Clinical and Experimental Health Sciences

Postgraduate Dental Students' Knowledge Levels Toward Medication-Related Osteonecrosis of the Jaws

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ABSTRACT

Objective: Medication-related osteonecrosis of the jaws (MRONJ), is often described as a side-effect of bisphosphonates within the dental school curriculum. However, as highlighted in the current literature, some antiresorptive and antiangiogenic drugs may also cause MRONJ. This study aimed to investigate the awareness and knowledge of post-graduate dental students (PDSs) from different specialty/doctoral programs towards MRONJ.

Methods: An electronic questionnaire containing 28 questions in 3 different sections focusing on demographic characteristics, general information, and clinical attitude, was prepared. Two-thousand PDSs from 27 universities were invited to participate in the survey in December 2021. The obtained data were evaluated statistically using descriptive statistics and the Chi-Square test (p=.05).

Results: The response rate of the survey was 10%. The number of PDSs showed a homogeneous distribution for each specialty, whereas the number of women participants was higher than that of men (p<.05). In the general information section, the highest correct answer rates belonged to students from Oral and Maxillofacial Surgery and Oral and Maxillofacial Radiology departments. However, there was no statistically significant difference between different dental specialties regarding correct answer rates (p>.05). PDSs had higher rates of correct answers to general information questions about antiresorptive drugs than for antiangiogenic drugs. 92% of participants stated that they obtained their knowledge about MRONJ from their undergraduate education.

Conclusion: The findings of this study reveal the necessity of updating the dental school curriculum in line with the current literature on MRONJ, as well as including more postgraduate courses on MRONJ during the specialty/doctoral education period.

Keywords: Bisphosphonate-associated osteonecrosis of the jaw, dental education, dental students, medication-related osteonecrosis of the jaws, postgraduate dental students

1. INTRODUCTION

Medication-related osteonecrosis of the jaws (MRONJ) is an adverse effect characterized by the progressive destruction of the jawbones caused by drugs used in the treatment of metabolic bone diseases, rheumatologic diseases, and some cancer types (1). After it had first been reported as a bisphosphonate-induced side-effect in 2003, the American Association of Oral and Maxillofacial Surgeons (AAOMS) named this adverse effect as bisphosphonate-related osteonecrosis of jaws (BRONJ) in 2009 (2,3). However, the term BRONJ was later updated as MRONJ in consequence of the recent case reports presenting that the other antiresorptive drugs such as denosumab and some antiangiogenic drugs may have similar side-effects and cause destruction of the jawbones (4).

Even though the side-effect of antiresorptive and antiangiogenic drugs on bone tissues concerns the entire skeletal system, MRONJ tends to be observed more frequently in jawbones because of their higher vascularization rate, remodeling capacity, and turn-over speed (5). Moreover, since the infectious agents in the oral cavity can easily spread to the jawbone through teeth, gingival grooves, and extraction cavities, the jawbones are more prone to the development of MRONJ (6). Therefore, eliminating the focal infections and gaining the optimum health of oral tissues before antiresorptive and antiangiogenic therapy is of great benefit in preventing the development of MRONJ (5). In agreement with this statement, the AAOMS emphasizes the importance of consulting the patients with dentists and maintaining oral hygiene before the antiresorptive or antiangiogenic therapy (4). Hence, it is critical to increase the

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awareness and knowledge of dentists about antiresorptive, antiangiogenic drugs and the development of MRONJ, as well as evaluate their attitudes and behaviors toward these patients. Considering that a multidisciplinary approach has the utmost importance in the prevention and treatment of MRONJ, it is also essential for dentists from different specialties to have equal knowledge levels about MRONJ.

In the literature, there are too many studies investigating the awareness levels of dentists and physicians toward MRONJ (7-12). However, only a few involve or focus on undergraduate dental students (UDSs) (13-15), and there is no study specifically for post-graduate dental students (PDSs). It is noteworthy that most studies are directed toward antiresorptive drugs (7,10,11,14,16,17), whereas a limited number of them address antiangiogenic drugs (8,9,12,15). To our knowledge, there are only three studies including PDSs as a part of questionnaire participants (18-20). However, in those studies, PDSs did not have a homogeneous distribution according to their fields of specialty, and the questions within the scope of the survey were only about bisphosphonates and antiresorptive drugs.

Therefore, this study aimed to investigate the awareness and knowledge of PDSs, who are currently studying in different specialty/doctoral programs, toward MRONJ with a questionnaire containing questions oriented to both antiresorptive and antiangiogenic drugs.

2. METHODS

This study was approved by the Institutional Scientific Research and Publication Ethics Board (No: 2022 – 1159) and was carried out by the Declaration of Helsinki. An online questionnaire was designed by three oral and maxillofacial radiologists with different years of experience, according to the position paper of AAOMS (4) and a review of the related studies (8,16). The questionnaire consisted of twenty-eight questions and three sections as followed: Demographic characteristics, general information about MRONJ, and clinical attitude.

In the demographic characteristics section, six questions were asked to the participants to record their gender, age, year of graduation, specialty/doctoral program and the university where they have been receiving their postgraduate education. In the general knowledge section, participants' knowledge of MRONJ was investigated by twelve questions focusing on the definition of MRONJ, risk factors related to MRONJ, antiresorptive and antiangiogenic drug indications as well as their mechanism of action and route of administration. In the last section, the clinical attitude of PDSs toward MRONJ patients and the source of their knowledge about MRONJ were questioned.

The questionnaire was first administered to a pilot group of 20 PDSs in order to verify the validity, reliability and comprehensibility of the questions. Later then, 2000 PDSs studying in different specialty/doctoral programs at 27 universities in Turkey were invited to participate in the online questionnaire.

The data obtained were evaluated statistically using IBM SPSS Statistics 20.0 (SPSS Inc., Chicago, IL). Descriptive statistics were used to analyze the answers given to the demographic characteristics section. In order to compare the data between PDSs from different fields of dental specialties, Pearson's chi-square test was used. For all data, a p value <.05 was considered significant.

3. RESULTS

3.1. Demographic Characteristics

Two hundred PDSs (147 women and 53 men) studying in 27 different universities with a mean age of 26.7 ± 2.7, were included in the questionnaire. The demographic information of the participants obtained from the first section is summarized in Table 1. Even though PDSs showed a homogeneous distribution for each specialty/doctoral program, the number of women participants was significantly higher than that of men (p<.05).

Table 1. *Demographic information of PDSs.*

Demographic characteristics		N (%)
Gender	Women	147 (73.5%)
	Men	53 (26.5%)
Age	23-24	23 (11.5%)
	25-30	167 (83.5%)
	31-35	5 (2.5%)
	35+	5 (2.5%)
Year of graduation	Before 2015	9 (4.5%)
	2015	9 (4.5%)
	2016	15 (7.5%)
	2017	34 (17%)
	2018	45 (22.5%)
	2019	55 (27.5%)
	2020	29 (14.5%)
	2021	4 (2%)
Specialty/doctoral program	Oral and Max. Surgery	27 (13.5%)
	Oral and Max. Radiology	30 (15%)
	Prosthodontics	23 (11.5%)
	Restorative Dentistry	29 (14.5%)
	Endodontics	27 (13.5%)
	Periodontology	21 (10.5%)
	Orthodontics	20 (10%)
	Pediatric dentistry	23 (11.5%)

PDSs: Post-graduate dental students

3.2. General Knowledge About MRONJ

PDSs studying in the Departments of Oral and Maxillofacial Surgery and Oral and Maxillofacial Radiology had the highest correct answer rates to the general knowledge questions. However, when the total correct answer rates of different specialty/doctoral program were compared, the differences were found to be statistically insignificant (p>.05).

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Table 2a. *PDSs' general knowledge about MRONJ.*

General Knowledge Questions		N (%)
Do you have knowledge about MRONJ?	Yes No	190 (95%) 10 (5%)
Which of the following criteria is required for the diagnosis of MRONJ according to the AAOMS?† (more than one answer can be marked)	Current or previous treatment with antiresorptive or antiangiogenic agents No history of radiation therapy to the jaws or obvious metastatic disease to the jaws Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks	152 (76%) 109 (54%) 196 (98%)
Which of the following procedures and situations are among the risk factors associated with MRONJ? (more than one answer can be marked)	Dentoalveolar surgery Anatomical region Prosthesis-related trauma Dental infection Tobacco/alcohol use Type of cancer Duration/dose of the antiresorptive drug Concomitant corticosteroid use with antiresorptive and/or antiangiogenic therapy	187 (93.5%) 150 (75%) 153 (76.5%) 148 (74%) 123 (61.5%) 104 (52%) 183 (91.5%) 138 (69%)
Which of the following drugs/treatments can cause MRONJ? (more than one answer can be marked)	Bisphosphonate Antiangiogenic drugs Denosumab Radiotherapy Bisphosphonate, antiangiogenic drugs and denosumab	197 (98.5%) 143 (71.5%) 117 (58.5%) 54 (27%) 83 (41.5%)
Which of the following disease(s) requires antiresorptive therapy? (more than one answer can be marked)	Osteoporosis Osteogenesis imperfecta Paget's disease Multiple myeloma Malignant tumor metastasis I don't know	185 (92.5%) 61 (30.5%) 97 (48.5%) 125 (62.5%) 135 (67.5%) 3 (1.5%)
Which of the following disease(s) requires antiangiogenic therapy? (more than one answer can be marked)	Osteoporosis Gastrointestinal tumors Renal carcinoma Neuroendocrine tumors Malignant tumor metastasis I don't know	39 (19.5%) 61 (30.5%) 89 (44.5%) 78 (39.5%) 132 (66%) 44 (22%)
What is the route of administration of antiresorptive/antiangiogenic drugs?	Only oral Only intravenous Only subcutaneous Oral and intravenous Oral, intravenous and subcutaneous	1 (0.5%) 0 0 160 (80%) 39 (19.5%)

†According to the 2014 position paper of AAOMS (4)
PDSs: Post-graduate dental students, MRONJ: Medication-related osteonecrosis of the jaws, AAOMS: American Association of Oral and Maxillofacial Surgeons

According to the results presented in Table 2a, 95% of PDSs had knowledge about MRONJ. On the other hand, when the PDSs were asked about the definition of MRONJ suggested by the 2014 position paper of the AAOMS, only 52.5% answered this question correctly by selecting all three diagnostic criteria of MRONJ. The most stated risk factors related to MRONJ were dentoalveolar surgery and duration/dose of the antiresorptive drug, whereas the least were smoking/alcohol use and type of cancer (Table 2a).

When the answers according to the drug groups causing MRONJ were evaluated, eighty-three (41.5%) PDSs who chose bisphosphonate, denosumab, and antiangiogenic drugs together were aware that these three drug groups may have this side-effect. However, 54 (27%) participants answered this question incorrectly by identifying radiotherapy as a possible cause of MRONJ. Furthermore, when the answers given to the question about the route of administration of antiresorptive/antiangiogenic drugs were examined, only 19.5% of the participants knew about subcutaneous administration as well as oral and intravenous administration of antiresorptive and antiangiogenic drugs (Table 2a).

Most PDSs (92.5%) knew the drug mechanism of antiresorptive drugs. The relation between the route of administration and the risk of developing MRONJ was correctly identified by 83% of the participants. On the other hand, only 29% of PDSs were aware of the association between the different diseases treated with varying doses of antiresorptive drugs and the risk of MRONJ (Table 2b).

Among the antiresorptive drug groups, zoledronate (92%) and alendronate (85.5%) were the most frequently known ones, whereas denosumab was chosen by 55.5% of PDSs. Bevacizumab (31.5%) was the most commonly known antiangiogenic drug (Table 3). While 57% of the PDSs stated that they did not know any antiangiogenic drug, the rate of this option for the antiresorptive drugs was only 5.5%. Moreover, the participants had more knowledge about indications of antiresorptive drugs (66.5%) than that of antiangiogenic drugs (32.5%). Thirty-nine (19.5%) PDSs incorrectly selected osteoporosis as an indication for antiangiogenic drug use (Table2a).

3.3. Clinical Attitude and Information Sources About MRONJ

Table 4 summarizes the clinical attitudes of PDSs towards MRONJ patients, as well as the information sources about MRONJ. 100% and 96% of PDSs agreed that a comprehensive oral and dental examination is necessary prior to antiresorptive and antiangiogenic therapy, respectively. However, only 38.5% of PDSs stated that a patient was referred to them for dental consultation before antiresorptive therapy; and the rate was even lower (14%) for antiangiogenic therapy. 92% of the participants obtained their knowledge about MRONJ from undergraduate dental education. While internet and books/journals were selected respectively by 38.5% and 38% of PDSs, the rate for postgraduate dental education was only 21.5%.

Table 2b. *PDSs' general knowledge about MRONJ.*

General Knowledge True/False Questions		N (%)
Antiresorptive drug use reduces osteoclast function and bone remodeling (True)	True False I don't know	185 (92.5%) 10 (5%) 5 (2.5%)
The risk of developing MRONJ is higher for orally administered antiresorptive drugs than for intravenously administered drugs (False)	True False I don't know	12 (6%) 166 (83%) 22 (11%)
Compared with cancer patients treated with antiresorptive drugs, osteoporosis patients have a lower risk of developing MRONJ (True)	True False I don't know	58 (29%) 60 (30%) 82 (41%)

PDSs: Post-graduate dental students, MRONJ: Medication-related osteonecrosis of the jaws

Table 3. *PDSs' familiarity with antiresorptive and antiangiogenic drugs.*

Antiresorptive drugs	N (%)	Antiangiogenic drugs	N (%)
I dont't know any	11 (5.5%)	**I dont't know any**	114 (57%)
Alendronate (Fosamax)	171 (85.5%)	**Bevacizumab (Avastin)**	63 (31.5%)
Ibandronate (Bonviva)	104 (52%)	**Aflibercept (Zaltrap)**	12 (6%)
Zoledronate (Zometa)	184 (92%)	**Sunitinib (Sutent)**	21 (10.5%)
Risedronate (Actone)	55 (27.5%)	**Sorafenib (Nexavar)**	15 (7.5%)
Pamidronate (Aredia)	68 (34%)	**Temsirolimus (Torisel)**	33 (16.5%)
Clodronate (Bonefos)	50 (25%)	**Everolimus (Certican)**	22 (11%)
Denosumab (Prolia)	111 (55.5%)		

PDSs: Post-graduate dental students

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Table 4. *PDSs' clinical attitude and information resources regarding MRONJ.*

Clinical attitude questions		N (%)
Is a comprehensive oral and dental examination necessary prior to antiresorptive therapy?	Yes No I don't know	200 (100%) 0 0
Is a comprehensive oral and dental examination necessary prior to antiangiogenic therapy?	Yes No I don't know	192 (96%) 2 (1%) 6 (3%)
Should patients who are planned to use antiresorptive drugs be informed about the importance of oral and dental health?	Yes No I don't know	199 (99.5%) 0 1 (0.5%)
Should patients who are planned to use antiangiogenic drugs be informed about the importance of oral and dental health?	Yes No I don't know	195 (97.5%) 1 (0.5%) 4 (2%)
Is it necessary to consult a medical doctor before dental treatment of the patients using antiresorptive drugs?	Yes No I don't know	198 (99%) 0 2 (1%)
Is it necessary to consult a medical doctor before dental treatment of the patients using antiangiogenic drugs?	Yes No I don't know	197 (98.5%) 0 3 (1.5%)
Has a patient been referred to you for a dental examination prior to antiresorptive therapy by a medical doctor?	Yes No	77 (38.5%) 123 (61.5%)
Has a patient been referred to you for a dental examination prior to antiangiogenic therapy by a medical doctor?	Yes No	28 (14%) 172 (86%)
Are you familiar with international guidelines on risk factors and management of MRONJ?	Yes No I don't know	74 (37%) 96 (48%) 30 (15%)
Information resources	Undergraduate dental education Postgraduate dental education Congress/Seminar Internet Books/Journals National guidelines Other	184 (92%) 43 (21.5%) 57 (28.5%) 77 (38.5%) 76 (38%) 5 (2.5%) 10 (5%)

PDSs: Post-graduate dental students, MRONJ: Medication-related osteonecrosis of the jaws

4. DISCUSSION

The term osteonecrosis of jaws (ONJ) was first included in the undergraduate dental curriculum as a side-effect of bisphosphonate drugs in the 2006-2007 academic year and gained more importance with the AAOMS 2009 position paper on BRONJ (3,18). After the 2014 update of the AAOMS (4), which highlighted denosumab and antiangiogenic therapies as possible causes of osteonecrosis of the jaws, these drug groups also began to be included in the dental curriculum. According to Deveci and Uğar Çankal (18), the revised undergraduate curriculum in line with the AAOMS reports has a direct relationship with the knowledge levels of dentists about MRONJ. In agreement with this statement, previous studies suggest that younger dentists tend to be more knowledgeable about MRONJ, since MRONJ-related dental education is a recent concept in the undergraduate dentistry curriculum (7,16,21).

Ekmekcioglu et al (9) conducted a questionnaire among general dentists and specialists and showed that the latter were significantly more aware of MRONJ. With respect to their result, they concluded that postgraduate dental training is an effective factor for the dentists' knowledge levels about MRONJ. Similar to the mentioned study, Alhussain et al (21) reported that specialist dentists were more knowledgeable about MRONJ than general dentists. Concerning the aforementioned investigations, the present study only included recently graduated dentists who were currently under specialty/doctoral training in order to evaluate and compare the knowledge levels of different dental specialties using a homogeneously distributed group of participants.

To our knowledge, there are only three investigations involving PDSs among participants (18-20). Sahin (19) and Patil et al

(20) divided respondents into two groups and evaluated correct answers based on dentists' experience in surgical procedures and different years of experience, respectively. However, a comparison between different specialty/doctoral programs was not performed in both investigations (19,20). Although Deveci and Uğar Çankal (18) compared the correct answer rates between different dental specialties in their study, the participants did not show a homogeneous distribution according to their specialty/doctoral programs. Moreover, all three studies focused on antiresorptive drugs, thus awareness and knowledge level toward antiangiogenic drugs was not questioned (18-20). Therefore, to the authors knowledge, this is the first study evaluating the awareness and knowledge of PDSs from different specialty/doctoral programs towards MRONJ with a questionnaire covered both antiresorptive and antiangiogenic drugs.

The results of the present study revealed that oral and maxillofacial radiologists and surgeons were able to achieve higher correct answer rates than other dental specialties. Even though our result was statistically insignificant (p>.05), many studies agreed that oral and maxillofacial surgeons are more knowledgeable about MRONJ (19,21-23). This can be explained by the fact that MRONJ patients are encountered more frequently in university dental hospitals (22), and the mentioned specialties particularly have more experience with such patients. The reason for mentioning only oral surgeons regarding the high level of MRONJ knowledge in the previous questionnaires may be the absence (21-23) or the small number (18) of oral and maxillofacial radiologists in such studies. More investigations involving an equal number of participants from all dental specialties may be helpful to determine the actual knowledge levels of different specialties.

As observed in the current research, almost all PDSs knew the term MRONJ, but only half of them were able to identify the MRONJ definition described by the AAOMS. Even though this indicates a lack of knowledge among recently graduated dentists, the percentage obtained in the present study was still higher than that of the previous studies conducted with general and specialist dentists. Al-Eid et al (8) showed 35.1% of Saudi Arabian dentists knew the correct definition of MRONJ, while Almousa et al (12) reported a rate of 28.1%. Considering studies involving PDSs, Patil et al (20) stated 35% of the respondents were able to recognize the MRONJ definition. Despite the higher level of knowledge in the current study, it is alarming that only 54% of PDSs were confident that "no history of radiation therapy to the jaws or obvious metastatic disease to the jaws" (4) was a necessary criterion for MRONJ diagnosis. Consistent with this result, it is also worrying that 27% of respondents in the present research accepted radiotherapy as an MRONJ-causing treatment, and this rate was even higher (59.5%) in the study of Al-Eid et al (8).

Besides the diagnostic criteria of MRONJ, awareness of MRONJ-related risk factors is also critical for the management and treatment strategies for these patients. According to a Saudi Arabian research, the most cited risk factor regarding MRONJ was dentoalveolar surgery, consistent with the results of the present study, while corticosteroid therapy was identified only by 13.5% (8). Similarly, in a French study, less than a third (29.7%) of the participants were aware that concomitant corticosteroid therapy may increase the risk of developing MRONJ (16). In contrast to these investigations, the awareness level in the present study was found much higher (69%), indicating that corticosteroids have adequate importance within the MRONJ-related dental curriculum of Turkey. Almousa et al (12) reported that tobacco use was the most stated risk factor with a percentage of 52.5% in their study, which included both dentists and dental students. Additionally, they also observed that dentists were significantly more aware of smoking as a risk factor compared to students (12). Arnaud et al (16) conducted a questionnaire among general and specialist dentists, most of whom were over 30, and obtained a remarkably higher rate (92.1%) about this topic. According to the results of the present study, in which participants mainly were under the age of 30, 61.5% of PDSs identified tobacco use as a risk factor. Even though more than half of PDSs were aware of this risk factor, the percentage was still lower than that of Arnaud et al (16), which points to a possible lack of knowledge among younger dentists about this topic. A similar conclusion can also be reached for another risk factor, cancer type, considering only 52% of PDSs accepted it as an MRONJ-related risk factor.

In the questions where the indications of antiresorptive and antiangiogenic drugs were asked, the most cited indication for antiresorptive therapy was found as osteoporosis, whereas for antiangiogenic therapy as malignant tumor metastasis. Previous studies reporting osteoporosis as the most recognized therapeutic indication for bisphosphonates confirm this conclusion (15,18). Since the therapeutic indication questions in the current study had more than one correct answer, participants who chose three or more correct indications were accepted to have given the correct answer. Accordingly, two-thirds (66.5%) of respondents were able to answer this question correctly. On the other hand, only 14.5% of PDSs could identify all the diseases treated with antiresorptive therapy.

The most commonly known antiresorptive drugs in the current study were alendronate and zoledronate, consistent with the previous studies (9,12,13). It was a reasonable result, since physicians who prescribe antiresorptive medication usually prefer the aforementioned drug groups (24). Considering dentists' familiarity level of denosumab, two similar studies held in Spain and Turkey, including both general dentists and specialists, reported different knowledge rates, 61.7% and 18.4%, respectively (7,9). In the present questionnaire, in which all the participants were under specialty/doctoral training, 58.5% of PDSs were able to identify denosumab. It is noteworthy that this rate is closer to the results of the research from Spain, rather than the research from Turkey, where more than half (74.5%) of the respondents had no specialty/doctoral education (9). Even though this implies the effectiveness of postgraduate dental education, according

to the results of the present study, the primary source of information on MRONJ was found as undergraduate dental education with a rate of 92%. This finding was in agreement with the previous investigations (16,18,19). It is important that only 21.5% of PDSs identified postgraduate education as an information resource, which emphasizes the major role of undergraduate training in MRONJ knowledge.

Many studies in the literature acknowledge that recently graduated younger dentists are more knowledgeable about MRONJ, regardless of their field of specialty (7,16,21). However, the results of the present study revealed that even after eight years of the AAOMS updating the term BRONJ as MRONJ, PDSs are still more confident in their knowledge of antiresorptive drugs. This also highlights that although younger dentists have become more aware of MRONJ over the years (18), they still have insufficient knowledge about antiangiogenic drugs (12,16). On the other hand, the fact that only a few of the respondents (14.5%) in the current study identified all indications of antiresorptive therapy is thought-provoking about the adequacy of dental education regarding antiresorptive drugs.

The questionnaire in the present study was conducted based on the 2014 position paper of AAOMS (4), as there was no new update available at the time of the study design. Recently, the AAOMS released a 2022 update that includes changes in MRONJ definition criteria, medications, and management strategies (25). In this study, PDSs were asked about the 2014 definition of MRONJ, and the survey did not include a novel monoclonal antibody, Romosozumab, among drug familiarity questions. Therefore, this creates a limitation for the present study. Further investigations based on the AAOMS 2022 position paper, questioning the revisions about diagnosis and management strategies may be helpful to enlighten how undergraduate and specialist/doctoral education curricula overlap with the current literature.

5. CONCLUSION

The present investigation is of great importance in the following respects: It is the first study in which the participant group consisted only of PDSs as well as the questionnaire covered both antiresorptive and antiangiogenic drugs. Additionally, PDSs had a homogenous distribution according to their specialty/doctoral programs, which allowed us to compare different fields of dental specialties in terms of knowledge level about MRONJ. Although oral and maxillofacial radiologists and surgeons were found to be more knowledgeable, there was a remarkable lack of knowledge across all specialties, particularly with regard to antiangiogenic drugs. Therefore, the authors of this study suggest that both undergraduate and postgraduate dental education should be revised in line with the updated literature on MRONJ.

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