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META-ANALYSIS

Predictive risk factors of medication-related osteonecrosis of the jaw

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Abstract

Background: Medication-related osteonecrosis of the jaw (MRONJ) is a serious complication of the drug treatment of patients with cancer or with osteoporosis. Among the possible oral triggering factors are traumatic dental procedures such as dental extraction, implant placement, periodontal treatment, or removable denture use.
Aim: This study aims to assess the possible predictive risk factors related to the MRONJ.
Methodology: A PubMed database search of studies on predictive risk factors for MRONJ was performed. The odds ratio (OR) with the Haenszel-Mantel Chi-square formula with 95% confidence intervals (95% CI) for the dichotomous variables was used. The inverse of the variance for the mean difference (MD), also with 95% CI for the continuous variables was applied.
Results: Twenty-five studies on predictive risk factors of MRONJ were included in this meta-analysis. The predictive risk MRONJ factors were the intravenous-intramuscular (IV-IM) antiresorptive drug administration (OR: 4.03), an older age (MD: 1.87 years), female gender (OR: 1.23), tobacco consumption (OR: 1.76), and tooth extraction as a potential triggering factor (OR: 6.85). Corticosteroids or antiangiogenic agents intake, periodontal treatment, removable denture use or being diabetic, had no significant influence.
Conclusions: History of tooth extraction and the IV-IM administration of the antiresorptive drug were the most important predictive risk factors for MRONJ.
Clinical Significance: In patients treated with antiresorptive drugs, especially intravenously-intramuscularly, surgical dental treatments should be avoided due to the increased risk of MRONJ.

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a serious complication of drug treatment of patients with cancer or with osteoporosis. Although the incidence of MRONJ is relatively low, it very negatively affects the quality of life of patients and its treatment is complicated.[1]

It is estimated that the overall risk of MRONJ among patients taking antiresorptive drugs for the treatment of osteoporosis ranges between 0.004% and 0.2% (4–200 cases per 100,000 subjects), although most studies indicate that this risk is lower than 0.1% (<1 case per 1000 patients with osteoporosis treated with this medications). In the case of cancer patients treated with antiresorptive and/or antiangiogenic drugs, MRONJ risk is higher, between 1% and 3% (1–3 cases per 100 cancer patients).[2]

The development of an MRONJ depends on factors such as the type of drug, the route of administration, the total cumulative dose of the same, the duration of treatment, the association with other drugs (biological, antiangiogenic, corticosteroids, etc.), and systemic diseases such as diabetes mellitus, tobacco consumption, or genetic susceptibility through the expression of single-nucleotide polymorphisms associated with MRONJ. Among the possible oral triggering factors are invasive dental procedures (tooth extraction, implant placement, periodontal treatment, removable denture wearers, etc.).[3] The aim of this study was to assess the possible predictive factors related to MRONJ.

Methodology

A search of studies on MRONJ in the PubMed database was made combining the following terms of the Medical Subject Headings

(MeSH terms) "jaw," "osteonecrosis," "bisphosphonate-associated osteonecrosis of the jaw," and "risk factors." Two hundred and ten articles published between 2006 and 2018 were found. The inclusion criteria were as follows: (a) Type of studies: Clinical studies, clinical trials, comparative studies, evaluation studies, meta-analysis, multicenter studies, and observational studies (n = 98) and (b) studies with full-text availability (n = 94). The exclusion criteria were as follows: (a) Studies that did not include a control group without MRONJ treated with antiresorptive drugs (n = 46), (b) studies with irrelevant/non-usable data (n = 21), and (c) studies carried out in experimental animals (n = 2). After applying the above criteria, 25 studies were analyzed in this meta-analysis [Figure 1].

Statistical analysis

The meta-analysis was performed using the RevMan 5.3 program (The Cochrane Collaboration, Oxford, UK). The odds ratio (OR) with the Haenszel-Mantel Chi-square formula with 95% confidence intervals (95% CI) for the dichotomous variables was used. The inverse of the variance (IV) for the mean difference (MD), also with 95% CI for the continuous variables was applied. The level of statistical heterogeneity was established considering P values and the Higgins statistic (I^2). The random effects model was used in cases of high heterogeneity. Minimum significance level was set at $P < 0.05$.

Results

Table 1 shows the prevalence of MRONJ according to the different diseases of patients being treated with antiresorptive drugs. The highest prevalence of MRONJ (14.7%) was observed in patients with multiple myeloma, followed in decreasing order by patients with metastases from renal cancer (12.7%), lung cancer (3.9%), prostate cancer (3.4%), and breast cancer (2.6%). The lowest prevalence was found in patients with osteoporosis (1.7%).

Distribution of MRONJ studies according to the administration route of antiresorptive drug: Intravenous-intramuscular (IV-IM) or oral route and the drug administration time (in months) are shown in Table 2.

According to the studies on IV-IM administered drugs,[4-16] of 1909 patients, 288 (15.1%) developed MRONJ. The drugs most related to the MRONJ were, in descending order, the following: Denosumab + zoledronic acid (50.0% of cases), pamidronate + zoledronic acid (30.9%), denosumab (28.6%), zoledronic acid (17.2%), and pamidronate (12.9%).

In the studies on orally administered drugs,[5-7,16-19] of the 15,174 patients treated with these drugs, only 111 (0.7%) had MRONJ. Oral medications related to MRONJ, in decreasing order, were as follows: Risedronate (30.0% of cases), etidronate (17.6%), ibandronate (5.0%), and alendronate (0.6%).

Table 3 shows the main predictive risk factors associated with MRONJ.

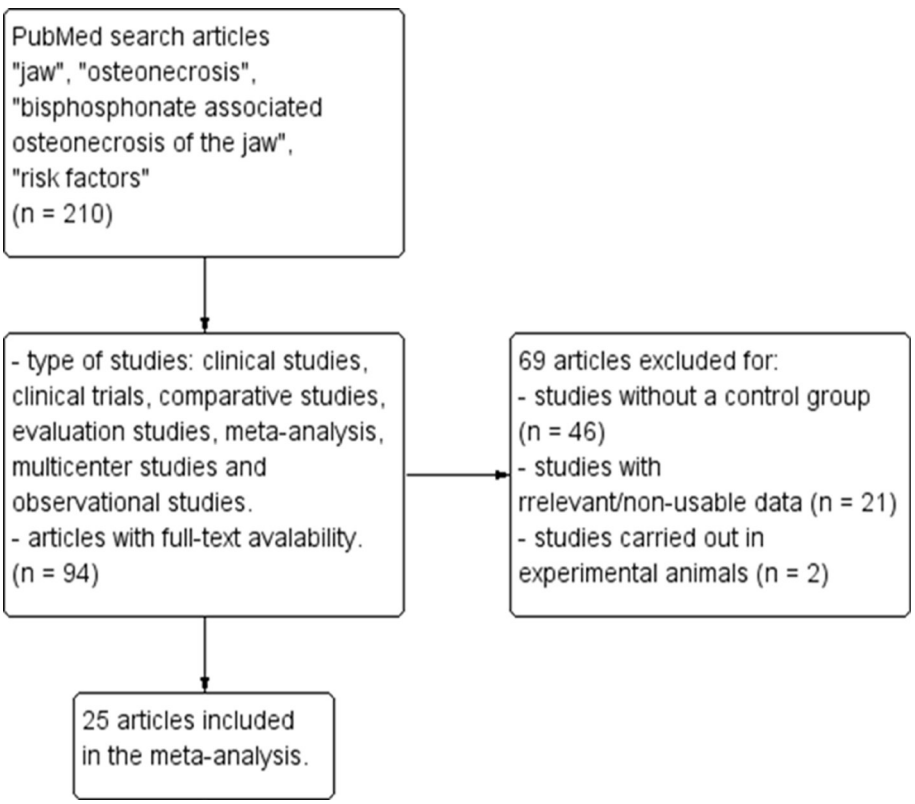

Figure 1: Study flow diagram

Twenty studies[6-10,12-27] considered age as a possible risk factor for MRONJ, observing a higher mean age (1.87 years more on average) in MRONJ patients compared to controls with a statistically very significant relationship (MD=1.87, 95% CI: 0.50–3.24, $P < 0.01$).

Regarding gender, 19 studies[7,8,10-13,15-24,26-28] analyzed this parameter as a potential risk factor, finding 1.23 times more probability of MRONJ in women than in men, with a statistically significant association (OR=1.23, 95% CI: 1.04–1.45, $P = 0.01$).

Drug administration by IV-IM route increased 4.03-fold the MRONJ risk with statistically significant differences (OR=4.03, 95% CI: 1.10–14.72, $P = 0.04$).

Regarding the drug administration time, MRONJ patients received the antiresorptive drug for longer (8.77 months more on average) than those who did not have MRONJ. After statistical analysis, a very significant association was found (MD=8.77, 95% CI: 3.14–14.41, $P < 0.01$).

Twelve studies[4,8,10,11,13,17-19,21,23,26,27] assessed the possible influence of corticosteroid intake on the MRONJ risk without finding any statistically significant effect (OR=0.84; 95% CI: 0.42–1.66, $P = 0.61$). On the other hand, five studies[4,8,21,13,17] also analyzed the role of the antiangiogenic agents intake on the MRONJ risk with no statistically significant relationship (OR=0.83, 95% CI: 0.40–1.81, $P = 0.67$).

Eight studies[8,9,12,13,16,18,22,27] considered the tooth extractions, finding an important increase of 6.85 times in the MRONJ risk. After the statistical analysis, highly significant differences were observed (OR=6.85, CI: 4.21–11.16, $P < 0.001$). Two studies[8,16] investigated the dental implant placement as a possible triggering factor of MRONJ without a statistically significant relationship (OR=0.88, 95% CI: 0.29–2.74, $P = 0.83$). Five studies[4,8,11,16,22] analyzed the periodontal treatments although no statistically significant association was found (OR=0.97, 95% CI: 0.51–1.84, $P = 0.92$). Finally, other five studies[8,9,11,16,25] assessed whether being a removable denture wearer could be an MRONJ risk. There was no significant influence after statistical analysis (OR=0.96, 95% CI: 0.57–1.64, $P = 0.89$).

Table 1: Prevalence of MRONJ considering the different diseases

Disease	*n*	Study references	n/N (%)
Breast cancer metastasis	12	[4-12,20-22]	130/5091 (2.6)
Multiple myeloma	11	[4,6,10,13-17,21-23]	134/914 (14.7)
Prostate cancer metastasis	9	[4,6-8,10-12,20,21]	70/2053 (3.4)
Osteoporosis	7	[7,16,18,22,26-28]	334/19352 (1.7)
Lung cancer metastasis	6	[6,7,10,12,20,22]	9/230 (3.9)
Kidney cancer metastasis	4	[6,10,11,12]	25/206 (12.1)

n: Number of studies; n/N: Number of MRONJ cases/total number of individuals taking antiresorptive drugs; %: Percentage of MRONJ patients. MRONJ: Medication-related osteonecrosis of the jaw

Table 2: Data about MRONJ according to the antiresorptive drug administration

IV-IM route drugs	*n*	Study references	n/N (%)
Zoledronic acid	13	[4-16]	194/1126 (17.2)
Pamidronate	7	[4-6,10,13,15,16]	43/333 (12.9)
Pamidronate+zoledronic acid	6	[4-7,10,13]	46/149 (30.9)
Denosumab	2	[7,12]	2/7 (28.6)
Denosumab+zoledronic acid	2	[7,12]	3/6 (50.0)
Oral route drugs	*n*	Study references	n/N (%)
Alendronate	5	[7,16-19]	98/15,107 (0.6)
Risedronate	3	[7,16,19]	9/30 (30.0)
Ibandronate	3	[5,6,16]	1/20 (5.0)
Etidronate	1	[19]	3/17 (17.6)

IV-IM route: Intravenous-intramuscular route; *n*: Number of studies; n/N: Number of MRONJ cases/total number of individuals taking antiresorptive drugs; %: Percentage of MRONJ patients. MRONJ: Medication-related osteonecrosis of the jaw

Table 3: Main predictive risk factors for MRONJ

Predictive risk factor	*n*	Reference value	Statistic	95% CI	I^2 (%)	*P* value
Age	20	↑ age (years)	MD: 1.87	0.50–3.24	70	<0.01*
Gender	19	Female	OR: 1.23	1.04–1.45	37	0.01*
Drug administration route	17	IV-IM	OR: 4.03	1.10–14.72	64	0.04*
Drug administration time	10	↑ time (months)	MD: 8.77	3.14–14.41	53	<0.01*
Corticosteroids	12	Yes	OR: 0.84	0.42–1.66	88	0.61
Antiangiogenic agents	5	Yes	OR: 0.85	0.40–1.81	61	0.67
Tooth extraction	8	Yes	OR: 6.85	4.21–11.16	65	<0.001*
Dental implant placement	2	Yes	OR: 0.88	0.29–2.74	0	0.83
Periodontal treatments	5	Yes	OR: 0.97	0.51–1.84	83	0.92
Removable denture wearers	5	Yes	OR: 0.96	0.57–1.64	0	0.89
Tobacco consumption	7	Yes	OR: 1.76	1.13–2.75	0	0.01*
Diabetes mellitus	12	Yes	OR: 1.78	0.93–3.41	90	0.08

n: Number of studies; MD: Mean differences; OR: Odds ratio; 95% CI: 95% confidence interval; I^2 (%): Higgins statistic for heterogeneity; ↑: Higher; IV-IM: Intravenous-intramuscular route; *Statistically significant. MRONJ: Medication-related osteonecrosis of the jaw

Regarding tobacco consumption, seven studies[8-11,16,20,27] reviewed its role as a possible MRONJ risk. Smoking increased 1.76-fold the MRONJ risk with a statistically significant relationship (OR=1.76, 95% CI: 1.13–2.75, $P = 0.01$).

Twelve studies[9-11,15,18-21,23,26-28] analyzed the influence of diabetes mellitus as a possible MRONJ risk factor. Diabetes mellitus did not have a significant influence on the MRONJ risk (OR=1.78, 95% CI: 0.93–3.41, $P = 0.08$).

Discussion

In the present meta-analysis on the possible risk factors associated with MRONJ, data from 28 studies have been included.

Antiresorptive drugs are fundamentally used for the treatment of tumors or metastatic bone lesions and for the treatment of osteoporosis. Patients with multiple myeloma were the most frequent group with MRONJ (14.7%), followed by patients with metastases from different tumors: Kidney cancer (12.1%), lung cancer (3.9%), prostate cancer (3.4%), and breast cancer (2.6%). In patients with osteoporosis, this frequency was the lowest (1.7%). The 22 studies[4-18,20-23,26-28] that reviewed the epidemiological data coincide in pointing out that the MRONJ appears mainly in oncology patients and in a much lower percentage in osteoporosis patients. Probably, this higher prevalence in multiple myeloma is due to the existence of multiple bone lesions in this disease where the myeloid plasma cells infiltrate the bone marrow, inhibiting the normal mechanisms of bone repair, and activating its destruction.[16] In the MRONJ, colonies of *Actinomyces* and other bacteria are frequently isolated, especially in the areas of bone resorption and necrotic bone. Bacterial metabolism liberates lipopolysaccharides that induce the production of multiple pro-inflammatory cytokines and biological mediators involved in bone resorption and in the inhibition of the expression of osteoprotegerin, a bone protective factor.[14]

In this study, patients with MRONJ had a higher mean age (1.87 years more on average) than subjects without MRONJ with statistically significant differences ($P < 0.01$). Fourteen[6-10,12-16,21,24,26,27] of the 20 studies that analyzed this parameter coincide in pointing out that patients with MRONJ were older. However, this higher average age is not due to the MRONJ itself but to the underlying disease (cancer and osteoporosis) of the patients who develop it.[16]

With regard to gender, women were 1.23 times more likely to had MRONJ, with a statistically significant association ($P = 0.01$). Eight[8,11,18-20,25-27] of the 19 studies that considered this variable found a greater number of women than men with MRONJ. As with age, this predilection for female gender may not be directly related to MRONJ, but rather to certain pathologies such as osteoporosis or breast cancer that is especially prevalent in women. For example, in the case of osteoporosis, treatment with bisphosphonates to prevent osteoporotic fractures has replaced hormone replacement therapy due to the relationship between estrogens and breast cancer.[19]

Antiresorptive drug administration route (IV-IM or oral) as well as the drug administration time were also considered. Among drugs administered by IV-IM route, the drug most linked to MRONJ was the combination of denosumab plus zoledronic acid with 50% of cases, followed by pamidronate + zoledronic acid (30.9% of cases), denosumab (28.6%), zoledronic acid (17.2%), and pamidronate (12.9%). The greater frequency of MRONJ in patients with joint administration of denosumab and zoledronic acid and could be explained by the possible synergism of its adverse effects that increase the risk of developing it. The main adverse effects of denosumab and zoledronic acid administration are anemia, back pain, anorexia, nausea, fatigue, constipation, bone pain, asthenia, arthralgia, vomiting, hypocalcemia, renal toxicity, and new primary malignancies. Denosumab presents less risk of anemia, anorexia, and renal toxicity, while zoledronic acid is associated with a lower risk of hypocalcemia and new primary malignancies.[29] Antiresorptive drug administered orally that presented the highest number of cases of MRONJ was risedronate (30% of cases), followed in decreasing order, etidronate (17.6%), ibandronate (5%), and alendronate (0.6%).

IV-IM-administered antiresorptive drugs increased 4.03-fold the MRONJ risk with statistically significant differences ($P = 0.04$). Several studies have confirmed this increased MRONJ risk with IV-IM-administered antiresorptive drugs.[5,15,26] These patients tend to receive high-potency drugs at high cumulative doses for the treatment of life-threatening diseases such as multiple myeloma and several types of cancer with bone metastases,[15] which lead to an increased MRONJ risk.[16]

With regard to the drug administration time, MRONJ patients were treated for a longer time (8.77 months more on average), with a statistically significant association ($P < 0.01$). MRONJ risk increased as the drug administration time raised.[5,13]

Other drugs (corticosteroids and antiangiogenic agents) were studied as possible MRONJ risk factors. These drugs were not an MRONJ risk factor without a statistically significant relationship both in the case of corticosteroids ($P = 0.61$) as in that of antiangiogenic drugs ($P = 0.67$). The possible role of steroid drugs in the pathogenesis of this disease is not clear. Although corticosteroids are commonly used in the cancer treatment,[4] its immunosuppressive activity could have several effects on tissues, delaying healing, and disturbing oral microbiota composition with the subsequent risks of superinfection and MRONJ.[21]

In the case of antiangiogenic agents, these could inhibit the mechanisms of vascular repair in the maxillary bones, contributing in this way to the potential development of MRONJ.[21] MRONJ has been associated with various triggering factors including different dental treatments. In the present study, tooth extraction was the most risk dental treatment since it raised 6.85 times the MRONJ risk with highly significant statistically differences ($P < 0.001$). Eight studies[8,9,12,13,16,18,22,27] evidenced this increased risk related to dental extractions. Antiresorptive drug treatment interferes with the post-extraction healing process, with the absence of bone resorption, deficient vascularity, and a low number of osteoclasts that alter bone maturation and favor

the development of osteonecrosis.[8] In addition, the MRONJ risk increased as the time of the use of these drugs raised, especially when it was longer than 2 years. Therefore, the health professional must always keep this possibility in mind, establishing appropriate preventive measures and carrying out the early diagnosis of this complication in case of presenting itself.[16]

In this study, neither dental implant placement ($P = 0.83$), nor periodontal treatment ($P = 0.92$), nor the treatment with removable dentures ($P = 0.89$) had a significant influence on MRONJ risk. Both periodontitis and the antiresorptive drug intake could interfere with bone resorption in the maxillary bones. In periodontal disease, the bone is exposed to bacterial toxins, inflammatory cytokines, and an environment of oxidative stress that would favor osteonecrosis.[8] The tissues of removable denture wearers suffer more frequently from traumatic events and alterations in the bone apposition-resorption pattern due to local pressure areas. These facts could act as possible precipitating factors of MRONJ.[25]

With respect to tobacco consumption, smokers had a 1.76-fold higher risk of MRONJ with a statistically significant relationship ($P = 0.01$). The seven studies[8-11,16,20,27] that considered this harmful habit proved its influence. Tobacco consumption alters bone metabolism, creating adequate conditions for the development of osteonecrosis in conjunction with other factors.[16]

Finally, in the present study, some systemic diseases such as diabetes mellitus had no significant influence on MRONJ risk ($P = 0.08$). However, some hypoglycemic drugs may induce changes in the oral microbiota composition favoring gingival infections, in addition to affecting bone turnover.[26] On the other hand, microangiopathy of diabetes mellitus patients might be an event that favors the development of MRONJ.[15]

The preventive measures of the MRONJ should be implemented before starting treatment with the antiresorptive agents. A complete and exhaustive dental examination (clinical and radiological) should be performed. Teeth that cannot be restored or that have a poor prognosis should be removed. Any infection in the oral cavity must be adequately treated. Removable denture wearers are susceptible to local trauma and dentures should be periodically checked to ensure a good fit and stability of the denture to avoid mucosal lesions. Dental surgery must be performed before antiresorptive therapy is initiated. Tooth extractions must be very careful to achieve good wound closure and restitution of the oral mucosal integrity.[30]

This study has some limitations. When searching in PubMed database, almost exclusively English language studies were considered, assuming a language restriction and the chance of language and publication bias. Another potential limitation lies in the large differences in the sample sizes existing in the studies included in this meta-analysis. Studies with small sample sizes tend to have low statistical power and may induce erroneous inferences. Moreover, other interesting variables such as type, site or complexity of tooth extractions, or the amounts and form of tobacco and/or alcohol consumption could not be contemplated.

The results of this meta-analysis should be interpreted with caution due to the high heterogeneity of some of the studies included in it. The differences between different studies would be conditioned by several factors that could be sources of bias.

Conclusions

In this meta-analysis, 15.1% of patients who received IV-IM antiresorptive drugs and 0.7% of those who received orally antiresorptive drugs had MRONJ. The risk factors related to MRONJ were as follows: the IV-IM drug administration (OR: 4.03), an older age (MD: 1.87 years), female gender (OR: 1.23), tobacco consumption (OR: 1.76), and tooth extraction as a dental background (OR: 6.85). Corticosteroids or antiangiogenic agents intake, dental implant placement, periodontal treatment, be a removable denture wearer or be diabetic, had no significant influence.

References

1. Omolehinwa TT, Akintoye SO. Chemical and radiation-associated jaw lesions. Dent Clin North Am 2016;60:265-77.
2. Dodson TB. The frequency of medication-related osteonecrosis of the jaw and its associated risk factors. Oral Maxillofac Surg Clin North Am 2015;27:509-16.
3. Campisi G, Fedele S, Fusco V, Pizzo G, Di Fede O, Bedogni A, *et al.* Epidemiology, clinical manifestations, risk reduction and treatment strategies of jaw osteonecrosis in cancer patients exposed to antiresorptive agents. Future Oncol 2014;10:257-75.
4. Estilo CL, Van Poznak CH, Wiliams T, Bohle GC, Lwin PT, Zhou Q, *et al.* Osteonecrosis of the maxilla and mandible in patients with advanced cancer treated with bisphosphonate therapy. Oncologist 2008;13:911-20.
5. Fehm T, Beck V, Banys M, Lipp HP, Hairass M, Reinert S, *et al.* Bisphosphonate-induced osteonecrosis of the jaw (ONJ): Incidence and risk factors in patients with breast cancer and gynecological malignancies. Gynecol Oncol 2009;112:605-9.
6. La Ferla F, Paolicchi E, Crea F, Cei S, Graziani F, Gabriele M, *et al.* An aromatase polymorphism (g.132810C and gt;T) predicts risk of bisphosphonate-related osteonecrosis of the jaw. Biomark Med 2012;6:201-9.
7. Iwata E, Akashi M, Kishimoto M, Kusumoto J, Hasegawa T, Furudoi S, *et al.* Meaning and limitation of cortical bone width measurement with dentascan in medication-related osteonecrosis of the jaws. Kobe J Med Sci 2017;62:E114-9.
8. Manfredi M, Mergoni G, Goldoni M, Salvagni S, Merigo E, Meleti M, *et al.* A 5-year retrospective longitudinal study on the incidence and the risk factors of osteonecrosis of the jaws in patients treated with zoledronic acid for bone metastases from solid tumors. Med Oral Patol Oral Cir Bucal 2017;22:e342-8.
9. Pilanci KN, Alco G, Ordu C, Sarsenov D, Celebi F, Erdogan Z, *et al.* Is administration of trastuzumab an independent risk factor for developing osteonecrosis of the jaw among metastatic breast cancer patients under zoledronic acid treatment? Medicine (Baltimore) 2015;94:e671.
10. Thumbigere-Math V, Michalowicz BS, Hodges JS, Tsai ML, Swenson KK, Rockwell L, *et al.* Periodontal disease as a risk factor for bisphosphonate-related osteonecrosis of the jaw. J

Periodontol 2014;85:226-33.
11. Vidal-Real C, Pérez-Sayáns M, Suárez-Peñaranda JM, Gándara-Rey JM, García-García A. Osteonecrosis of the jaws in 194 patients who have undergone intravenous bisphosphonate therapy in spain. Med Oral Patol Oral Cir Bucal 2015;20:e267-72.
12. Watanabe S, Nakajima K, Mizokami A, Yaegashi H, Noguchi N, Kawashiri S, *et al.* Bone scan index of the jaw: A new approach for evaluating early-stage anti-resorptive agents-related osteonecrosis. Ann Nucl Med 2017;31:201-10.
13. 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.
14. Cetiner S, Sucak GT, Kahraman SA, Aki SZ, Kocakahyaoglu B, Gultekin SE, *et al.* Osteonecrosis of the jaw in patients with multiple myeloma treated with zoledronic acid. J Bone Miner Metab 2009;27:435-43.
15. Jarnbring F, Kashani A, Björk A, Hoffman T, Krawiec K, Ljungman P, *et al.* Role of intravenous dosage regimens of bisphosphonates in relation to other aetiological factors in the development of osteonecrosis of the jaws in patients with myeloma. Br J Oral Maxillofac Surg 2015;53:1007-11.
16. Koth VS, Figueiredo MA, Salum FG, Cherubini K. Interrelationship of clinical, radiographic and haematological features in patients under bisphosphonate therapy. Dentomaxillofac Radiol 2017;46:20160260.
17. Then C, Hörauf N, Otto S, Pautke C, Von Tresckow E, Röhnisch T, *et al.* Incidence and risk factors of bisphosphonate-related osteonecrosis of the jaw in multiple myeloma patients having undergone autologous stem cell transplantation. Onkologie 2012;35:658-64.
18. 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.
19. Etminan M, Aminzadeh K, Matthew IR, Brophy JM. Use of oral bisphosphonates and the risk of aseptic osteonecrosis: A nested case-control study. J Rheumatol 2008;35:691-5.
20. Kajizono M, Sada H, Sugiura Y, Soga Y, Kitamura Y, Matsuoka J, *et al.* Incidence and risk factors of osteonecrosis of the jaw in advanced cancer patients after treatment with zoledronic acid or denosumab: A Retrospective cohort study. Biol Pharm Bull 2015;38:1850-5.
21. Saad F, Brown JE, Van Poznak C, Ibrahim T, Stemmer SM, Stopeck AT, *et al.* Incidence, risk factors, and outcomes of osteonecrosis of the jaw: Integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol 2012;23:1341-7.
22. Yuh DY, Chang TH, Huang RY, Chien WC, Lin FG, Fu E, *et al.* The national-scale cohort study on bisphosphonate-related osteonecrosis of the jaw in Taiwan. J Dent 2014;42:1343-52.
23. Torres SR, Chen CS, Leroux BG, Lee PP, Hollender LG, Lloid M, *et al.* Mandibular inferior cortical bone thickness on panoramic radiographs in patients using bisphosphonates. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119:584-92.
24. Cardemil C, Thomsen P, Wexell CL. Jaw bone samples from bisphosphonate-treated patients: A Pilot cohort study. Clin Implant Dent Relat Res 2015;17 Suppl 2:e679-91.
25. Tsao C, Darby I, Ebeling PR, Walsh K, O'Brien-Simpson N, Reynolds E, *et al.* Oral health risk factors for bisphosphonate-associated jaw osteonecrosis. J Oral Maxillofac Surg 2013;71:1360-6.
26. Chiu WY, Chien JY, Yang WS, Juang JM, Lee JJ, Tsai KS, *et al.* The risk of osteonecrosis of the jaws in taiwanese osteoporotic patients treated with oral alendronate or raloxifene. J Clin Endocrinol Metab 2014;99:2729-35.
27. Hasegawa T, Kawakita A, Ueda N, Funahara R, Tachibana A, Kobayashi M, *et al.* A multicenter retrospective study of the risk factors associated with medication-related osteonecrosis of the jaw after tooth extraction in patients receiving oral bisphosphonate therapy: Can primary wound closure and a drug holiday really prevent MRONJ? Osteoporos Int 2017;28:2465-73.
28. Kwon JW, Park EJ, Jung SY, Sohn HS, Ryu H, Suh HS, *et al.* A large national cohort study of the association between bisphosphonates and osteonecrosis of the jaw in patients with osteoporosis: A Nested case-control study. J Dent Res 2015;94:212S-9.
29. Chen F, Pu F. Safety of denosumab versus zoledronic acid in patients with bone metastases: A Meta-analysis of randomized controlled trials. Oncol Res Treat 2016;39:453-9.
30. Otto S, Pautke C, Van den Wyngaert T, Niepel D, Schiødt M. Medication-related osteonecrosis of the jaw: Prevention, diagnosis and management in patients with cancer and bone metastases. Cancer Treat Rev 2018;69:177-87.

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