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Knowledge Level of Physicians Prescribing Bisphosphonates: Prevention and Treatment of Medication-Related Osteonecrosis of the Jaw

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ABSTRACT

Introduction: Medication-related osteonecrosis of the jaw (MRONJ) is an important uncommon complication. Due to its complexity, its prevention requires a multidisciplinary approach, involving physicians and dental clinicians.

Materials and Methods: This study aimed to assess the knowledge level of physicians prescribing bisphosphonates in Tehran, Iran, about dental considerations in such patients and the prevention and treatment of MRONJ in 2019. This descriptive, cross-sectional study evaluated 100 physicians (rheumatologists, endocrinologists, oncologists, and orthopedists) practicing in Tehran. A questionnaire comprising a demographic section and knowledge questions regarding dental considerations in patients taking bisphosphonates was administered among the physicians. The frequency of qualitative variables such as gender, type of specialty, and physicians' responses to each question was calculated, and the knowledge scores were analyzed separately based on the physicians' specialty types using one-way ANOVA followed by Tukey's test for pairwise comparisons. The effect of different variables on knowledge scores was analyzed by simple regression.

Results: The mean knowledge score of physicians was 5.19±1.78 (range 2-8). The mean knowledge score of oncologists was significantly higher than that of endocrinologists (5.88 versus 4.52, P=0.03). No other significant differences were noted. Work experience (P=0.04), age (P=0.02), orthopedics specialty (P=0.05), and oncology specialty (P=0.006) had significant effects on the knowledge score.

Conclusion: Considering acquiring about 50% of the total score, physicians seem to have limited knowledge about dental considerations in patients taking bisphosphonates.

Keywords: Knowledge; Tehran; Bisphosphonates; Bisphosphonate-associated osteonecrosis of the jaw.

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Introduction

Bisphosphonates are a group of medications prescribed for conditions such as osteoporosis and malignant bone metastasis. Bisphosphonates caused great progress in the treatment of musculoskeletal disorders such that they are currently among the most commonly used medications for the clinical treatment of osteoporosis. Moreover, some reports are available regarding their effective role in the management of some other skeletal and joint diseases such as Paget's disease, bone metastasis, developmental anomalies, dysplastic fibrosis, Charcot arthropathy, sympathetic dystrophy, aseptic osteomyelitis, multiple myeloma, osteopenia, and osteogenesis imperfecta [1,2].

Despite the numerous advantages of bisphosphonates, recently, osteonecrosis of the jaw was proposed as a major complication developing in patients taking bisphosphonates. Medication-related osteonecrosis of the jaw (MRONJ) was first described by Marx in 2003; since then, the number of reported cases of MRONJ has increased [3-6]. The exact mechanism of MRONJ has not yet been clarified. MRONJ is characterized by an exposed area of the jawbone, remaining for more than 8 weeks in patients who have not undergone radiotherapy but have a history of, or are currently taking bisphosphonates [7]. Bisphosphonates are deposited in bone and are integrated into the bone matrix and by suppressing the recruitment and activity of osteoclasts inhibit bone resorption. They also have anti-angiogenic properties. Under such circumstances, the bone turnover greatly decreases, and the bone undergoes slight physiological remodeling over time. Thus, the bone becomes brittle and cannot repair the tiny fractures that occur during daily activities [8]. Available studies show that physician information about bisphosphonates and their side effects is insufficient. Patients should be informed by a dentist or oral surgeon about the possible risk of these drugs [9]. This study aimed to assess the knowledge level of physicians prescribing bisphosphonates (oncologists, orthopedists, rheumatologists, and endocrinologists) in Tehran city about dental considerations in such patients and the prevention and treatment of MRONJ.

Materials and Methods

This descriptive, cross-sectional study evaluated four groups of physicians namely oncologists, orthopedists, rheumatologists, and endocrinologists practicing in private and public sectors in Tehran city. The sample size of this study is 89 physicians which are increased to 100, determined by the confidence interval for the one-proportion option in PASS software, with $\propto$=0.05, P=0.7, and a confidence limit of 2%. The list of names of all specialists practicing in Tehran in 2019 was obtained from the Medical Council of Iran. After obtaining their address and necessary coordination, they were provided with a questionnaire and a return envelope. An arrangement was then made with their secretary for the collection of the completed questionnaires. The physicians were ensured of the confidentiality of their information, and the questionnaires were filled out anonymously.

Some of the physicians from the list of eligible physicians have been selected. The inclusion criteria were being a member of the Medical Council of Iran, having a permanent work permit, and having clinical practice in the private or public sector in Tehran city. Physicians without clinical practice and those unwilling to participate in the study were excluded. A researcher-designed questionnaire was used to assess the knowledge level of physicians about MRONJ, and its prevention and treatment. The first part of the questionnaire asked for the demographic information of participants such as their age, gender, and work experience (in years). The second part of the questionnaire contained questions to assess the knowledge level of participants regarding dental considerations in patients taking bisphosphonates and the prevention and treatment of MRONJ.

The questionnaire consisted of 10 questions and the range of total possible scores was 0 to 10 (Table 1). Each correct answer was given a score of 1 while each incorrect answer was allocated a 0 score. To assess the content validity of the questions, three faculty members were requested to read the questionnaire and apply the necessary modifications. Inappropriate questions were deleted according to their expert opinion, and necessary modifications were made. In case of no response to over 25% of the questions, the respective questionnaire would be excluded from the final analysis. After the completion of 20 questionnaires by the physicians, the reliability of the questions was evaluated using Cronbach's alpha. The Cronbach's alpha coefficient can range from 1 to 0 and indicates the internal consistency of the questions. Cronbach's alpha=0 indicates the absence of internal consistency and reliability while Cronbach's alpha=1 indicates complete internal consistency or reliability. The reliability of the questionnaire after two assessments were calculated to be 0.75, which was acceptable.

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Statistical Analysis

A total of 100 physicians practicing in Tehran participated in this study including 25 orthopedists, 25 oncologists, 25 rheumatologists, and 25 endocrinologists. There were 36 females and 63 males in the study; the gender of one participant was not specified. Table 1 is the questionnaire and table 2 summarizes the frequency of correct answers from physicians. Accordingly, the mean knowledge score of physicians was found to be 5.19±1.78 (range 2-8). According to one-way ANOVA, a significant difference existed in the knowledge score of different specialty groups (P=0.05). Thus, pairwise comparisons were carried out using Tukey's test, which revealed a significant difference between endocrinologists and oncologists regarding their knowledge level about dental considerations in patients taking bisphosphonates (P=0.03). However, the difference between orthopedists and rheumatologists (P=0.88), orthopedists and endocrinologists (P=0.33), oncologists and rheumatologists (P=0.29), and rheumatologists and endocrinologists (P=0.76) was not significant. Table 3 shows the measures of central dispersion of the knowledge score of different specialty groups. According to the results of the regression test, parameters such as work experience (P=0.04), age (P=0.02), orthopedics specialty (P=0.04), and oncology specialty (P=0.006) had significant relation with the knowledge score. However, the type of practice (private or public sector) (P=0.75), gender (P=0.32), and rheumatology specialty (P=0.07) had no significant relation to the knowledge score.

Table 1. Answers of physicians in Tehran about questions related to awareness of dental considerations for patients treated with bisphosphonate in 2019.

Number	Question	Response choices	Correct answer
1	A patient under treatment with intravenous bisphosphonates has a severe toothache. What protocol should be followed?	A. Tooth extraction B. Analgesics and antibiotics C. Endodontic treatment D. Nothing	C
2	What is the latest time for dental procedures prior to injection of bisphosphonates?	A. One month earlier B. Two weeks earlier C. Two months earlier D. One week earlier	C
3	Do you recommend a dental checkup prior to initiation of bisphosphonate injections?	A. Yes B. No C. It is not important	A
4	In case of development of MRONJ following bisphosphonate injection, who would you refer the patient to?	A. General dentist B. Oral and maxillofacial surgeon C. Periodontist D. ENT specialist	B
5	Do you have any information regarding the treatment of MRONJ?	A. No B. My information is sufficient for its treatment C. My information is sufficient for its diagnosis and referral of patient D. My information is not sufficient for its diagnosis and treatment.	C
6	What is the most common clinical manifestation of MRONJ?	A. Irregular mucosal ulceration and exposure of mandible or maxilla B. Suppurative infection C. Pain or swelling of the jaw D. Paresthesia or sensation of heaviness	A
7	Which dental procedures are the safest in patients taking bisphosphonates and do not require special considerations?	A. Tooth extraction and dental surgery B. Scaling and restoration of teeth C. Endodontic treatment and endodontic surgery D. Bone grafting and dental implantation	C
8	Do we need to discontinue oral bisphosphonates in a patient that requires dental surgery and implant placement?	A. Yes B. No C. It is not important	A
9	In case of discontinuation of bisphosphonate, what protocol should be followed?	A. It should be discontinued from 3 months before to 3 months after the surgery B. It should be discontinued from 1 month before to 3 months after surgery C. It should be discontinued from 2 months before to 1 month after surgery D. It should be discontinued from 1 week before to 1 week after surgery	A
10	In patients with MRONJ, what medication would you prescribe in what dosage after tooth extraction?	A. 500 mg amoxicillin 3 times a day for 3 weeks B. 500 mg amoxicillin 3 times a day for 2 weeks C. 500 mg amoxicillin 3 times a day for 4 weeks D. 500 mg amoxicillin 3 times a day for 3 days	B

Table 2. Frequency of correct answers of physicians practicing in Tehran city regarding dental considerations in patients treated with bisphosphonates in 2019.

Question number	Number of physicians answered this question	Frequency of correct answer(percentage)
1	n=99	(23.2 %) 23
2	n= 100	(38.0 %) 38
3	n= 100	(64.0 %) 64
4	n= 100	(51.0 %) 51
5	n=99	(15.2 %) 15
6	n=98	(29.6 %) 29
7	n=100	(9.0 %) 9
8	n=98	(52.5 %) 52
9	n=100	(21.0 %) 21
10	n=100	(39.0 %) 39

Table 3. Central dispersion indices of awareness scores of physicians practicing in Tehran regarding dental considerations of patients treated with bisphosphonates in 2019.

Specialty	Mean	Std. deviation	Std. error	Minimum	Maximum
Orthopedists	5.36	1.32	0.26	3.0	8.0
Oncologists	5.88	2.22	0.44	3.0	10.0
Rheumatologists	5.0	1.66	0.33	2.0	8.0
Endocrinologists	4.52	1.64	0.33	2.0	7.0

Discussion

The general aim of this study is to evaluate the knowledge of physicians on MRONJ. It seems that physicians' information about dental considerations in patients receiving bisphosphonates is insufficient. Since the first report regarding MRONJ in 2003, several clinical and experimental studies have been conducted regarding its diagnosis, treatment, and prognosis; however, many aspects related to this condition are still unclear [10]. Due to the risk of recurrence of osteonecrosis of the jaw, there is no doubt that prevention is the best method of treatment. Thus, physicians should refer the patients for dental assessments and determination of risk factors before administration of bisphosphonates for them [11-13]. In 2005, the Food and Drug Administration pointed to the risk of MRONJ to raise awareness about this condition among health professionals. Kim et al, in 2016 reported that 9.21% of medical professionals had not heard about MRONJ while 9.9% correctly answered all five questions about it, indicating the poor knowledge of medical professionals about MRONJ [7]. Treatment of periodontal disease and oral and dental care is highly important in patients requiring bisphosphonate therapy [13,14]. Thus, they need to be informed about the incidence and significance of MRONJ and should be provided with the necessary instructions in this respect. The incidence of MRONJ following intravenous injection of bisphosphonates is 0.8% to 1.2% [15]. This rate is 0.00038% to 0.06% in patients with oral intake of bisphosphonates [16]. The diagnosis of MRONJ is not easy, and a diagnosis may not be reached due to conditions related to oral surgery [17].

Thus, a correct diagnosis of MRONJ is imperative in patients taking bisphosphonates. Mucosal ulceration and suppurative infection exposing the underlying bone is the most common clinical presentation of MRONJ. On the other hand, MRONJ does not well respond to different treatments. Thus, its prevention and early and accurate diagnosis are highly important [15]. Osteonecrosis of the jaw often develops in patients with intravenous administration of bisphosphonates; however, patients with oral intake of bisphosphonates may also develop MRONJ in some cases. The risk of development of osteonecrosis is low in patients using oral bisphosphonates for less than 3 years; therefore,

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this period is ideal for the assessment of the oral and dental status of patients [18,19]. A review of the literature on this topic revealed that most available studies have been conducted on the knowledge level of dental clinicians about MRONJ, and information regarding the knowledge level of physicians on this topic is limited. Hristamyan-Cilev et al, in 2019 evaluated the knowledge level of dentists practicing in Plovdiv, Bulgaria, and reported that 17.03% of the participants did not know about bisphosphonates and their side effects. Half of them reported that they had not visited any patient with complications of bisphosphonate treatment in their office, which could be related to their lack of knowledge in this respect [20]. In this study, the mean knowledge score of physicians about bisphosphonates and their side effects was found to be 5.19±1.78 (range 2-8). Kim et al. assessed the knowledge level of internal medicine specialists, family physicians, and orthopedists practicing in six medical centers in Seoul, and found that less than 30% of the patients had been referred to dental clinicians by physicians.

Oncologists better detected the need for referral of patients to dental clinicians, followed by endocrinologists, rheumatologists, family physicians, and orthopedists [7]. In this study the knowledge score of oncology specialists is significantly higher than that of endocrinology specialists (5.88 vs. 4.52); (p=0.03, but no significant differences were seen in this respect among other medical professionals. Senturk et al, in 2016 evaluated the knowledge level of oncologists in Ankara city about the adverse side effects and positive effects of bisphosphonates; 66% of them reported that MRONJ was the most common complication of taking bisphosphonates, and 39.6% reported referral of patients to dental clinicians, which was almost similar to the rate in our study [21]. Al-Mohaya et al. found that knowledge level had a significant correlation with expertise, work experience (years), and having a specialty degree [22]. It seems that aging and gaining work experience improve the knowledge of physicians about different diseases and their prevention and treatment. Since male and female physicians receive the same instructions in medical schools, the insignificant effect of gender on knowledge level is expected. On the other hand, younger graduates still have a fresh memory of what they have been taught in the university; this may explain the difference in the knowledge level of physicians with variable work experiences. When physicians do not encounter such patients, they may forget the management of such cases over time unless they receive complementary education in this respect.

Dentoalveolar surgery is the main risk factor for MRONJ. Moreover, periodontal disease, denture use, and implant placement can serve as predisposing factors for MRONJ [11,23]. In addition to local factors, parameters such as the type of bisphosphonate, duration of treatment, and form of prescribed medication can affect the development of MRONJ. Also, bisphosphonates containing nitrogen that is administered intravenously for a long time are a major risk factor for the development of MRONJ [11].

In patients at high risk of MRONJ, dental procedures such as tooth extraction, endodontic surgery, and implant placement should be preferably avoided [24]. Some dental procedures such as tooth extraction are a major risk factor for MRONJ. Evidence shows that tooth extraction is a common cause of MRONJ, causing this condition in 52% to 61% of the cases [11,25,27]. A cohort study reported that patients receiving bisphosphonate IV (zoledronate) who were candidates for dentoalveolar surgery (tooth extraction) had 33 times higher risk of development of MRONJ compared with those who were not candidates for this type of surgery. Some specialists discontinue the medication until its side effects vanish; this was particularly emphasized by Senturk et al [21]. Temporary discontinuation of medication (drug holiday) has been beneficial for the prevention of MRONJ in some cases and seems to be the first treatment strategy for MRONJ [28,29]. Nonetheless, temporary discontinuation of the drug seems to have no short-term benefit, but long-term discontinuation can help reach stability in areas of MRONJ, and decrease its signs and symptoms. [30-32].

As mentioned earlier, prevention is the best option for the treatment of MRONJ. Accordingly, the risk of the development of MRONJ decreases in the case of a referral of such patients by physicians to dentists. It is suggested to assess the oral health status of patients before the initiation of treatment with bisphosphonates and enhance the knowledge of patients regarding the risk of MRONJ [29]. Also, the patients should be provided with necessary oral hygiene instructions and should be informed about the signs and symptoms of MRONJ [30]. Screening and routine dental examination should be repeated every 3 months for such patients because bisphosphonates have long-term effects on bone [23]. Thus, dental clinicians should be involved in the treatment of such patients. The strengths of this study are the diversity of experts participating in it, the inclusion and exclusion criteria were accurately determined by professionals, and the results of

the study were evaluated by detailed tests. This study can inform physicians about the importance of dental considerations in patients receiving bisphosphonates and be the beginning of further studies in this field. Also, the current research problems include the lack of proper cooperation of selected physicians in some cases and Lack of knowledge of the subject in some cases by them, the geographical diversity of offices and clinics, which requires a lot of intra-city travel, and the need to visit each office twice for distribution and the withdrawal of the questionnaire.

Conclusion

According to the findings of the present study, it seems that the knowledge of physicians on dental considerations of patients taking bisphosphonates is limited. Enhanced knowledge of healthcare providers such as physicians and dentists about bisphosphonates can decrease the incidence of MRONJ and lead to a more favorable recovery [26]. Also, improved instruction of patients regarding the use and side effects of bisphosphonates by physicians can promote the quality of care and decrease the side effects of medical and dental treatments [33].

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Conflict of Interest

There is no conflict of interest to declare.

References

[1] Chapurlat RD, Delmas PD, Liens D, Meunier PJ. Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. J Bone Miner Res. 1997; 12(10):1746-1152.

[2] Verenna M, Zucchi F, Ghiringhelli D, Binelli L, Bevilacqua M, Bettica P. Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind, placebo controlled study. J Rheumatol. 2000; 27(6):1477-1483.

[3] Rosenberg TJ, Ruggiero S. Osteonecrosis of the jaws associated with the use of bisphosphnates. J Oral Maxillofac Surg. 2003; 61(8):60-61.

[4] Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg. 2004; 62(5):527-534.

[5] Greenberg MS. Intravenous bis-phosphonates and osteonecrosis. Oral Surg Oral Med Oral Radiol Endod. 2004; 93(3):259-260.

[6] Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis osteopetrosis) of the jaws: risk factors, recognition, prevention and treatment, J Oral Maxillofac Surg. 2005; 63(11):1567-1575.

[7] Kim JW, Jeong SR, Kim SJ, Kim Y. Perceptions of medical doctors on bisphosphonate-related osteonecrosis of the jaw. BMC Oral Health. 2016; 16(1):92.

[8] Hupp JR, Ellis IIIE, Tucker MR. Contemporary Oral and Maxillofacial Surgery. Mosby Co. Elsevier. 7th Edition 2019.

[9] IŞık, G, Özden Yüce, M, Özveri Koyuncu, B. & Mandıracıoğlu, A. Medication-related osteonecrosis of the jaw: awareness and level of knowledge of a group of Turkish physicians. Selcuk Dental Journal. 2022; 9 (2), 494-500.

[10] Reid IR, Cornish J. Epidemiology and pathogenesis of osteonecrosis of the jaw. Nat Rev Rheumatol. 2012; 8:90–96.

[11] Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O'Ryan F. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw–2014 update. J Oral Maxillofac Surg. 2014; 72:1938–1956.

[12] Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watt NB, Brandi ML, Peters E, Guise T, Eastell R, Cheung AM, Morin SN, Masri B, Cooper C, Morgan SL, Obermayer-Pietsch B, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res. 2015; 30:3–23.

[13] Lam DK, Sandor GK, Holmes HI, Evans AW, Clokie CM. A review of bisphosphonate-associated osteonecrosis of the jaws and its management. J Can Dent Assoc. 2007; 73:417–422.

[14] Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, et al. Bisphosphonate-associated osteo-

 DOI: 10.18502/jcr.v11i2.17024

necrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2007; 22:1479–1491.

[15] Pazianas M, Miller P, Blumentals WA, Bernal M, Kothawala P. A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonate: prevalence, risk factors, and clinical characteristics. Clin Ther. 2009; 29:1548–1558.

[16] Paeng JY. Diagnosis and management of BRONJ (bisphosphonate related osteonecrosis of jaw). J Korean Dent Assoc. 2011; 49:378–388.

[17] Choi SW, Kim SR, Lee KB. Osteonecrosis of the jaw in a patient with osteoporosis treated with oral bisphosphonates. J Korean Orthop Assoc. 2010; 45:151–154.

[18] Khan AA, Sandor GK, Dore E. Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaw. J Rheumatol. 2008; 35(7):1391-1397.

[19] Epstein JB, Kish RV, Hallajian L, Sciubba J. Head and neck oral and orophryngeal cancer: a review of medicolegal cases. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015; 119:177-186.

[20] Hristamyan-Cilev MA, Pechalova PP, Raycheva RD, Hristamyan VP, Kevorkyan AK, Stoilova YD. Bisphosphonate-associated osteonecrosis of the jaws: a survey of the level of knowledge of dentists about the risks of bisphosphonate therapy. Folia Med (Plovdiv). 2019;1; 61(2):303-311.

[21] Senturk MF, Cimen E, Tuzuner Oncul AM, Cambazoglu M. Oncologist's awareness about bisphosphonate related osteonecrosis of the jaws. J Pak Med Assoc. 2016; 66(7):880-883.

[22] Al-Mohaya MA, Al-Khashan HI, Mishriky AM, Al-Otaibi LM. Physicians' awareness of bisphosphonates-related osteonecrosis of the jaw. Saudi Med J. 2011; (8):830-835.

[23] Ruggiero SL, Dodson TB, Assael LA, Landsberg R, Mars RE, Mehrotra B. American Association of oral and maxillofacial surgeons' positions paper on bisphosphonate-related osteonecrosis of the jaws–2009 update. J Oral Maxillofac Surg. 2009; 67:2-12.

[24] Moinzadeh AT, Shemesh H, Neirynck NA, Aubert C, Wesselink PR. Bisphosphonates and their clinical implications in endodontic therapy. Int Endod J. 2013; 46(5):391-398.

[25] Vahtsevanos K, Kyrgidis A, Verrou E, Katodritou E, Triaridis S, Andreadis CG, Boukovinas I, Koloutsos GE, Teleioudis Z, Kitikidou K, Paraskevopoulos P, Zervas K, Antoniadaes K. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. J Clin Oncol. 2009; 27:5356-5362.

[26] Saad F, Brown JE, Van Poznak C, Ibrahim T, Stemmer SM, Stopeck AT, Diel IJ, Takahashi S, Shore N, Henry DH, Barrios CH, Facon T, Senecal F, Fizazi K, Zhou L, Daniels A, Carriere P, Dansey R. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bonemetastases. Ann Oncol. 2012; 23:1341-1347.

[27] Fehm T, Beck V, Banys M, Lipp HP, Hairass M, Reinert S, Solomayer EF, Wallwiener D, Krimmel M. Bisphosphonate-induced osteonecrosis of the jaw (ONJ): Incidence and risk factors in patients with breast cancer and gynecological malignancies. Gynecol Oncol. 2009; 112:605-609.

[28] Dickinson M, Prince HM, Kirsa S, Zannettino A, Gibbs SD, Mileshkin L, OGrady J, Seymour JF, Szer J, Horvath N, Joshua DE. Osteonecrosis of the jaw complicating bisphosphonate treatment for bone disease in multiple myeloma: an overview with recommendations for prevention and treatment. Intern Med J. 2009; 39:304-316.

[29] Kwon YD, KimYR, Choi BJ, Lee DW, Kim DY. Oral bis-phosphonate related osteonecrosis of the jaws: favorable outcome after bisphosphonate holiday. Quintessence Int. 2009; 40:277-278.

[30] McLeod NM, Brennan PA, Ruggiero SL. Bisphosphonate osteonecrosis of the jaw: a historical and contemporary review. Surgeon. 2012; 10:36-42.

[31] Vescovi P, Merigo E, Meleti M, Manfredi M, Guidotti R, Nammour S. Bisphosphonates-related osteonecrosis of the jaws: a concise review of the literature and a report of a single-centre experience with 151 patients. J Oral Pathol Med. 2012; 41:214-221.

[32] Patel V, McLeod NM, Rogers SN, Brennan PA. Bisphosphonate osteonecrosis of the jaw--a literature review of UK policies versus international policies

on bisphosphonates, risk factors and prevention. Br J Oral Maxillofac Surg. 2011; 49:251-257.

[33] Migliorati CA, Mattos K, Palazzolo MJ. How patients' lack of knowledge about oral bisphosphonates can interfere with medical and dental care. J Am Dent Assoc. 2010; 141(5):562-566.

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