

RESEARCH

Medication-Related Osteonecrosis of the Jaw: Awareness and Level of Knowledge of Turkish Physicians

Gözde Işık(0000-0001-9572-3049)^α, Meltem Özden Yüce(0000-0002-7088-9701)^α,

Banu Özveri Koyuncu(0000-0002-0074-0055)^α, Aliye Mandıracıoğlu(0000-0002-0873-4805)^β

Selcuk Dent J, 2022; 9: 494-500 (Doi: 10.15311/selcukdentj.978802)

Başvuru Tarihi: 04 Ağustos 2021
Yayına Kabul Tarihi: 08 Eylül 2021

ABSTRACT

Medication-Related Osteonecrosis of the Jaw: Awareness and Level of Knowledge of Turkish Physicians

Background: The aim of this study was to evaluate physicians' level of knowledge and awareness regarding the side effects of bisphosphonates (BPs).

Methods: A cross-sectional descriptive study was conducted at University Hospital. Data were collected through a self-administered questionnaire given to a group of research assistants all of whom were required to prescribe BPs, including internists (oncologists, endocrinologists and rheumatologists), orthopaedic specialists, physiotherapists, obstetricians and gynaecologists, and urologists. The questionnaire consisted of a range of questions covering such matters as length of time in occupation, how information is given out, whether a dentist is consulted before or in the course of prescribing the medicine, and previous experience of medication-related osteonecrosis of the jaw (MRONJ) and any treatment modifications.

Results: Ninety-one out of 106 physicians included in our sample were found to be treating patients with BPs. Although 89% of the physicians informed their patients about the side effects of BPs, only 16.5% advised their patients to consult a dentist for dental treatment before prescribing BPs. When the different specialist groups were ranked in terms of their rate of dental referrals, from highest to lowest, the order was as follows: physiotherapists, internists, obstetricians and gynaecologists, urologists and orthopaedists. A statistically significant correlation was found between knowledge and specialty ($p=0.02$), but no significant correlation was observed between knowledge and years of experience ($p=0.3$).

Conclusion: There is a lack of awareness among research assistants about the risk of MRONJ when prescribing BPs. Therefore, continuous education programmes and multiple interventions are needed to increase awareness.

KEYWORDS

Medication-Related Osteonecrosis of The Jaws; Drug-Related Side Effects; Knowledge; Awareness

ÖZ

İlaç Kullanımına Bağlı Gelişen Çene Osteonekrozu: Tıp Doktorlarının Farkındalığı ve Bilgi Düzeyleri

Amaç: Bu çalışma, bifosfonatların (BPs) yan etkilerine karşı tıp hekimlerinin bilgisi ve farkındalık seviyesini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Bu kesitsel çalışma Tıp Fakültesi Hastanesinde gerçekleştirilmiştir. Veriler, BPs reçete eden iç hastalıkları (onkolog, endokrinolog ve romatolog) ortopedi, fizik tedavi, kadın doğum ve hastalıkları ve üroloji araştırma görevlilerine uygulanan anket sorularıyla toplanmıştır. Sorular mesleki yıl, ilaçla ilgili bilgi verme, ilacı reçete etmeden önce ve reçete ettikten sonra diş hekimine yönlendirme, ilaç kullanımına bağlı gelişen çene osteonekrozu (MRONJ) deneyimi ve BPs alım şekli ile kesilmesi gibi tedavi modifikasyonlarından oluşturulmuştur.

Bulgular: 106 araştırma görevlisinden 91'i hastalarını BPs ile tedavi ettiğini bildirmiştir. Araştırma görevlilerinin %89'u hastalarına BPs yan etkilerinden bahsetmesine rağmen, sadece %16,5'u BPs reçete etmeden önce hastalarını diş hekimine yönlendirdiğini belirtmiştir. Uzmanlık alanlarına göre diş hekimine yönlendirme en yüksekte en düşüğe göre; fizik tedavi, iç hastalıkları, kadın doğum ve hastalıkları, üroloji ve ortopedi olarak sıralanmıştır. İstatistiksel olarak bilgi düzeyi ve çalışma yılı arasında belirgin bir farklılık olmamakla birlikte ($p=0.3$) uzmanlık dalına göre ortopedistlerin bilgi düzeyi ve farkındalığı daha düşük bulunmuştur ($p=0.02$).

Sonuç: BPs reçete eden araştırma görevlileri MRONJ riskinin çoğunlukla farkında değildir. Bu yüzden eğitim programlarının devamlılığı ve hekimler arası iş birliği, farkındalığın artırılması için gereklidir.

ANAHTAR KELİMELER

İlaç Kullanımına Bağlı Gelişen Çene Osteonekrozu; İlaç Yan Etkileri; Bilgi Düzeyi; Farkındalık

INTRODUCTION

Bisphosphonates (BPs) are group of medicines with antiresorptive action used to treat several conditions associated with bone loss.^{1,2} BPs are commonly prescribed by physicians for the treatment of osteoporosis (especially for aged post-menopausal women), hypercalcaemia, Paget's disease and several malignancies, including multiple myeloma, breast cancer and prostate cancer.³ The biological behaviour

of BPs is to reduce bone resorption both by inducing osteoclast apoptosis and by inhibiting function of osteoclasts. While, these medications increase bone density and reduce the risk of fracture, BPs may lead to adverse oral effects.⁴

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a side effect that occurs either spontaneously in non-extractive sites such as dentate or non-dentate areas, without any trauma, or after

^α Ege University, School of Dentistry, Department of Oral and Maxillofacial Surgery, İzmir, Turkey

^β Ege University, School of Medicine, Department of Public Health, İzmir, Turkey

Questionnaire

Descriptive statistics were performed for professional experience, sample size between the departments, BPs prescription, diagnosis of MRONJ and multidisciplinary relation. The data were collected through a self-administered questionnaire which requested details of experience and departments, as well as questions specifically relating to MRONJ. The physicians' knowledge of MRONJ was evaluated using the AAOMS guidelines. This consisted of questions regarding how information is given out about the drug, whether there was consultation with a dentist before or during the prescribing of BPs and any treatment modification such as changing administration route or discontinuation of BPs.⁶

The questions were designed to elicit simple answers such as "always", "sometimes" and "never". To evaluate degree of knowledge, two points were given for each correct answer and one point was given for an acceptable answer. The questions related to informing patients about side effects, consultation with a dentist before and during the prescribing of BPs, observation of MRONJ and consultation with an oral surgeon after MRONJ diagnosis. To evaluate the degree of dental referrals, the question took the form of a 2-point scale with the answer options of 'before or during BP administration' and 'after MRONJ diagnosis'. When all the knowledge questions were evaluated, the total score available was 18 points.

Statistical Analysis

Statistical analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Categorical data were described using observed frequencies and percentages. After frequency and percentage analyses, One-way Tukey and Duncan tests were performed to evaluate scores. All values were considered statistically significant at $P < 0.05$.

RESULTS

A total of 106 research assistants participated in the survey. Ninety-one of them, including 37 research assistants in internal medicine, 15 in orthopaedics, 14 in physiotherapy, 16 in obstetrics and gynaecology and 9 in urology, prescribed BPs to their patients (Figure 1).

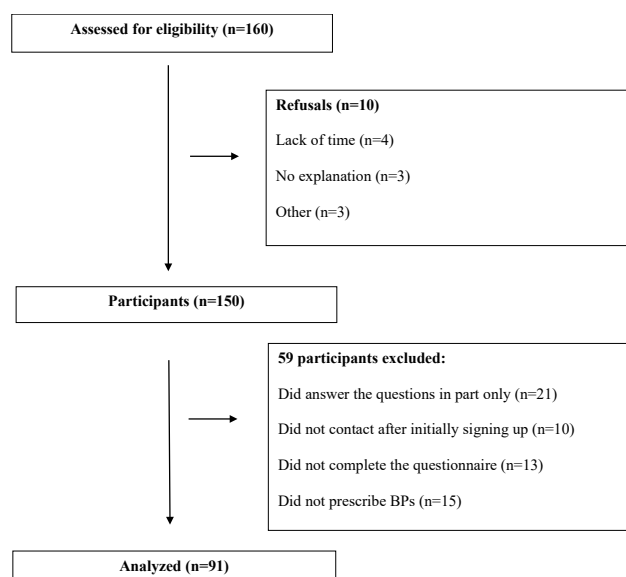


Figure 1.

A diagram describing the number of excluded participants

The mean length of time in occupation of the research assistants was calculated as 3.85 years. The professional experience of research assistants did not yield significant results ($p > 0.05$). The results of the questionnaire are presented in Table 2.

Table 2.

Distribution of responses to questionnaire on MRONJ knowledge and awareness, as actual number and as percentage.

Questions	Always	Sometimes	Never
	N (%)	N (%)	N (%)
Did you provide information about side effects of prescribed medicine to patients?	81 (89 %)	6 (6.6 %)	4 (4.4 %)
Did you refer the patient to a dentist before prescribing medicine?	15 (16.5 %)	33 (36.3 %)	43 (47.3 %)
Did you consult the patient with a dentist during bisphosphonate usage?	9 (9.9 %)	34 (37.4 %)	48 (52.7 %)
Did you identify MRONJ in patients treated with oral BPs?	None	25 (27.5 %)	66 (72.5 %)
Did you identify MRONJ in patients treated with IV BPs?	1 (1.1 %)	14 (15.4 %)	76 (83.5 %)
Did you stop drug intake of patients who were diagnosed with MRONJ?	53 (58.2 %)	25 (27.5 %)	13 (14.3 %)
Did you change the dosage of the medicine for patients who were diagnosed with MRONJ?	20 (22 %)	35 (38.5 %)	36 (39.6 %)
Did you change the intake form of the medicine in patients who were diagnosed with MRONJ?	18 (19.8 %)	27 (29.7 %)	46 (50.5 %)
Did you consult patients who were diagnosed with MRONJ with a dentist?	82 (90.1 %)	4 (4.4 %)	5 (5.5 %)

Moreover, 46 research assistants (50.5%) did not change the intake form of BP in their patients diagnosed with MRONJ; 27 (29.7%) changed the intake form of the medicine in some patients and 18 (19.1%) changed the intake form in all their patients.

According to the responses of the research assistants, the lowest score was 4 points and the highest 14. For all the participants, the mean average total score was 10.16.

From these scores, the research assistants could be ranked in descending order according to specialism: physiotherapists (10.64), internists (10.59), obstetricians and gynaecologists (10.17), urologists (10.11) and orthopaedic specialists (8.88). So, orthopaedic specialists were the most unaware group with a difference of 2 points. Statistically significant associations were found between knowledge and specialty ($p=0.02$; Table 3).

Table 3.

Description of total scores for specialist groups who prescribed BPs.

Research assistants	Mean \pm SD	Min-Max
Internists	10.59 \pm 1.67	7-13
Orthopaedists	8.8 \pm 1.74	4-11
Urologists	10.11 \pm 1.36	8-13
Physiotherapists	10.64 \pm 2.01	8-13
Obstetricians and Gynaecologists	10.17 \pm 1.79	8-11

F: 3.01
p: 0.02

DISCUSSION

The main finding in the present study was the lack of knowledge and awareness of participants about MRONJ. Guidelines of the American Society of Clinical Oncology (ASCO) and the European Medicines Agency (EMA) recommend that all patients have a comprehensive dental examination and preventive dentistry (pre-emptive extraction of unsalvageable teeth and optimised periodontal health) before beginning BP therapy.^{16,22} Despite all these efforts, the questionnaire studies showed that the physicians had low awareness and deficient knowledge with regard to the occurrence of MRONJ.¹⁸⁻²¹

Yoo et al.²³ reported that the dentists with < 5 years' clinical experience were significantly more aware than those with >5 years' experience. El Osta et al.¹⁹ reported that the professional experience of physicians was not related to awareness of MRONJ. Our own results also indicated that physicians' knowledge of this issue was not related to professional experience.

El Osta et al.¹⁹ and Al-Mohaya et al.²⁰ reported that there were statistically significant differences between level of knowledge and physicians' specialty. On the other hand, Kim et al.¹⁸ reported that there was no statistically significant difference in the level of MRONJ knowledge between different specialties. In our study, among the research assistants, orthopaedic specialists were the group who were most unaware of the occurrence of MRONJ.

Physicians must provide information about the possible risks and side effects of BPs to patients. Powell et al.²⁴ and Cuaveas-Gonzalez et al.²⁵ questioned the prevalence of MRONJ in patients who were receiving BPs therapy.

The authors suggested that local risk factors such as periodontal disease should be identified before initiating treatment with BPs, to reduce the risk of MRONJ. Estefania et al.²⁶ and Hewitt et al.²⁷ reported that if BPs therapy is indicated, to prevent the occurrence of MRONJ, periodic evaluation of oral conditions and adequate oral hygiene should be observed.

Similarly, Kholsa et al.²⁸ and Lam et al.²⁹ reported that management of periodontal disease and oral hygiene are crucial among patients using BPs, emphasizing the necessity of informing them of the risk of MRONJ, and of the importance of dental treatment, before and during drug administration.

Our study results showed that 89% of the physicians informed their patients about the side effects of BPs, while 9.9% advised their patients to visit a dentist for dental treatment during BP usage.

Al-Mohaya et al.²⁰ found that more than half of the physicians never recommended pre-treatment dental screening. Kim et al.¹⁸ reported that the percentage of dental referrals before, during and after the administration of BPs remains low in < 30% of total patients. Our results were in accordance with the findings of Kim et al.¹⁸, as we found that consultation with dentists before prescribing medicine occurred in 16.5% of total participants. Approximately 47.3% did not advise their patients at all, while 37.3% advised only some of their patients.

The reason why a high percentage of physicians do not consult with dentists or oral surgeons before prescribing BPs remains unclear. Are they really unaware of MRONJ? Or is it the case that, despite their awareness of MRONJ, they do not emphasize this disease because it is such a rare side effect of BPs? The present study does not address these questions, and therefore further questionnaire studies on this topic are required in future.

In considering the purpose of BPs therapy, The Japanese Society of Oral and Maxillofacial Surgeons (JSOMS) and other academic societies including the Korean Society for Bone and Mineral Research (KSMBR), the Korean Association of Oral and Maxillofacial Surgeons (KAOMS) and the International Association of Oral and Maxillofacial Surgeons (IAOMS) all take the view that manipulations or cessation should be done in consultation with the physician.^{30,31}

Our study results showed that participants preferred different approaches with regard to drug holidays after the occurrence of MRONJ. The AAOMS position paper recommended that a drug holiday for a 2-month period, before and after dental surgery, may be prudent for patients receiving BPs therapy,⁴ but this recommendation was not evidence-based.

One of the limitations of this study is that it is a cross-sectional study. Therefore, the results do not reveal any direct cause-effect relationship. The results cannot be generalized to all physicians in Turkey. However, it may provide a useful insight into the level of knowledge of physicians.

Ideally, every patient should receive a dental examination prior to initiation of antiresorptive and antiangiogenic therapies to identify existing periodontal and periapical infection, ill-fitting dental prostheses or other conditions which may contribute to soft tissue trauma. Physicians' awareness of the potential risks of MRONJ and the value of patient education about the maintenance of good oral health are essential. Therefore, physicians and dentists must communicate to guide patients regarding to therapeutic protocols.²¹ The educational programmes, workshops or symposiums might be beneficial to understand the possible adverse effects, and the available preventive practices.

CONCLUSION

The target sample of the study was research assistants who had prescribed BPs to their patients. Based on the results, we concluded that patients using BPs, must be informed about the side effects of BPs therapy and the management of the treatment. To prevent the occurrence of MRONJ, physicians should consult with a dentist or oral surgeon before BPs therapy is commenced. Moreover, strategies to increase the awareness of this side effect must be developed among all healthcare professionals. Levels of knowledge and awareness of physicians are crucial factors for the prevention and control of MRONJ.

Acknowledgement

The authors are thankful to Prof. Dr. Mehmet N. Orman for the valuable assistance in statistical analysis.

Source of funding

None declared.

Conflict of interest

The authors declare that they have no competing interests.

REFERENCES

- 1- Mahdaviyazad H, Keshtkar V, Emami MJ. Osteoporosis guideline awareness among Iranian family physicians: results of a knowledge, attitudes, and practices survey. *Prim Health Care Res Dev* 2018;19:485-491. <https://doi.org/10.1017/S1463423618000014>
- 2- Voss PJ, Poxleitner P, Schmelzeisen R, Stricker A, Semper-Hogg W. Update MRONJ and perspectives of its treatment. *J Stomatol Oral Maxillofac Surg* 2017;118:232-235. <http://doi.org/10.1016/j.jormas.2017.06.012>
- 3- McLeod NMH, Davies BJB, Brennan PA. Bisphosphonate osteonecrosis of the jaws; an increasing problem for the dental practitioner. *Br Dent J* 2007;203:641-644. <https://doi.org/10.1038/bdj.2007.1065>
- 4- Aparecida Cariolato F, Carelli J, de Campos Moreira T, Pietrobon R, Rodrigues C, Bonilauri Ferreira AP. Recommendations for the prevention of bisphosphonate-related osteonecrosis of the jaw: a systematic review. *J Evid Based Dent Pract* 2018;18:142-152. <http://doi.org/10.1016/j.jebdp.2017.11.002>
- 5- Baqain ZH, Sawair FA, Tamimi Z, Bsoul N, Edwan GA, Almasad JK, et al. Osteonecrosis of jaws related to intravenous bisphosphonates: the experience of a Jordanian teaching hospital. *Ann R Coll Surg Engl* 2010;92:489-94. <https://dx.doi.org/10.1308%2F003588410X12699663903395>
- 6- Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. *J Oral Maxillofac Surg* 2014;72:1938-1956. <https://doi.org/10.1016/j.joms.2014.04.031>
- 7- 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;104:83-93. <https://doi.org/10.1002/cncr.21130>
- 8- 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;24:945-952. <https://doi.org/10.1200/JCO.2005.04.2465>
- 9- Campisi G, Di Fede O, Musciotto A, Lo Casto A, Lo Muzio L, Fulfaro F, et al. Bisphosphonate-related osteonecrosis of the jaw (BRONJ): run dental management designs and issues in diagnosis. *Ann Oncol* 2007;6:168-172. <https://doi.org/10.1093/annonc/mdm250>
- 10- Sarin J, DeRossi SS, Akintoye SO. Updates on bisphosphonates and potential pathobiology of bisphosphonate-induced jaw osteonecrosis. *Oral Dis* 2008;14:277-285. <https://doi.org/10.1111/j.1601-0825.2007.01381.x>
- 11- Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003;61:1115-1117. [https://doi.org/10.1016/s0278-2391\(03\)00720-1](https://doi.org/10.1016/s0278-2391(03)00720-1)
- 12- 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;62:527-534. <https://doi.org/10.1016/j.joms.2004.02.004>
- 13- Vandone AM, Donadio M, Mozzati M, Ardine M, Polimeni MA, Beatrice S, et al. Impact of dental care in the prevention of bisphosphonate-associated osteonecrosis of the jaw: a single center clinical experience. *Ann Oncol* 2012;23:193-200. <https://doi.org/10.1093/annonc/mdr039>
- 14- Hinchy NV, Javaprakash V, Rossito RA, Anders PL, Korff KC, Canallatos P, et al. Osteonecrosis of the jaw-prevention and treatment strategies for oral health professional. *Oral Oncol* 2013;49:878-886. <https://doi.org/10.1016/j.oraloncology.2013.06.008>
- 15- Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;102:433-441. <https://doi.org/10.1016/j.tripleo.2006.06.004>
- 16- Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, et al. International Task Force on Osteonecrosis of the Jaw. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res* 2015;30:3-23. <https://doi.org/10.1002/jbmr.2405>
- 17- Rayman S, Almas K, Dincer E. Bisphosphonate-related jaw necrosis: a team approach to management and prevention. *Int J Dent Hyg* 2009;7:90-95. <https://doi.org/10.1111/j.1601-5037.2008.00331.x>
- 18- Kim JW, Jeong SR, Kim SJ, Kim Y. Perceptions of medical doctors on bisphosphonate-related osteonecrosis of the jaw. *BMC Oral Health* 2016;16:92. <https://doi.org/10.1186/s12903-016-0290-0>
- 19- El Osta L, El Osta B, Lakiss S, Hennequin M, El Osta N. Bisphosphonate-related osteonecrosis of the jaw: awareness and level of knowledge of Lebanese physicians. *Supportive Care Cancer* 2015;23:2825-2831. <https://doi.org/10.1007/s00520-015-2649-1>
- 20- Al-Mohaya MA, Al-Khashan HI, Mishriky AM, Al-Otaibi LM. Physicians' awareness of bisphosphonates-related osteonecrosis of the jaw. *Saudi Med J* 2011;32:830-835.

- 21-Miranda-Silva W, Montezuma MA, Benites BM, Bruno JS, Fonseca FP, Fregnani ER. Current knowledge regarding medication-related osteonecrosis of the jaw among different health professionals. *Support Care Cancer*. 2020;28:5397-5404. doi: 10.1007/s00520-020-05374-4.
- 22-Van Poznak CH, Temin S, Yee GC, Janjan NA, Barlow WE, Biermann JS, et al. American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. *J Clin Oncol* 2011;29:1221. <https://doi.org/10.1200/JCO.2010.32.5209>
- 23-Yoo JY, Park YD, Kwon YD, Kim DY, Ohe JY. Survey of Korean dentists on the awareness on bisphosphonate-related osteonecrosis of the jaws. *J Investig Clin Dent* 2010;1:90-95. <https://doi.org/10.1111/j.2041-1626.2010.00024.x>
- 24-Powell D, Bowler C, Roberts T, Garton M, Matthews C, McCall I, Davie M. Incidence of serious side effects with intravenous bisphosphonate: a clinical audit. *QJM* 2012;105:965-971. <https://doi.org/10.1093/qjmed/hcs112>
- 25-Cuevas-Gonzalez MV, Diaz-Aguirre CM, Perez EE, Cuevas-Gonzalez JC. Prevalence of osteonecrosis of the jaw and oral characteristics of oncologic patients treated with bisphosphonates at the General Hospital of Mexico. *J Korean Assoc Oral Maxillofac Surg* 2016;42:365-369. <https://dx.doi.org/10.5125%2Fjkaoms.2016.42.6.365>
- 26-Estefania FR, Ponte FR, Guirre Urizar JM. Bisphosphonates and oral pathology II. Osteonecrosis of the jaws: review of the literature before 2005. *Med Oral Patol Oral Cir Bucal* 2006;11:456-461.
- 27-Hewitt C, Farah CS. Bisphosphonate-related osteonecrosis of the jaws: a comprehensive review. *J Oral Pathol Med* 2007;36:319-328. <https://doi.org/10.1111/j.1600-0714.2007.00540.x>
- 28-Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, et al. Bisphosphonate-associated osteonecrosis 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. <https://doi.org/10.1359/jbmr.0707onj>
- 29-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.
- 30-Yoneda T, Hagino H, Sugimoto T, Ohta H, Takahashi S, Soen S, et al. Antiresorptive agent-related osteonecrosis of the jaw: Position Paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw. *J Bone Miner Metab* 2017;35:6-19. <https://doi.org/10.1007/s00774-016-0810-7>
- 31-Kim KM, Rhee Y, Kwon YD, Kwon TG, Lee JK, Kim DY. Medication Related Osteonecrosis of the Jaw: 2015 Position Statement of the Korean Society for Bone and Mineral Research and the Korean Association of Oral and Maxillofacial Surgeons. *J Bone Metab* 2015;22:151-65. <https://doi.org/10.11005/jbm.2015.22.4.151>

Corresponding Author:

Gözde IŞIK
Ege University, School of Dentistry,
Department of Oral and Maxillofacial Surgery,
Erzene AVE, 35040, Bornova, İzmir, Turkey
E-mail : gozdech@hotmail.com