

Knowledge Level of Yazd Dental Students about Medication-Related Osteonecrosis of the Jaw

Farzane Vaziri¹  | Sahar Chokami Rafiei²  | Amir Reza Taghavi³  | Mohammad Arab Farashahi^{1*} 

1. Department of Periodontics, Faculty of Dentistry, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

2. Department of Periodontics, Baqiyatallah University of Medical Sciences, Tehran, Iran.

3. Private Practice, Yazd, Iran.

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*Corresponding Author

Mohammad Arab Farashahi,
Department of Periodontics, Faculty
of Dentistry, Shahid Sadoughi
University of Medical Sciences, Yazd,
Iran.

Email: Sma.farashahi_69@yahoo.com

Abstract

Background and objectives: This study aimed to assess the knowledge level of Yazd dental students about bisphosphonate-related osteonecrosis of the jaw (MRONJ).

Materials and methods: This cross-sectional study was conducted on 113 fourth- to sixth-year dental students of School of Dentistry, Yazd Shahid Sadoughi University of Medical Sciences. A questionnaire was used to collect information regarding age, gender, academic year, grade point average (GPA), and history of encountering a case of MRONJ. The questionnaire had 13 multiple-choice questions regarding the knowledge level of students about the definition, classification, frequency of use, side effects, risk factors, and indications of bisphosphonates and treatment of MRONJ. Data were analyzed by t-test and Pearson's correlation test ($\alpha = 0.05$).

Results: A total of 69 (61.1%) female and 44 (38.9%) male dental students participated in this study. The mean knowledge score of students about MRONJ was 14.42 ± 3.84 out of 17. No significant difference was found in the mean knowledge score of male and female students ($P = 0.518$). Knowledge score of students had significant inverse correlations with their age ($r = -0.306$, $P = 0.001$) and academic year ($r = -0.184$, $P = 0.050$) and a significant direct correlation with their GPA ($r = 0.330$, $P = 0.000$).

Conclusion: The present results revealed good knowledge level of Iranian dental students regarding MRONJ. Knowledge level of students had significant inverse correlations with their age and academic year, and a significant direct correlation with their GPA.

Keywords: Bisphosphonate-associated osteonecrosis of the Jaw; Students; Dental; Knowledge.

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1. Introduction

Bisphosphonates are produced by synthesis of pyrophosphate analogues, and are characterized by a central structure composed of P-C-P chains. The mechanism of action of bisphosphonates has yet to be fully elucidated. However, several factors are believed to be implicated in this regard. Bisphosphonates accumulate in bone and are released during bone metabolism and

affect the activity of osteoclasts. Several mechanisms of action have been proposed for bisphosphonates: bisphosphonates inhibit the pre-osteoclasts, and induce apoptosis of osteoclasts. Moreover, they have a negative effect on angiogenesis, microenvironment, and communication of osteoclasts and osteoblasts regarding their function. Bisphosphonates are among the most important anti-resorptive and anti-angiogenic medications (1, 2). At present, bisphosphonates are the main

medications used for treatment of bone malignancies, osteoporosis, metabolic bone diseases, and Paget's disease due to their beneficial therapeutic effects (3, 4). Despite the favorable properties of bisphosphonates and their optimal efficacy in improving the quality of life of patients with bone metastasis or osteoporosis, bisphosphonate-related osteonecrosis of the jaw (MRONJ) is among their worst complications (5).

The first report regarding MRONJ was published in 2003 (6). Osteonecrosis is defined as bone necrosis due to impaired blood supply to the site. Upon occurrence, necrotic bone remains exposed at the site, leading to pain and infection. Clinically, MRONJ is characterized by an area of exposed alveolar bone, which appears spontaneously or following tooth extraction, apicoectomy, periodontal surgery, or dental implant placement (7).

The prevalent signs and symptoms of MRONJ include pain, swelling of soft tissue, draining fistula, infection and tooth mobility (8). The patients may also have eaten and speech problems, trismus, recurrent abscesses and halitosis while some others may experience uncommon symptoms such as dull pain and paresthesia. Some of the signs and symptoms of MRONJ may occur prior to development of clinical symptoms, such as changes in periodontal health status, non-healing mucosal ulcers, mobile teeth, and oral infections with no definite cause (9).

Duration of use of bisphosphonates, route of administration (intravenous or oral) and type of bisphosphonate (with or without nitrogen), are among the systemic risk factors for MRONJ (10). The correlation of bisphosphonates with osteonecrosis highlights the need for further attention to details (11).

The reason behind the occurrence of MRONJ is the unique structure of jawbone. Jawbone is constantly exposed to frequent micro-trauma due to the masticatory forces of the teeth. Moreover, the alveolar bone turnover is 10 times higher than that of long bones. Since bisphosphonates decrease bone turnover, their effect on the jawbone is greater than their effect on long bones (12).

In order to prevent MRONJ, a comprehensive dental examination should be performed before the initiation of bisphosphonate therapy. All potential oral and dental conditions should be treated to eliminate the need for invasive procedures after the onset of pharmaceutical therapy. Thus, dental clinicians should have adequate knowledge about bisphosphonates and their side effects to minimize the occurrence of MRONJ (6, 13, 14). Since the first report of MRONJ in 2003, it has been the topic of

numerous investigations (15). However, studies in the field of dental students' knowledge about MRONJ are limited (15, 16, 17, 18).

Therefore, this study aimed to assess the knowledge level of dental students in Yazd, Iran regarding MRONJ.

2. Materials and methods

2.1. Sample size

This cross-sectional study was conducted on 113 fourth- to sixth-year dental students of School of Dentistry of Yazd Shahid Sadoughi University of Medical Sciences in 2021.

2.2. Eligibility criteria

Fourth- to sixth-year dental students who were willing to participate in the study were randomly selected and enrolled. Incomplete questionnaires were excluded from the study.

2.3. Data collection

A researcher-designed questionnaire was employed for data collection. The questionnaire had 13 multiple-choice questions in four domains. The first domain included demographic information of patients such as their age, gender, academic year, grade point average (GPA), and history of encountering a case of MRONJ. The second domain included questions assessing the knowledge level of students about the definition, classification, and prevalence of intake of bisphosphonates. The third domain included questions assessing the knowledge about the side effects and risk factors of bisphosphonate intake. The fourth domain included questions regarding the indications for bisphosphonate intake, and treatment of MRONJ. The questions of this domain were designed according to the Newman and Carranza's Clinical Periodontology 2019, and their validity was confirmed by 5 faculty members of the Periodontics and Oral Medicine Departments of School of Dentistry of Yazd Shahid Sadoughi University of Medical Sciences. Ten questionnaires were filled out by dental students as pilot, and the results confirmed the reliability of the questionnaire with a Cronbach's alpha of 0.75. The participants were allowed 20 minutes to fill out the questionnaire.

Each correct answer was allocated one score. No negative score was allocated to wrong answers. Thus, the maximum and minimum scores that could be acquired were 17 and 0, respectively. Total scores between 0-6

indicated poor knowledge, scores between 7-12 indicated moderate knowledge and scores between 13-17 indicated good knowledge.

The questionnaire was designed in Porsline website as an online questionnaire and its link was sent to the participants through the social media. The questionnaires were filled out anonymously, and the participants were assured that their information would remain confidential.

2.4. Statistical analysis

Data were analyzed by SPSS version 25 using t-test and Pearson's correlation test at 0.05 level of significance.

3. Results

3.1. Demographics

All 113 participants returned the questionnaires (response rate of 100%), including 69 (61.1%) female and 44 (38.9%) male students. The mean age of dental students was 24.05 ± 13 years. The mean GPA of students was 16.72 ± 5 . There were 35 (31%) fourth-year, 33 (29.2%) fifth-year, and 45 (39.8%) sixth-year dental students. Of all, 7 (8.8%) dental students had encountered a case of MRONJ.

3.2. Frequency of responses to the questions

Tables 1 to 3 show the relative frequency of responses to the multiple-choice questions assessing knowledge about bisphosphonates, side effects and risk factors of

bisphosphonate intake, indications of bisphosphonates and treatment of MRONJ.

3.3. Knowledge level

The mean knowledge score of dental students about MRONJ was 14.42 ± 3.84 out of 17. The mean knowledge score was 14.66 ± 4.34 in males and 14.19 ± 3.35 in females. According to t-test, the difference in the mean knowledge score of male and female dental students was not significant ($P = 0.518$). The mean knowledge score was 9.71 ± 2.05 in dental students with a previous encounter with MRONJ cases and 14.55 ± 3.61 in those without such an encounter. This difference was statistically significant ($P = 0.001$).

The mean knowledge score of dental students had significant inverse correlations with their age ($r = -0.306$, $P = 0.001$) and academic year ($r = -0.184$, $P = 0.050$), and a significant direct correlation with their GPA ($r = 0.330$, $P < 0.01$).

The mean GPA was 15.50 ± 0.57 in those with a previous encounter with MRONJ cases and 16.75 ± 0.97 in those without such an encounter. This difference was statistically significant ($P = 0.017$).

Table 4 presents the responses of dental students to the question about their sources of information regarding MRONJ. As shown, the majority of dental students (65.5%) reported that they acquired their knowledge about MRONJ from their academic courses

Table 1. Frequency of responses to the multiple-choice questions assessing knowledge about bisphosphonates..

Question	Answer choices	Number	Frequency
Which of the followings correctly defines MRONJ?	Necrosis and exposure of jawbone for more than 8 weeks in patients taking bisphosphonate with no history of radiotherapy	56	49.6
	Necrosis and exposure of jawbone for over 4 weeks in patients taking bisphosphonate with a history of radiotherapy	9	8
	Necrosis and exposure of jawbone for over 4 weeks in patients taking bisphosphonate with no history of radiotherapy	18	15.9
	Necrosis and exposure of jawbone for over 8 weeks in patients taking bisphosphonate with a history of radiotherapy	27	23.9
Which of the followings is not a bisphosphonate?	(Fosamax) Alendronate	2	1.8
	(Acrel) Risendronate	0	0
	(Aredia) Disodinm Pamidronate	5	4.4
	(Zometa) Zoledronic Acid	33	29.2
	(Boniva) Ibandronate	6	5.3
	(Osteum) Etidronate	2	1.8
	(Skelide) Tiludronate	2	1.8
	(Bonefos) Clodronate**	61	54
Which medication form has	Oral	9	8

higher risk of MRONJ?	Intravenous injection**	97	85.8
	Topical	5	4.4
	Inhalation	2	1.8
How long is the half-life of bisphosphonates in bone?	10 years or more**	68	60.2
	1 year	16	14.2
	1 week	13	11.5
	1 month	14	12.4
Which statement best describes the correlation of bisphosphonate intake and MRONJ?	Only bisphosphonates without nitrogen can cause MRONJ.	5	4.4
	Only bisphosphonates containing nitrogen can cause MRONJ.	24	21.2
	Bisphosphonates containing nitrogen can cause MRONJ. **	47	41.6
	Bisphosphonates and all other medications containing nitrogen can cause MRONJ.	35	31
Which statement best describes the correlation of CTX and occurrence of MRONJ?	**Values ≤ 100 pg/mL of CTX are associated with high risk of occurrence of MRONJ.	19	16.8
	Values ≤ 101 -149 pg/mL are associated with low risk of occurrence of MRONJ.	59	52.2
	Values ≤ 150 -299 pg/mL are associated with moderate risk of occurrence of MRONJ.	22	19.5
	Values ≤ 300 -600 pg/mL are associated with moderate risk of occurrence of MRONJ.	4	3.5
Do you think it is important to ask patients about bisphosphonate intake?	Yes**	98	86.7
	No	5	4.4
Which jaw and which areas are at higher risk of MRONJ?	Maxilla- posterior	20	17.7
	Maxilla- anterior	18	15.9
	Mandible- posterior**	70	61.9
	Mandible- anterior	2	1.8
What are the more common sites of occurrence of MRONJ?	Symphysis	3	2.7
	Zygomatic arch	25	22.1
	Mylohyoid ridge**	48	42.5
	External oblique ridge	34	30.1

CTX: C- terminal of serum collagen. **Correct answer. Values < 100% indicate that some participants did not respond to the respective question.

Table 2. Frequency of responses to the multiple-choice questions regarding the side effects and risk factors of bisphosphonate intake.

Question	Answer choices	Number	Percentage
Which of the followings is an oral side effect of bisphosphonate intake?	Xerostomia	11	9.7
	White and red lesions	16	14.2
	Periodontal problems	25	22.1
	Dental caries	15	13.3
	MRONJ	55	48.7
Which of the following risk factors can contribute to oral side effects of bisphosphonates?	Chronic corticosteroid therapy	57	50.4
	Diabetes mellitus**	58	49.6
	Tobacco use**	50	44.2
	Alcohol consumption**	68	60.2
	Poor oral hygiene**	65	57.5
	Route of medication administration**	62	54.9
	Duration of administration**	74	65.5
Which dental procedure can cause	Dosage of medication**	77	68.1
	Dental restoration	2	1.8

MRONJ?	Dental implant surgery**	104	92
	bleaching Tooth	2	1.8
	Nerve block injection	5	4.4

**Correct answer. Values > 100% indicate that some participants selected more than one answer.

Table 3. Frequency of responses to the multiple-choice questions regarding indications of bisphosphonates and treatment of MRONJ.

Question	Answer choices	Number	Percentage
Which of the followings is not an indication for bisphosphonate administration?	Multiple myeloma	16	14.2
	Osteoporosis	9	8
	Osteosarcoma**	57	50.4
	Paget’s disease	18	15.9
	Metastatic bone tumors	13	11.5
Which one is currently the accepted treatment protocol for MRONJ?	Radical surgery	10	8.8
	Hyperbaric oxygen	19	16.8
	Drug discontinuation	10	8.8
	Conservative debridement, antibiotic therapy, and chlorhexidine**	74	65.5
Can invasive dental procedures be performed for a patient who is under oral bisphosphonate therapy for over 3 years?	Yes	51	54.1
	No**	62	54.9
Can invasive dental procedures be performed for a patient under intravenous bisphosphonate therapy?	Yes	25	23
	No**	87	77
Do patients need to go for a dental checkup to eliminate possible sources of infection prior to bisphosphonate therapy?	Yes**	107	94.7
	No	6	5.3

**Correct answer

Table 4. Responses of dental students to the question about their sources of information regarding MRONJ.

Information source*	Number	Percentage
Academic courses	74	65.5
Internet	36	31.9
Scientific journals	33	29.2
Friends and colleagues	19	16.8
Specific educational courses	12	10.6

*Participants could select more than one source.

4. Discussion

This study assessed the knowledge level of dental students in Iran regarding MRONJ. The American Association of Oral and Maxillofacial Surgeons defined MRONJ as exposure and necrosis of jawbone for more than 8 weeks in patients taking bisphosphonates with no history of radiotherapy (20). of all, 49.6% of students in the present study and 30.61% of students in the study by Rosella et al. (15) in Italy knew the correct definition of MRONJ. MRONJ is a serious adverse side effect of bisphosphonate intake5. In the present study, 92% of students in our study and 58% of students in Brazilian study (18) were not aware of

osteonecrosis of the jaw as a side effect of bisphosphonate intake in their study. Prevention is highly important to minimize the risk of MRONJ in patients who use bisphosphonates (19). Patients should be informed about this side effect and receive oral hygiene instructions (21); also, dental students should be familiar with different types of bisphosphonates. In the present study, 54% of students knew that clodronate (Bonefos) is not a bisphosphonate, and the frequency of wrong answers regarding other types named in the questionnaire was low. However, a noteworthy finding was that 29.2% of dental students did not know that zoledronic acid (Zometa) is a bisphosphonate while it is a potent bisphosphonate used to control bone malignancies (22). Unlike the present results, Escobedo et al. (23) in Spain reported that alendronate and zoledronic acid were the most widely known bisphosphonates, and only a small percentage of students in their study were aware of other medications causing MRONJ. In the study by Rosella et al. (15) 99% of students announced that they were well familiar with bisphosphonates; however, when they were asked to name some of them, they had poor knowledge about some types of bisphosphonates. Similarly, de Lima et al. (18) showed

that 86% of students did not know the commercial name of drugs. Knowledge about the commercial name of drugs is important because patients mostly know their medications by their commercial names and mention the commercial names of their medications when asked about their medication intake. If dental clinicians are not aware of the commercial names of bisphosphates, they cannot inform the patients regarding the risks and precautions. Monwell et al. (24) suggested that a list of medications should be preferably used instead of open questions. It does not take long but provides more information compared with open questions. Using a list of medications also enhances the knowledge of clinicians regarding the newly released drugs in the market. Of all, 86.7% of students believed that it would be important to ask patients regarding bisphosphonate intake in routine dental visits.

In patients taking bisphosphonates, discontinuation of oral bisphosphonates, unlike intravenous bisphosphonates, decreases the risk of osteonecrosis (25), because less than 1% of the orally taken dosage is absorbed and enters the bone; whereas, over 50% of the intravenously administered dosage is bound to bone matrix (21). In the present study 85.8% of students were aware of the higher risk of MRONJ in intravenous administration of bisphosphonates, and 60.2% were aware of the fact that the half-life of bisphosphonates in bone is over 10 years. The majority of MRONJ cases occur in patients taking bisphosphonates for more than 3 years (26). In the present study 54.9% of students knew that invasive dental procedures should not be performed for patients who are taking oral bisphosphonates for more than 3 years. Also, 77% of patients were aware of the fact that such procedures cannot be performed for patients under intravenous bisphosphonate therapy. This result was in line with the findings of Rosella et al. (15) A noteworthy issue is that dental students should know how to perform a safe dental treatment for such patients to minimize the risk of MRONJ.

Physicians should also refer patients for a dental visit and comprehensive dental examination prior to initiation of bisphosphonate therapy to find and eliminate the potential sources of infection in their oral cavity (13). This is particularly important in patients who are going to receive intravenous bisphosphonates (27). In the present study 94.7% of students were well aware of the significance and necessity of a dental check-up for elimination of possible sources of infection prior to initiation of bisphosphonate therapy.

Markers of bone turnover such as N-terminal telopeptide

of type I collagen (NTX) and C-terminal telopeptide of type I collagen (CTX) are used to assess the progression of MRONJ. CTX is part of the collagen released during bone turnover and remodeling. Individuals whose fasting serum CTX is less than 100 pg/mL are at high risk of MRONJ after dental surgeries. Values between 100-150 pg/mL indicate a moderate risk, and values > 150 pg/mL indicate a low risk of MRONJ (27). Only 16.2% of students were aware of the fact that values ≤ 100 pg/mL are associated with high risk of MRONJ.

Type of medication, route of administration of drug (oral, intravenous), duration of use, accumulated dosage, reason of administration of bisphosphonate, adjuvant treatments (chemotherapy, corticosteroid therapy, or intake of anti-angiogenic medications), patient habits (smoking, alcohol consumption), gender, age, genetics, and other diseases such as diabetes mellitus, and rheumatoid arthritis (28) are among the systemic risk factors for MRONJ. Of all dental students, 68.1% had adequate knowledge about the dosage of bisphosphonates; this rate was 65.5% regarding the course of treatment, 60.2% regarding alcohol consumption, 57.5% regarding poor oral hygiene, 54.9% regarding routes of drug administration, 49.6% regarding diabetes mellitus and 44.2% regarding tobacco consumption.

Type of bisphosphonate (with or without nitrogen) is another systemic risk factor for osteonecrosis (10). The second and third generations of bisphosphonates have a nitrogen atom, which increases their therapeutic efficacy (7). Of all, 41.6% of students knew that bisphosphonates containing nitrogen can cause MRONJ. Rogers et al. (29) showed that risk of MRONJ was higher in patients taking zoledronate (containing nitrogen) compared with other bisphosphonates.

Anatomical factors can also serve as a risk factor for MRONJ (28). MRONJ often appears as a typical ulcer in the alveolar bone. Its risk of occurrence in the mandible is twice that in the maxilla. Unhealed dentoalveolar ulcers, traumatized torus and exposed parts of the mylohyoid ridge are all susceptible to MRONJ. Of all, 61.9% of students were well aware of the higher prevalence of MRONJ in the posterior mandible, and 42.5% were well aware of its higher prevalence in the mylohyoid ridge.

Bisphosphonates inhibit trabecular bone resorption by osteoclasts, interfere with bone turnover, preserve the bone density, and impair angiogenesis and blood supply to the bone. Thus, routine oral surgical procedures such as tooth extraction may result in bone exposure into the oral cavity, and subsequent pain, infection, and even jaw fracture in more severe cases (13). Since insertion of

dental implants can also cause bone damage (30), dental implant surgery should not be performed for patients taking bisphosphonates; 92% of dental students were well aware of this fact.

No definite treatment is currently available for MRONJ. Its management commonly includes elimination of necrotic bone, systemic antibiotic therapy, and use of antiseptic solutions (31). In the present study, 65.5% of the participants had adequate knowledge about the accepted treatment protocol for MRONJ. However, only 13.33% of students in the study by López-Jornet et al. (16) knew the accepted treatment protocol for osteonecrosis.

In the present study, the mean knowledge score of students regarding MRONJ was 14.42 ± 3.84 out of 17. No significant difference was found in the mean knowledge score of male and female students. Knowledge score of students had significant inverse correlations with their age and academic year, and a significant direct correlation with their GPA. In other words, by an increase in age and academic level, knowledge of students decreased, which may be due to distancing of students in higher academic levels from the theoretical courses and forgetting some of the taught topics. Also, the majority of dental students did not have any encounter with MRONJ cases to revisit the taught topics in this regard. This finding highlights the need for repetition of theoretical topics for students in clinical courses. Rosella et al. (15) assessed the knowledge level of 4th and 6th year dental students and found that students with higher academic grades had insignificantly higher knowledge level. Their results were different from the present findings. Lower knowledge level of students who had encountered MRONJ cases compared with others may be attributed to their lower GPA. However, increased knowledge level by an increase in GPA clearly indicates that students with higher GPA had better learned the related topics. In agreement with this finding, 65.5% of students reported that their academic courses were their main sources of information regarding MRONJ.

Higher knowledge level of healthcare providers can decrease the risk of occurrence of MRONJ and result in better management of MRONJ cases³² Also, instruction of patients regarding the side effects of bisphosphonates can improve their quality of care and decrease the complications related to dental procedures (29).

Future studies are required regarding the knowledge level of other healthcare workers about MRONJ. Also, the efficacy of educational pamphlets and courses for

enhancement of knowledge level of dental clinicians regarding MRONJ should be assessed.

5. Limitations

Small sample size and limited to specific location are the limitation of our study.

6. Conclusion

The present results revealed good knowledge level of Yazd dental students regarding MRONJ and had a significant direct correlation with their GPA.

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Ethics

The study protocol was approved by the ethics committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.REC1399.280).

Author contributions

Farzane Vaziri: Conceptualization, Methodology

Sahar Chokami Rafiei: Software

Amir Reza Taghavie: Data curation, Validation

Mohammad Arab Farashahi: Writing - Original draft, Writing - Review & Editing, Supervision

Conflict of interest

The authors declare no conflict of interest.

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References

1. Woo SB, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. *Annals of internal medicine*. 2006;144(10):753-61.
2. Vasconcelos ACU, Azambuja Berti-Couto S, Figueiredo MA, Salum FG, Lopes TG, Cherubini K. Laboratory methods and biomarkers in the evaluation of bisphosphonate effects on body tissues: a literature review. *Journal of Oral Pathology & Medicine*. 2013;42(8):577-86.
3. Migliorati CA, Siegel MA, Elting LS. Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. *The lancet oncology*. 2006;7(6):508-14.

4. Dannemann C, Grätz K, Riener M, Zwahlen R. Jaw osteonecrosis related to bisphosphonate therapy: a severe secondary disorder. *Bone*. 2007;40(4):828-34.
5. Yazdani J, Mortazavi A, Abbasi E. Knowledge of Tabriz Dentists about Bisphosphonate-Related Osteonecrosis of the Jaw in 2015. *Med J Tabriz Uni Med Sciences Health Services*. 2019;41(3):101-5.
6. Assael LA. Oral bisphosphonates as a cause of bisphosphonate-related osteonecrosis of the jaws: clinical findings, assessment of risks, and preventive strategies. *Journal of Oral and Maxillofacial Surgery*. 2009;67(5):35-43.
7. Heidari M, motevali S, Maboodi A, Sobouti F. Is using Bisphosphonate a Contraindication for Dental Treatments? *Journal of Mazandaran University of Medical Sciences*. 2017;27(154):232-44.
8. Migliorati CA, Schubert MM, Peterson DE, Seneda LM. Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy. *Cancer*. 2005;104(1):83-93.
9. Ficarra G, Beninati F, Rubino I, Vannucchi A, Longo G, Tonelli P, Pini Prato G. Osteonecrosis of the jaws in periodontal patients with a history of bisphosphonates treatment. *Journal of clinical periodontology*. 2005;32(11):1123-8.
10. Madrid C, Sanz M. What impact do systemically administrated bisphosphonates have on oral implant therapy? A systematic review. *Clinical oral implants research*. 2009;20 Suppl 4:87-95.
11. Lo JC, O'Ryan FS, Gordon NP, Yang J, Hui RL, Martin D, Hutchinson M, Lathon PV, Sanchez G, Silver P, Chandra M. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. *Journal of Oral and Maxillofacial Surgery*. 2010;68(2):243-53.
12. Beninati F, Pruneti R, Ficarra G. Bisphosphonate-related osteonecrosis of the jaws (BRONJ). *Medicina oral, patologia oral y cirugía bucal*. 2013;18(5):e752-8.
13. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws—2009 update. *Journal of Oral and Maxillofacial Surgery*. 2009;67(5):2-12.
14. Markiewicz MR, Margarone JE, Campbell JH, Aguirre A. Bisphosphonate-associated osteonecrosis of the jaws: a review of current knowledge. *The Journal of the American Dental Association*. 2005;136(12):1669-74.
15. Rosella D, Papi P, Pompa G, Capogreco M, De Angelis F, Di Carlo S. Dental students' knowledge of medication-related osteonecrosis of the jaw. *European journal of dentistry*. 2017;11(4):461-8.
16. López-Jornet P, Camacho-Alonso F, Molina-Miñano F, Gomez-Garcia F. Bisphosphonate-associated osteonecrosis of the jaw. Knowledge and attitudes of dentists and dental students: a preliminary study. *Journal of evaluation in clinical practice*. 2010;16(5):878-82.
17. Escobedo M, García-Consuegra L, Junquera S, Olay S, Ascani G, Junquera L. Medication-related osteonecrosis of the jaw: A survey of knowledge, attitudes, and practices among dentists in the principality of Asturias (Spain). *Journal of stomatology, oral and maxillofacial surgery*. 2018;119(5):395-400.
18. de Lima PB, Brasil VL, de Castro JF, de Moraes Ramos-Perez FM, Alves FA, dos Anjos Pontual ML, da Cruz Perez DE. Knowledge and attitudes of Brazilian dental students and dentists regarding bisphosphonate-related osteonecrosis of the jaw. *Supportive care in cancer*. 2015;23(12):3421-6.
19. Newman MG, Klokkevold PR, Elangovan S, Kapila Y. Newman and Carranza's Clinical Periodontology and Implantology E-Book: Newman and Carranza's Clinical Periodontology and Implantology E-Book. Elsevier Health Sciences; 2023 Apr 28.
20. 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. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons*. 2014;72(10):1938-56.
21. Zargaran M, Baghaei F. A review of bisphosphonates and bisphosphonate-related osteonecrosis of the jaw. *Journal of dentistry (Shiraz university of medical sciences)*. 2012;12(4):376-87.
22. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons*. 2003;61(9):1115-7.
23. Escobedo MF, García-Consuegra L, Gay S, Álvarez L, Olay S, Ascani G, Junquera L. Influence of the teaching program on the learning in knowledge and practice of osteonecrosis of the jaws produced by antiresorptives in dental students of the Principality of Asturias (Spain). *Journal of clinical and experimental dentistry*. 2017;9(12):e1402-7.
24. Monwell B, Blix O, Gerdner A, Bülow P. Drug List as a Cognitive Support to Provide Detailed Information on a Patient's Drug Use: A Comparison of Two Methods Within the Assessment of Drug Misuse and Dependence. *Substance use & misuse*. 2016;51(11):1470-6.
25. Fonseca RJ, Marciani RD, Turvey TA. Oral and Maxillofacial Surgery. 2th ed. St.Louis. Saunders Elsevier ; 2009. (pp 395-396, 557-564).
26. Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics*. 2006;102(4):433-41.
27. Marx RE, Cillo JE, Jr., Ulloa JJ. Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons*. 2007;65(12):2397-410.
28. Gavalda C, Bagán JV. Concept, diagnosis and classification of bisphosphonate-associated osteonecrosis of the jaws. A review of the literature. *Medicina oral, patologia oral y cirugía bucal*. 2016;21(3):e260-70.

29. Rogers MJ, Watts DJ, Russell RG. Overview of bisphosphonates. *Cancer*. 1997;80(8 Suppl):1652-60.
30. Durie BG, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. *The New England journal of medicine*. 2005;353(1):99-102.
31. Samiee rad S, labafchi a. Management of Medication-Related Osteonecrosis of the Jaw Using Platelet-Rich Fibrin: A Case Report and Literature Review. *Journal of Mashhad Dental School*. 2020;44(2):191-200.
32. George EL, Lin YL, Saunders MM. Bisphosphonate-related osteonecrosis of the jaw: a mechanobiology perspective. *Bone Reports*. 2018;8:104-9.