further microbial invasion to periapical tissue. While Vahtsevanos et al. reported that root canal treatment does not increase the risk of ONJ, the relationship between root canal treatment and ONJ has not been identified [16].

Some studies have demonstrated that pulp and periapical disease is related to BP and ONJ. These studies were based on animal models of ONJ and are not sufficient to explain the causal relationship between pulp and periapical disease and ONJ. We aimed to verify the relationship between ONJ and pulp and periapical disease in patients administered BP with a nationally representative cohort database in Korea.

Methods

Data source

Health screening for the entire population is conducted by the National Health Insurance Service (NHIS) every year or every alternate year, depending on the age and occupation of people covered in the insurance and released to the public [17]. We conducted a longitudinal cohort study based on the general health screening database of the NHIS. The sampling research database was extracted by sampling high-demand information from the national health insurance data. We used the health examination cohort database to analyze the medical use and examination results. Approximately 510,000 people (aged 40-79 years) underwent routine checkups from 2002 to 2003. The data were extracted from January 01, 2002 to December 31, 2015.

This study was conducted with the approval of the institutional review board (IRB No. X-2004/606-905, Seoul National University Bundang Hospital).

Study population

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

The inclusion criteria were women (i) aged over 50 years, (ii) who were administered BP for more than 1 year, and (iii) demonstrated compliance $\geq 0\%$ during the year (or those with a medication possession

ratio $\geq 80\%$). Both the oral and injectable routes were covered. Thus, the analysis eventually included BP, namely alendronate, ibandronate, residronate, pamidronate, and zoledronate.

However, the underlying condition or some contributing factor would have effects on the onset of ONJ, and the estimated ONJ frequency is quite higher in cases of cancer or other bone diseases that need to use BP. Therefore, the case of using BP above the dose for osteoporosis treatment, and the case of cancer were excluded.

In addition, we excluded cases where ONJ occurred within 1 year of the use of BP. This can be attributed to our difficulty in determining the result of BP use. Deaths before the index date were also excluded from the analysis.

Definition of ONJ, pulp and periapical disease, and caries

We combined the KCD-7 code and treatment code to diagnose ONJ. First, we categorized ONJ into two parts as follows: definite ONJ and possible ONJ. The condition was defined as definite ONJ if it included one of the following: Osteonecrosis due to drugs, multiple site (M87.1), Inflammatory conditions of jaws (K10.2) as a diagnosis, and one of the treatment were registered together, or both diagnoses were registered after the index date (Supplementary Table 1).

Possible ONJ is a broader concept that covered the diagnosis and treatment used in cases of suspected ONJ. It included Osteonecrosis due to drugs, multiple sites (M87.1, 87.3, 87.8, 87.9), Inflammatory conditions of jaws (K10.2, 10.3 10.8), Acute haematogenous osteomyelitis, multiple sites (M86), Disorders of teeth and supporting structures, unspecified (K08.9), as a diagnosis, and treatment code (Supplementary Table 2).

Pulp and periapical disease, and caries were defined as the diagnosis code in registration, following the index date (Supplementary Table 3).

Root canal treatment was defined as the root canal treatment code on record between pulp and periapical disease, or caries diagnosis and ONJ diagnosis (Supplementary Table 4).

Confounding variables

We included patient demographics on the baseline year, age, income level, and disability. The income quintile refers to an index in which the National Statistical Office divides Korea's total households into ten levels by 10%, according to the quarterly income level. The income level in the first quintile is the lowest. Moreover, the higher the quintile, the higher is the income. The analysis was divided into five stages. Disability was categorized as yes or no (Table 1, Supplementary Table 5). The prevalence of diseases was defined by 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, Supplementary Table 5).

Statistical analyses

Baseline characteristics were reported using numbers (%) for categorical variables and means $\pm$ standard deviation. We conducted the χ^2 test, median with interquartile range for continuous variables, and t-test or analysis of variance. Moreover, we adjusted the cohort data of 14 years, baseline year, age, comorbidities, income disability, the type of BP administered, and cumulative proportion of days to analyze the hazard ratio (HR) of ONJ, according to the prevalence of pulp and periapical disease, caries, or pulp and periapical disease or caries. Cox proportional hazards models were used to evaluate the associations between the independent variables and the occurrence of ONJ events. In addition, we calculated the HRs and 95% confidence intervals (CIs) to evaluate the associations between the independent variables and the occurrence of ONJ events. Statistical significance was defined as two-tailed p-values <0.05 . Statistical analysis was conducted using R programming (version 3.3.3; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Excluding patients with cancer diagnosis, death, and ONJ diagnosis before the index date, we eventually 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 caries, respectively. Moreover, 6,260 (23.04%) patients were diagnosed with either pulp and periapical disease or caries.

Definite ONJ accounted for 26 (0.62%) cases and 69 (0.30%) cases of the pulp and periapical disease groups and the non-pulp and periapical disease groups, respectively. Possible ONJ accounted for 62 (1.47%) and 158 (0.69%) of the pulp and periapical disease groups and non-pulp and periapical disease groups, respectively. Moreover, definite ONJ accounted for 36 (0.58%) cases and 59 (0.28%) cases in the pulp and periapical disease or caries group and non-pulp and periapical disease or caries group, respectively. Possible ONJ accounted for 80 (1.28%) cases and 140 (0.67%) cases in the pulp and periapical disease or caries group and non-pulp and periapical disease or caries group, respectively. The statistical difference varied depending on the diagnostic criteria. However, the pulp and periapical disease and the pulp and periapical disease or caries increased both definite and possible ONJ development (Table 1). On the other hand, the proportion of patients with ONJ was higher in the caries group in definite and possible ONJ, but there was no significant difference (Supplementary Table 5).

Pulp and periapical disease significantly increased ONJ development compared with non-pulp and periapical disease [HR 2.21 (95% CI 1.40-3.48) and 2.22 (95% CI 1.65-2.98) in definite ONJ and possible ONJ, respectively]. And caries addition to pulp and periapical disease increased ONJ development compared with non-pulp and periapical or caries as well [HR 2.28 (95% 1.50-3.47) and 2.05 (95% 1.55-2.70) in definite ONJ and possible ONJ, respectively]. However, the caries group was not significant (Table 2).

We analyzed the HR of ONJ in case of root canal treatment among patients in the pulp and periapical disease and caries groups. While only possible ONJ in the pulp and periapical disease or caries group significantly increased risk of possible ONJ development [2.17 (95% CI 1.04-4.52)], others were not significant (Table 3).

Discussion

While tooth extraction is a major risk factor for ONJ, chronic inflammation that is caused by pulp and periapical disease and results in tooth extraction have been disregarded in ONJ. BP induces the depression of osteoclast activity, which results in a decrease in bone modeling. Thus, the periapical radiolucent lesion in the alveolar bone of patients taking BP is masked. Furthermore, the morbidity of pulp and periapical disease in patients taking BP is supposedly underestimated. This results in a lack of interest and study of the relationship between pulp and periapical disease and ONJ. However, few studies, such as the one conducted by Cheong et al., have mentioned uptake of BP increases at the pulp and periapical disease site [14]. Kang et al. demonstrated that pulp and periapical disease and BP results in ONJ in mice [15], these studies are limited because they are based on animal models of ONJ that imply a correlation between pulp and periapical disease and ONJ. However, we confirmed an increase in the morbidity of definite ONJ and possible ONJ in patients with pulp and periapical disease, who were administered BP for over 1 year. We hypothesized that pulp and periapical disease induces inflammation in the alveolar bone near the root. This inflammation causes the over-accumulation of BP and results in ONJ development, as mentioned in the animal model studies.

In addition, while tooth extraction is a definite risk factor for ONJ, lesions that cause inflammation, such as periodontitis and pulp and periapical disease, increase the susceptibility of sites to developing ONJ. Difficulties in analyzing or studying ONJ have led to a focus on consequent intervention. However, it is necessary to discover the effects of inflammation on ONJ to identify the mechanism of ONJ, and to overcome it. The jaw bone has a higher turnover rate than peripheral bones, and leads to high BP accumulation [18]. Gong mentioned that jaw bone site-specific bone marrow stromal cell is more susceptible to BP than the iliac and tibial bone [19]. Moreover, the osseous healing mechanism is different site-dependently, as mentioned by Lim [20]. These different characteristics would play an important part of ONJ. Hence, it would be helpful to understand the relationship between osteoimmunology and inflammation to treat ONJ.

While pulp and periapical disease may result from various reasons, most cases arise from the advancement of caries. Despite being a pulp-limited disease, caries causes pulp and periapical disease that results in chronic inflammation of the jaw bone. Inflammation is a definite risk factor for the development of ONJ. We further identified the morbidity of ONJ in patients with caries. However, caries did not significantly increase the risk of ONJ. We suggest that caries is insufficient to cause inflammation to induce ONJ. In other words, inflammation within the dental pulp tissue is not correlated with ONJ. Our findings support the position paper guidelines that recommend performing caries treatment before or during BP use.

Furthermore, we explored the impact of root canal treatment for pulp and periapical disease on the risk of ONJ. Root canal treatment did not supposedly influence the risk of ONJ with BP, similar to the results of Vahtsevanos [16]. Therefore, root canal treatment does not exert any effect on BP accumulation in pulp and periapical disease. However, this finding was insignificant, and the number of events included in analysis was extremely low to analyze. And, root canal treatment may be performed in case of pulp only lesion or before the development of an osteolytic lesion. Our findings suggested preemptive root canal treatment would be necessary, prior to BP use. Moreover, a BP drug holiday would be required for the patient requiring root canal treatment during BP use. This support studies, including the American Association of Oral and Maxillofacial Surgeons articles and reviews recommend patients who would be administered an anti-resorptive agent, to treat or control the dental disease with screening dental health before commencing the treatment. Moreover, they should maintain good oral hygiene even after treatment to reduce the risk of ONJ [21–23].

This study proposed that pulp and periapical disease is the risk for ONJ. BP is generally used for bone diseases, such as Paget's disease, multiple myeloma, and cancer that have the possibility of bone metastasis, such as breast cancer, besides osteoporosis. Despite excluding the aforementioned diseases in this study, patients should undergo routine dental check-ups to identify caries and pulp and periapical disease, before or during BP use. In addition to anti-resorptive agents, such as BP, agents inducing medication-related ONJ, including anti-angiogenic agents, are other concerns [24, 25]. This necessitates confirmation of the relationship between anti-angiogenic agents and periapical agents on ONJ in future.

The first limitation of this study was the inclusion of a small number of events, owing to its restriction to the NHIS cohort database including only women aged over 50 years. Second, it was difficult to assert a grade and stage ONJ because the condition was not confirmed by medical records or a direct oral examination of ONJ. Therefore, further studies are required to determine the correlation between pulp and periapical disease and ONJ.

Conclusions

Considering nationally representative databases, the risk of ONJ would increase significantly with pulp and periapical disease. Pulp and periapical disease should be considered as risk factors for ONJ. Furthermore, future studies should clarify the effect of low-grade inflammation on ONJ development.

Abbreviations

Osteonecrosis of the jaw (ONJ), bisphosphonate (BP), Korean Standard Classification of Diseases and Causes of Death-7 (KCD-7), hazard ratios (HRs), confidence intervals (CIs), National Health Insurance Service (NHIS), skeletal-related events (SREs)

Declarations

None

Ethics approval and consent to participate

The study was performed in accordance with the guidelines of the Helsinki Declaration (2013), protecting the participants' anonymity, privacy and maintaining public confidence.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are not publicly available due to limitations of ethical approval involving the patient data and anonymity but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

KSK, MJK and TYL contributed to methodology and data curation. JRL, HJL and JHP contributed to formal analysis, investigation and data curation. HJB contributed to conceptualization, formal analysis, data curation, interpretation of data and wrote the original article. HJL and JWK contributed to conceptualization, funding acquisition, project administration, and supervision. All authors read and approved the final manuscript.

References

1. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc.* 2008;83(9):1032–45.
2. Migliorati CA, Hupp WS, Migliorati EK. Treatment of bisphosphonates-associated osteonecrosis. *Clin Cases Miner Bone Metab.* 2007;4(1):62–8.
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(3):209–11.

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(4):e253-7.
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(4):151–65.
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(1):45–50.
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;90:133–141.
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(4):e0196419.
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 Surg.* 2012;41(11):1397–1403.
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(1):8–24.
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(12):2015–9.
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(6):945–52.
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(4):299–307.
14. 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(12):2461–8.
15. 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(7):1631–40.
16. 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(32):5356–62.
17. 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(9):e016640.

18. 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(1):30.
19. 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.
20. 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(1):8–19.
21. 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(10):1938–56.
22. 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(11):1049–57.
23. 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(2):553–60.
24. Migliorati CA, Brennan MT, Peterson DE. Medication-related osteonecrosis of the jaws. *J Natl Cancer Inst Monogr.* 2019;2019(53).
25. 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(4):843–54.

Tables

Due to technical limitations, table 1-3 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Flow diagram of study participant selection

Supplementary Files

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