OPEN ACCESS

Review

Journal of Dental Science, Oral and Maxillofacial Research

Prevalence of bisphosphonate-related osteonecrosis of the jaws associated with dental extraction: systematic review

Luiza Bastos Nozari, Viviane Neves Pacheco, Angelo Luiz Freddo, Deise Ponzoni, Adriana Corsetti

Faculty of Dentistry of Federal University of Rio Grande do Sul, Brazil

Correspondence: Luiza Bastos Nozari, Faculty of Dentistry of Federal University of Rio Grande do Sul. Rua Ramiro Barcelos, 2492. Porto Alegre, Rio Grande do Sul, Brazil, CEP: 90035-003, Email luizanozari@gmail.com

Received: August 10, 2018 | **Published:** August 17, 2018

Abstract

Objectives: This paper aims to analyse this subject through a systematic review to get a closer understanding of the use of bisphosphonates and their connection to the occurrence of osteonecrosis associated with tooth extraction. The identification and selection of papers began after approval by the Research Commission. Materials and methods: It was made a search in the databases Pub Med and Scoppus in order to select studies that were published between the 2003-year period until April 2016.

Results: Two articles with control group and seven with no control group were selected. The studies revealed a higher prevalence of osteonecrosis in bisphosphonate users intravenously.

Conclusions: There is no evidence to justify a break from treatment for performing tooth extraction in users of bisphosphonates orally but when it occurs is very hard to treat. While, in patients using intravenous bisphosphonates it becomes clear the impediment of surgical tooth extraction procedures. Clinical Relevance: There is no need to break a treatment with oral bisphosphonate to do surgeries of teeth extraction.

Keywords: hypocellularity, osteonecrosis, bisphosphonates, radiotherapy, BRONJ

Introduction

Bisphosphonate-Related osteonecrosis of the jaws (BRONJ) is a condition characterized by hypocellularity, dehiscence, chronic bone osteonecrosis, and presence of osteolytic areas in the radiographic examination.[1] Bone exposure to the oral environment for a period longer than eight weeks associated with symptoms such as pain, erythema, ulceration, tooth mobility, and sensitivity alteration of the area[2] indicates an occurrence of BRONJ in those patients who use bisphosphonates (BPP), but have no history of radiotherapy on the jaw.[3]

Investigations have shown that around 10% of the patients undergoing a treatment with BPP, and who have developed BRONJ were submitted to tooth extraction.[4] Moreover, dental extraction has been considered one of the main causes of BRONJ, followed by implant placement, periodontal disease, trauma caused by ill-fitting dental prosthesis, and lesions that appears spontaneously in the mouth.[5] Nonetheless, there is no exactly proportion of BRONJ related to dentoalveolar surgeries, but it is known that there are risk factors to the occurrence of the osteonecrosis, as the use of drugs or medication local (biofilm presence, infections), demographic, systemic, and genetic factors.[6]

The diagnose criteria of BRONJ, defined according to the American Association of Oral and Maxillofacial Surgeons, (AAOMS)[7] is as follows:

i. Bone exposure in the maxillofacial region for a period longer than eight weeks;

ii. Previous or current treatment with bisphosphonates;

iii. No previous history of radiotherapy on the jaws.

The stages of the disease were defined following the criteria of the AAOMS 2009[3] as follows:

Stage I: Exposed necrotic bone non associated with pain and/or infection signals (asymptomatic);

Stage II: Exposed necrotic bone associated with pain and/or infection signals (symptomatic);

Stage III: Exposed necrotic bone associated with pain and/or infection signals plus one or more of the following signals: pathologic fracture, orocutaneous fistula, maxillary sinus involvement, or a necrosis extended to the inferior board or to the ramus of the jaw;

Stage 0: Absence of exposed bone, but presence of clinical, radiographic, or histological signals of ONJ.

Although a significant progress had been achieved since its recognition in 2003,[8] the current knowledge concerning BRONJ is still limited.

These advances have been encouraging investigations on this topic, which is essential to Odontology, specially to the area of Oral Maxillofacial Surgery.

As there is no consensus in the literature about the execution of dental surgical procedures in patients undergoing a treatment with BPP, and given the risk that they have for developing BRONJ, this study aims to investigate, through a systematic literature review, the data published about the occurrence of BRONJ in patients submitted exclusively to tooth extraction.

Methods

The investigation search was performed in Portuguese, Spanish, and English on the databases MEDLINE (PubMed) and Scoppus, and with the time restricted to the period from 2003 to March 2016. The initial time mark was chosen based on the first publication of an occurrence of osteonecrosis related to the use of BPP. The risk of bias of the studies was evaluated through the tool currently recommended by the Cochrane Collaboration, which is known as PRISMA. To the initial search, the descriptors were used following the Medical Subject Headings (MeSH) with the algorithms: (((((((extraction tooth) OR dental procedure) OR dental surgery) OR extraction) AND oral surgery) AND humans[Mesh])) AND (((((jaw osteonecrosis) OR bisphosphonate related osteonecrosis) OR bisphosphonate osteonecrosis) OR bisphosphonate) AND humans.

Only studies performed in adults under the use of BPP or not, and who were submitted to tooth extraction composed the selection from the initial search, and the prevalence of osteonecrosis was evaluated only in these cases. The type of studies included were case-control, clinical assays, and retrospective studies. The inclusion criteria adopted were studies in humans, investigations on patients of any age or gender with the clinical diagnose of BRONJ, and studies that evaluated the development of bisphosphonate-related osteonecrosis after dental extraction. On the other hand, the exclusion criteria is BRONJ case reports, laboratory studies, series of cases with less than ten patients, literature reviews, letters, editorials, PhD thesis, and abstracts.

Literature reviews were not included in the search, but they had the role of providing additional information through their bibliographic references, which allowed a manual guided search. The initial list was composed by publications that were selected through their title, considering the inclusion and exclusion criteria. A table containing the information to be extracted from the studies (type of study, type and name of the BPP, average age, gender, publication year, denouement, and statistical analysis) was drawn and applied to the search.

Results

The literature search identified 598 publications, from which 363 were excluded during the reading of the titles because the studies did not directly match the inclusion criteria, or due to the fact that they could be also found on different databases. After that, the reading of the abstracts of the 235 studies left was performed applying the inclusion and exclusion criteria before mentioned in this paper, which resulted in the selection of 28 publications that were fully read by two evaluators. When a strong divergence was observed, a third evaluator was consulted as a matter of selection of the investigations found (Figure 1).

Studies with control group

Two publications were selected, both of them were cohort studies with a control group published in 2012 and 2013 (Figure 1). Altogether, 3308 patients were assessed, among which 1763(53.30%) were women, while 1545(46.70%) were men. From the patients evaluated, 179(5,41%) used BPP trough either intravenous and oral via, 3129(94,58%) of the patients belonged to the control group, which means that they did not undergo any treatment with BBP. The age means was 65years old (20-92), and all of them were older than 18years old.

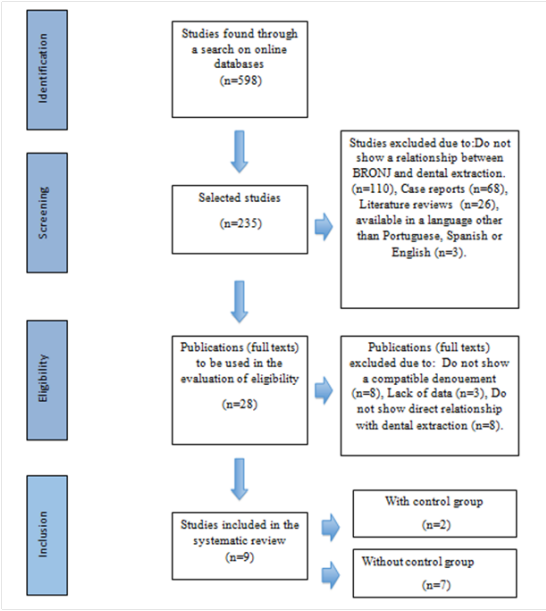

Figure 1 Flowchart of the process of systematic review.

The investigations[9,10] demonstrated seven occurrences of osteonecrosis, six of them in patients under the use of BPP (BRONJ), and the other one was not related to the use of the medication (Table 1). Five (12,5%) out of the 40 patients who were under IV use of BPP developed BRONJ, while only one (0,76%) of those who were taking BPP via oral experienced BRONJ. Three out of the 33 male patients (9,09%) developed a case of BRONJ.

In the investigation performed by Miglioratti the average time of use of IV BPP for the 13patients evaluated was 12months, whereas for the 32 other ones under via oral treatment the average time were 84months. The study demonstrates that the time of exposure to BPP had no significative effect over the mucosa healing process (HR, 1.00; 95 percent CI, 0.99-1.00). The average time for those patients suffering from BRONJ (13.5, 7-49months) was higher than for those who did not developed the disease (7.5, 1-96months), but this difference did not expressed results statistically significant.[9]

Studies without control groups

Among the studies that did not present control groups, seven publications were selected, four cohort studies and three retrospective investigations, which were published between 2012 and 2015. These investigations evaluated 815patients with an age average of 64.95years old (601[73.74%] females and 214 [26.25%] male), and who were under the use of intravenous and oral BPP. It was observed a correlation between BRONJ and tooth extraction in 44 cases (5.40%), from all the samples evaluated, and only in one investigation there were no cases of BRONJ (Table 2).

In the investigations that analyzed the intravenous administration of BPP, 437 patients were evaluated, and 40 of them developed

BRONJ (9.15%). The studies[14,16,20,25] subdivided the occurrence of osteonecrosis relating it to the administration via, which made possible the observation that in 21(4.5%) out of the 462 patients evaluated the occurrence of BRONJ was associated with the administration of BPP via IV, whereas 6cases (1.29%) were related to the use of BPP via oral.

The investigations that did not present a control group in their outlines made difficult the data compilation, since they lacked important information and did not feature a detailed experimental design.

Table 1 Studies with control groups included in the final selection F=females/M=Males/ONJ=osteonecrosis of the jaws

Authors	Yamazaki T et al.[10]	Migliorati CA et al.[9]
Title and year of publication	Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: a cohort study. 2012	Assessing the association between bisphosphonate exposure and delayed mucosal healing after tooth extraction. 2013
Journal	IJOMS	JADA
Type of study	Cohort	Cohort
N of the sample	3216	92
Gender	F: 1.703 M: 1.513	F: 60 M:32
Use of Bisphosphonates	126 (F:103 M:23)	53 (F:43 M:10)
No use of Bisphosphonates (control)	3090 (F: 1600 M:1490)	39 (F:17 M:22)
Administration via	IV+ORAL	IV+ORAL
Age	>20 means =66 (20-88)	>18 means=64 (32-92)
Denouement		
Use of BPP:	5 ONJ ONJ	1 ONJ
No use of BPP:	1 ONJ	
Method of evaluation of the denouement	According to the AAOMS' criteria	Healing time

Table 2 Final results of the selected publications without group control F=female/M=male

Authors	Title of the publication	Year	Journal	Type of study	N of the sample	Type of BPP	Average age	Gender	BRONJ
O'Connell JE et al.[11]	A role for C-terminal cross-linking telopeptide (CTX) level to predict the development of bisphosphonate-related osteonecrosis of the jaws (BRONJ) following oral surgery?	2012	Irish Journal of Medical Science	Cohort	23	IV e Oral	59	F: 22 M: 1	0
Kato GF et al.[12]	Evaluation of socket healing in patients undergoing bisphosphonate therapy: Experience of a single Institution.	2013	Medicina Oral Patologia Oral y Cirugia Bucal	Retrospective	20	IV	62,2	F:16 M :4	4
Taylor T et al.[25]	A study of 225 patients on bisphosphonates presenting to the bisphosphonate clinic at King's College Hospital.	2013	British Dental Journal	Retrospective	225	IV e Oral	62	F: 168 M: 57	13
Vescovi P et al.[20]	Case series of 589 tooth extractions in patients under bisphosphonates therapy. Proposal of a clinical protocol supported by Nd:YAG low-level laser therapy.	2013	Medicina Oral Patologia Oral y Cirugia Bucal	Cohort	217	IV e Oral	68,72	F: 179 M: 38	5

Citation: Nozari LB, Pacheco VN, Freddo AL, et al. Prevalence of bisphosphonate-related osteonecrosis of the jaws associated with dental extraction: systematic review. *J Dent Maxillofacial Res.* (2018);1(2):72–77

(Table 2 continue)

Bodem JP et al.[13]	Incidence of bisphosphonate-related osteonecrosis of the jaw in high-risk patients undergoing surgical tooth extraction.	2015	Journal of Cranio-Maxillo-Facial Surgery	Cohort	61	IV	65,65	F: 42 M: 19	8
Kos M.[19]	Incidence and risk predictors for osteonecrosis of the jaw in cancer patients treated	2015	Archives of Medical Science	Retrospective	197	IV	66,59	F: 121 M: 76	11
Otto S et al.[22]	Tooth extraction in patients receiving oral or intravenous bisphosphonate administration: A trigger for BRONJ development?	2015	Journal of Cranio-Maxillo-Facial Surgery	Cohort	72	IV e Oral	67,5	F: 53 M: 19	3

Discussion

Due to the lack of consensus in the literature about the execution of dental extractions in patients undergoing a therapy with BPP, it was observed, through the process of selection of the publications, a difficulty in finding studies with controlled groups that had BRONJ as a denouncement related exclusively to tooth extraction, which was reflected in the final selection of only two publications that composed this literature systematic review. These selected studies[9,10] reported that from those patients under the use of BPP, only six developed BRONJ, while this condition was observed in only one sample from the controls. Moreover, these investigations highlighted that the average type of use of BPP, as well as the administration via – IV or oral- did not have influence on the occurrence of BRONJ.

It was also emphasized that the incidence of BRONJ was significantly associated with the type of BPP rather than with other potential risk factors.[10] This indicates that the development of osteonecrosis might be related to the use of the medication in the presence of osteoporosis rather than to the simple use of BPP.[9,11]

In regards to gender, from a total of 395 female patients, 10(2,5%) developed BRONJ, while 13(11,4%) out of the 114male patients develop the condition. All of them were under treatment with BPP via oral or IV. It has to be pointed out that the higher number of males stricken by BRONJ might be related to the fact that a largest number of them were under intravenous therapy with BPP.

The average age of 62 to 65years old was similar to the majority of the studies about the topic,[12,13] and it was directly related to the use of BPP via oral for female subjects[12,14] due to the treatment of osteoporosis. The occurrence of BRONJ in other studies corroborates with the findings of this systematic review, which found lower rates of post-operatory complications in patients under the use of BPP via oral.[10,13,15–17] However, it was observed a higher and significative occurrence of complications when the IV via was administered. When it was observed a post-operatory complication, the studies referred it as the first stage of BRONJ according to the protocol of the AAOMS. Nonetheless, there are controversies about the classification of in which stage BRONJ begins, since this level one might be considered as BRONJ in some cases.[14]

It was also observed a relationship between the occurrence of BRONJ and the execution of procedures that require osteotomy, once a rate of 24.4% of BRONJ is found in patients who have undergone this type of surgical maneuver. This rate is even higher (33%) in patients that underwent an osteotomy on the jaw, which is explained due to the fact that the mandible (33%) is less irrigated when compared to the maxilla.[16] Moreover, other factors related to osteonecrosis are associated to the time of use of BPP, since the recurrence is higher in subjects that use these medicaments for a period longer than 30 days, and take them through IV via of administration,[13,16,17] a point about which studies without a control group disagree.[9,10]

The average time of use of BPP via oral exceeds the one for the IV via of administration, which is directly related to the occurrence of BRONJ, which is higher in those subjects that used BPP for a longer period. This fact can be observed in studies[9] that had an average time of 13.5months for those who developed BRONJ against 7.5months of use for those that did not developed the illness.

Regarding to pre-operatory therapies, the studies related a lower number of occurrences of BRONJ to a possible outcome of an antibiotic therapy with Amoxicillin associated with potassium clavulanate or erythromycin (when an allergy to penicillin is present).[15,17,18] This antibiotic therapy, could be also associated with the use of chlorhexidine 0.2% once a day in conjunct with professional oral hygiene 2 or 3weeks in advance to the dental extraction, followed by the application of chlorhexidine gel 1% after the tooth extraction.[19] However, there is no consensus about the prophylaxis of BRONJ, but once the condition takes place the treatment is difficult.

The investigations [17,20,21] agree that a prolonged therapy with IV BPP offers higher risks to the development of BRONJ for those patients submitted to oral surgeries, which is intensified in female subjects due to the higher rates of breast cancer, a fact that makes the occurrence of BRONJ 6 times greater in these patients when comparing them to the control groups.[20] In contrast, there are evidences that show a higher occurrence of BRONJ in men, which is explained by the use of IV BPP to the treatment of prostate cancer.[22,23]

The authors affirmed that the oral via exhibits a lower risk for the occurrence of BRONJ,[11] but the interruption of a therapy with BPP due to the necessity of oral surgery can bring potential damage to the systemic condition of a patient, which is considered worse than the development of BRONJ.[24]

Osteoporosis, the main cause of treatment with BPP via oral, has an important role in the development of BRONJ when compared to control groups. However, studies compared the incidence of BRONJ among patients suffering from osteoporosis and undergoing a treatment with BPP to the incidence among those who were not under treatment with BPP, and the results showed no statistically significant differences.[25–27]

Citation: Nozari LB, Pacheco VN, Freddo AL, et al. Prevalence of bisphosphonate-related osteonecrosis of the jaws associated with dental extraction: systematic review. *J Dent Maxillofacial Res*. (2018);1(2):72–77

Conclusion

The results of this systematic review revealed that the risk of occurrence of BRONJ has been considered a concern. Among the occurrences of BRONJ, the most affected are elder patients, with average age of 65years old, and that use BPP via IV administration to the treatment of malign neoplasms. There is no evidence that supports or justifies a pause in the treatment with BPP in order for an dental extraction to be performed. However, it is important to highlight that when BRONJ occurs its treatment it is extremely hard. It is, then, clear that in those patients undergoing IV administration of BPP oral surgeries have to be avoided. When classified as an elective procedure, a tooth extraction must not be executed, or it has to be postponed.

Whenever this is possible, it is indicated to perform an adequacy of the oral cavity before the execution of any treatment with BPP, which can decrease the exposure of the patient to the risk of developing BRONJ, as well as it is important to maintain an excellent level of oral hygiene, which has to be oriented by a professional. It is fundamentally important that the patients submitted to tooth extraction have a following up period in order for the healing process to be evaluated. Longitudinal clinical studies still need to be performed in order for the scientific evidence concerning the topic to become more consistent, since the discussion of the relationship between BPP and BRONJ is recent and faces the lack of scientific basis.

Acknowledgements

The study presented is part of a final graduation paper. The authors like to thank Professors from Faculty of Dentistry for their valuable comments.

Conflict of interest

The author declares no conflict of interest.

Funding

The study was not supported by research grants or any other sources.

References

1. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg*. 2003;61(9):1115–1117.
2. Varun BR, Sivakumar TT, Nair BJ, et al. Bisphosphonate induced osteonecrosis of jaw in breast cancer patients: A systematic review. *J Oral Maxillofac Pathol*. 2012l;16(2):210–214.
3. Ruggiero SL, Dodson TB, Assael LA, et al. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate–Related Osteonecrosis of the Jaw–2009 Update. *J Oral Maxillofac Surg*. 2009;67(5 Suppl):2–12.
4. Edwards BJ, Gounder M, McKoy JM, et al. Pharmacovigilance and reporting oversight in US FDA fast–track process: bisphosphonates and osteonecrosis of the jaw. *Lancet oncol*. 2008;9(12):1166–1172.
5. Fliefel R, Tröltzsch M, Kühnisch J, et al. Treatment strategies and outcomes of bisphosphonate–related osteonecrosis of the jaw (BRONJ) with characterization of patients: a systematic review. *Int J Oral Maxillofac Surg*. 2015;44(5):568–585.
6. Ruggiero SL, Dodson TB, Fantasia J, 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):1938–1956.
7. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate–related osteonecrosis of the jaws. *J Oral Maxillofac Surg*. 2007;5(3):369–376.
8. Anavi–Lev K, Anavi Y, Chaushu G, et al. Bisphosphonate related osteonecrosis of the jaws: clinico–pathological investigation and histomorphometric analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;115(5):660–666.
9. Migliorati C, Hewson I, Lalla RV, Antunes HS, et al. Systematic review of laser and other light therapy for the management of oral mucositis in cancer patients. *Supportive Care in Cancer*. 2013;21(1):333–341.
10. Yamazaki T, Yamori M, Ishizaki T, 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.
11. O'Connell JE, Ikeagwani O, Kearns GJ. A role for C–terminal cross–linking telopeptide (CTX) level to predict the development of bisphosphonate–related osteonecrosis of the jaws (BRONJ) following oral surgery? *Ir J Med Sci*. 2012;181(2):237–242.
12. Saia G, Blandamura S, Bettini G, et al. Occurrence of bisphosphonate–related osteonecrosis of the jaw after surgical tooth extraction. *J Oral Maxillofac Surg*. 2010;68(4):797–804.
13. Bodem JP, Kargus S, Eckstein S, et al. Incidence of bisphosphonate–related osteonecrosis of the jaw in high–risk patients undergoing surgical tooth extraction. *J Craniomaxillofac Surg*. 2015;43(4):510–514.
14. Otto S, Tröltzsch M, Jambrovic V, et al. Tooth extraction in patients receiving oral or intravenous bisphosphonate administration: A trigger for BRONJ development? *J Craniomaxillofac Surg*. 2015;43(6):847–854.
15. Schubert M, Klatte I, Linek W, et al. The Saxon Bisphosphonate register–therapy and prevention of bisphosphonate–related osteonecrosis of the jaws. *Oral oncology*. 2012;48(4):349–354.
16. Lopes RN, Jaguar GC, Silva AP, et al. Evaluation of socket healing in patients undergoing bisphosphonate therapy: Experience of a single Institution. *Med Oral Patol Oral Cir Bucal*. 2013;18(4):e650.
17. Barasch A, Cunha–Cruz J, Curro FA, et al. Risk factors for osteonecrosis of the jaws a case–control study from the CONDOR Dental PBRN. *Journal of dental research*. 2011;90(4):439–444.
18. Carini F, Saggese V, Porcaro G, et al. Surgical protocol in patients at risk for bisphosphonate osteonecrosis of the jaws: clinical use of serum telopetide CTX in preventive monitoring of surgical risk. *Annali di stomatologia*. 2012;3(1):31–36.
19. Kos M. Incidence and risk predictors for osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *Archives of medical science (AMS)*. 2015;11(2):319–324.
20. Vescovi P, Meleti M, Merigo E, et al. Case series of 589 tooth extractions in patients under bisphosphonates therapy. Proposal of a clinical protocol supported by Nd: YAG low–level laser therapy. *Med Oral Patol Oral Cir Bucal*. 2013;18(4):e680–e685.
21. Lodi G, Sardella A, Salis A, et al. Tooth extraction in patients taking intravenous bisphosphonates: a preventive protocol and case series. *Journal of Oral and Maxillofacial Surgery*. 2010;68(1):107–110.
22. Otto S, Schreyer C, Hafner S, et al. Bisphosphonate–related osteonecrosis of the jaws–characteristics, risk factors, clinical features, localization and impact on oncological treatment. *J Craniomaxillofac Surg*. 2002;40(4):303–309.
23. Zavras AI, Zhu S. Bisphosphonates are associated with increased risk for jaw surgery in medical claims data: is it osteonecrosis? *J Oral Maxillofac Surg*. 2006;64(6):917–923.

24. Gabbert TI, Hoffmeister B, Felsenberg D. Risk factors influencing the duration of treatment with bisphosphonates until occurrence of an osteonecrosis of the jaw in 963 cancer patients. *J Cancer Res Clin Oncol*. 2015;141(4):749–758.

25. Taylor T, Bryant C, Popat S. A study of 225 patients on bisphosphonates presenting to the bisphosphonate clinic at King's College Hospital. *Br Dent J*. 2013;214(7):E18–18.

26. Huang YF, Chang CT, Muo CH, et al. Impact of bisphosphonate–related osteonecrosis of the jaw on osteoporotic patients after dental extraction: a population–based cohort study. *PloS one*. 2015;10(4):e0120756.

27. Hasegawa T, Ri S, Umeda M, et al. The observational study of delayed wound healing after tooth extraction in patients receiving oral bisphosphonate therapy. *J Craniomaxillofac Surg*. 2013;41(7):558–563.