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## Knowledge and Prevention Practices Regarding Medication-related Osteonecrosis of the Jaws (MRONJ) among Jordanian Dentists: Cross-sectional Observational Study

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### ABSTRACT

**Objectives:** The aim of this study is to evaluate the knowledge and prevention practices of Jordanian dentists regarding medication-related osteonecrosis of the jaws (MRONJ).

**Materials and methods:** An electronic-based survey was distributed among dentists practicing in Amman-Jordan. Survey sections included 16 items on: socio-demographic information, knowledge regarding MRONJ, and clinical practices concerning the prevention and management of MRONJ. A knowledge score was devised to evaluate each participant's overall understanding of MRONJ and the related medications. The data was statistically analyzed, and a P-value of <0.05 was considered significant.

**Results:** The total number of participants in the study who completed the questionnaire was 186 (105 females and 81 males, with a mean age of 34.3 years). The mean Knowledge Score (KS) of the study population was 9.5 out of 18. This indicates that the largest variety of participants responded correctly to more than 50% of the questions related to knowledge about MRONJ. The highest mean KS of 15 was observed among oral medicine specialists, while the lowest mean KS of 8.5 was found among general practitioner dentists. Regarding the clinical management and whether the participants would proceed with exodontia in different clinical scenarios, the majority of the participants were unsure and would rather refer the patient to a specialist before exodontia in patients taking IV bisphosphonates. As for the study participants, most of them were able to correctly identify the preventative measures, and as the mean KS increased, more preventative measures and more treatment options were correctly identified.

**Conclusions:** Reinforcement of MRONJ awareness and knowledge among general dentists and dental specialists is essential in the management and prevention of MRONJ in 'at-risk' patients.

**Keywords:** Knowledge score, Medications, MRONJ, Prevention, Osteonecrosis.

### 1. Introduction

Medication-related osteonecrosis of the jaws (MRONJ) is defined as exposed bone or the presence of an intraoral or extraoral fistula in the maxillofacial region persisting for more than 8 weeks in a patient with ongoing or antecedent treatment with anti-angiogenic or anti-resorptive drugs, and no patient history of radiation therapy or manifest metastasis of the jaws. This term was updated from bisphosphonate-related osteonecrosis

of the jaws (BRONJ) in 2014 by the American Association of Maxillofacial Surgeons (AAOMS) (1).

The implicated medications are: [1] denosumab is a RANK-ligand inhibitor, which inhibits osteoclast function, decreases bone resorption, and increases bone density, [2] bevacizumab is a humanized monoclonal anti-body, [3] sirolimus targets the rapamycin pathway, and finally [4] sunitinib and sorafenib are tyrosine kinase receptor inhibitors (2,3).

There are numerous risk factors associated with the progression of the disease. These risk factors are divided into local, drug-related, and systemic-related factors (2). The most important risk factors contributing to the development of MRONJ are the route of drug administration and the length of therapy; however, the risk varies from a low to a high risk depending on multiple variables (1,4,5).

There are a few staging systems proposed by R.E. Marx; the AAOMS, and the Italian Society of Dentistry and Maxillofacial Surgery (SCIMF-SIPMO), based on the clinical presentation and accordingly, different management procedures are recommended (6). One of the most commonly used staging systems was proposed in 2009 by the AAOMS (1,7).

The tendency of developing MRONJ has been rising in the past years due to dentists underestimating the risk of osteonecrosis in patients taking these medications (8,9). Lack of dentists' knowledge regarding the appropriate management coupled with low awareness levels of patients regarding the risk can have very severe consequences. Since no definitive treatment is available, proper prevention is crucial to avoid osteonecrosis of the jaws (10,11).

The authors of this study, affiliated with the University of Jordan and Jordan University Hospital, have decided upon observations of recently graduated dentists in the university clinics, and they have opted to extend their investigation to a larger sample. Mostly all the dentists in the capital Amman were eligible to participate in this study, in order to measure the awareness level. The aim of this study is to evaluate the knowledge and prevention practices of Jordanian dentists toward medication-related osteonecrosis of the jaws (MRONJ), and hence to improve the quality of care provided to patients.

## 2. Materials and Methods

### 2.1 Study Design

The questionnaire was constructed by the authors based on previous studies (12,13), and it was further validated and refined by a pilot study conducted on 10 participants. This survey comprised three sections with 16 items. A valid, reliable semi-structured questionnaire was used to gather data using a non-probability convenience-sampling technique. The first section assessed dentists' demographics, while the second section included items that assessed basic knowledge

regarding MRONJ. Finally, the third section determined the knowledge regarding clinical practices. The questionnaire was distributed on social media platforms; in four official Facebook groups for dentists in Jordan.

The sample size was calculated using Cochran's formula for finite populations, considering the total population of the registered dentists in Amman (Jordan), based on the most recent data provided by the Jordan Dental Association (JDA) being 8025 dentists at the time of the study (14). Accordingly, a 95% confidence level ( $Z=1.96$ ), a 5% margin of error, and a population proportion of 50% ( $p=0.5$ ) resulted in a required sample size of 95 respondents.

### 2.2 Ethical Permission

The study was approved by the Scientific Research Committee at the School of Dentistry/UJ. Additionally, the study was approved by the Institutional Review Board (IRB) at the Jordan University Hospital. Participation in the study was voluntary and anonymous. Informed consent was ensured by the presence of an introductory section of the questionnaire. All collected data was treated confidentially and used for scientific-research purposes only.

### 2.3 MRONJ Knowledge Score

A knowledge score (KS) was used to evaluate each participant's overall knowledge of MRONJ and the related medications. A total of 18 points were included in the KS, with 5 points awarded to the medications/therapies that predispose to MRONJ, 4 points given to the uses of bisphosphonates, 5 points used to determine the knowledge on the category of drugs (these medications belong to Alendronate, Bevacizumab, Denosumab, Sirolimus, and Sorafenib/Sunitib, and lastly 4 points were awarded to the knowledge on the risk factors of MRONJ. A correct response to these questions is considered as a single point and a non-response to a wrong option is considered as a single point as well, with a minimum score of zero and a maximum score of 18.

### 2.4 Statistical Analysis

Measures of central tendency were used to characterize the study variables. We used the chi-squared test ( $\chi^2$ ) to examine the significance of relationships between categorical variables, while the Mann-Whitney U test was used to assess the association

between scale and binary categorical variables. The statistical significance was considered to be  $p < 0.050$ . The data was entered and analyzed using IBM SPSS Statistics 28.0.

### 3. Results

#### 3.1 Characteristics of the Study Population

The questionnaire used in this study was pre-tested and successfully validated and approved. The total number of participants in the study who completed the questionnaire was 186. The mean age of the study participants was 34.3 years (median: 33 years,

interquartile range (IQR): 25.8-39 years). Females predominated the study population ( $n = 105$ , 56.8%). The majority of the participants were general practitioners ( $n=101$ , 54.3%), oral and maxillofacial surgeons (OMFS) ( $n=42$ , 22.6 %), and the remaining specialties were grouped together comprising 23.1%, starting with prosthodontics ( $n=10$ , 5.4 %), pediatric dentists ( $n=7$ , 3.8%), endodontists ( $n=6$ , 3.2%), periodontists ( $n=6$ , 3.2%), orthodontists ( $n=5$ , 2.7%), radiologists ( $n=4$ , 2.1%), operative dentists ( $n=3$ , 1.6%), and oral-medicine specialists ( $n=2$ , 1.1%) (Table 1).

**Table 1:** Characteristics of the study participants

Characteristic	N (%)
Age (median)	33
<b>Gender</b>	
Male	81 (43.5)
Female	105 (56.5)
<b>Dental Specialty</b>	
General practitioners	101 (54.3)
Oral and maxillofacial surgeons	42 (22.6)
Prosthodontics	10 (5.4)
Pediatric dentists	7 (3.8)
Endodontists	6 (3.2)
Periodontists	6 (3.2)
Orthodontists	5 (2.7)
Radiologists	4 (2.1)
Operative dentists	3 (1.6)
Oral Medicine specialists	2 (1.1)

The years of experience ranged between 1 year and 36 years with an average of 9.5 years. The study participants who have not encountered or treated a patient with MRONJ are 104 (55.9%). The majority of the participants did not feel comfortable treating patients with MRONJ and would rather refer ( $n=117$ , 62.9%), while 21 (11.3%) did not know and 48 (25.8%) felt comfortable treating patients with their current knowledge.

#### 3.2 General Knowledge of MRONJ

The vast majority of the study participants (91.4%) are aware of MRONJ ( $n=170$ , 91.4%). The mean KS of the study population is 9.5 out of 18. Regarding the sub-

categories of the KS components, participants who correctly identified the role of radiotherapy in MRONJ makeup were about 38.7% ( $n=72$ ), chemotherapy ( $n=109$ , 58.6%), anti-resorptive medications ( $n=140$ , 75.3%), corticosteroids ( $n=152$ , 81.7%), and anti-angiogenic medications ( $n=62$ , 33.3%).

Participants who were able to identify the following conditions where bisphosphonates are used as a treatment method; osteoporosis ( $n=176$ , 94.6%), multiple myeloma ( $n=76$ , 40.8%), bone metastases ( $n=105$ , 56.5%), and osteogenesis imperfect ( $n=32$ , 17.2%).

The correctly chosen answers regarding the category of drugs that these medications belong to were:

Alendronate (n=140, 75.3%), Bevacizumab (n=39, 21.0%), Denosumab (n=50, 26.9%), Sirolimus (n=24, 12.9%), and Sorafenib/Sunitib (n=32, 17.2%).

Furthermore, in terms of knowledge regarding the risk factors, 164 participants correctly identified that patients taking IV bisphosphonate are at a higher risk to develop MRONJ than patients taking oral bisphosphonate (88.2%). A high percentage of participants knew that patients taking oral bisphosphonate for cancer therapy are at a higher risk of

developing MRONJ than patients taking oral bisphosphonate for osteoporosis therapy (n=169, 90.9%). However, only 47.8% of the participants knew that patients taking IV bisphosphonate for cancer therapy are at a higher risk of developing MRONJ than patients taking IV bisphosphonate for osteoporosis therapy (n= 89). Finally, 73.7% of the participants correctly answered, “Oral bisphosphonates can only cause MRONJ after 5 years of usage” (n= 137) (Table 2).

**Table 2:** MRONJ knowledge score (KS out of 18)

Item	Correct responses N (%)	
<b>Which of these medications/therapies predispose to MRONJ?</b>	Radiotherapy	72 (38.7)
	Chemotherapy	109 (58.6)
	Anti-resorptive medications	140 (75.3)
	Corticosteroids	152 (81.7)
	Anti-angiogenic medications	62 (33.3)
<b>What are bisphosphonates used for?</b>	Osteoporosis	176 (94.6)
	Multiple myeloma	76 (40.9)
	Bone metastasis	105 (56.5)
	Osteogenesis imperfecta	32 (17.2)
<b>Which category of drugs do these medications belong to?</b>	Alendronate	140 (75.3)
	Bevacizumab	39 (21.0)
	Denosumab	50 (26.9)
	Sirolimus	24 (12.9)
	Sorafenib/ Sunitib	32 (17.2)
<b>Which of the following statements are true about the risk factors of MRONJ?</b>	Patients taking IV bisphosphonates are at a higher risk to develop MRONJ than patients taking oral bisphosphonates	164 (88.2)
	Patients taking oral bisphosphonates for osteoporosis therapy are at a higher risk to develop MRONJ than patients taking oral bisphosphonates for cancer therapy	169 (90.9)
	Patients taking IV bisphosphonates for cancer therapy are at a higher risk to develop MRONJ than patients taking IV bisphosphonates for osteoporosis therapy	89 (47.8)
	Oral bisphosphonates can only cause MRONJ after 5 years of usage	137 (73.7)

Male participants had a higher mean KS compared to female participants (9.7 vs. 9.4,  $p < 0.001$ ). The mean KS regarding MRONJ among the OMFS was 12.0, compared to the other combined specialties which had a mean KS of 9.4, and finally, the lowest mean KS of 8.5 was found among general practitioner dentists ( $p < 0.001$ ). The highest observed mean KS among all the specialties was seen in oral-medicine specialists with a mean of 15 out of 18 (Table 2).

The highest mean KS of 12.4 was observed among participants who feel comfortable in treating patients with MRONJ with their current knowledge, while those who answered ‘No, I would rather refer’ and ‘I don’t know’ had a mean KS of 8.8 and 7.0, respectively ( $p < 0.001$ ).

There was no association detected between the age of the participant or the years of experience with the mean KS ( $p = 0.48$  and  $p = 0.14$ ) (Table 3).

**Table 3:** Mean knowledge score in relation to gender and specialty

Mean Knowledge Score (KS)		P-value
<b>Gender</b>		
Male	9.7	P<0.001
Female	9.4	
<b>Specialty</b>		
General practitioner dentists	8.5	P<0.001
Oral and maxillofacial surgeons	12.0	
<b>Others</b>	9.4	
Endodontists	10.7	
Operative dentists	7	
Oral medicine specialists	15	
Orthodontists	8.8	
Pedodontists	8	
Periodontists	9.8	
Prosthodontists	7.9	
Radiologists	13	
<b>How comfortable are you in treating MRONJ?</b>		
Yes	12.4	P<0.001
I don't know	7.0	
No, I would rather refer	8.8	

**3.3 Clinical Management and Prevention Methods**

The participant’s clinical judgment regarding patients taking medications that predispose to MRONJ in the dental clinic was tested through three different clinical scenarios. The majority of the participants were unsure and would rather refer the patients to a specialist before exodontia in patients taking IV bisphosphonates (n=86, 45.7%) with only 3.7% answering that they would extract the tooth (n=7). Secondly, most of the participants responded that patients taking oral

bisphosphonates for a period of less than 3 years were to be referred to a specialist (n=89, 47.3%), and a relatively high percentage of participants would extract the tooth (n=54, 28.7%). The final clinical scenario included patients taking oral bisphosphonate for more than 3 years, 54.3% would refer the patients to a specialist (n=102), while the second most common answer was to suspend the bisphosphonate treatment for 3 months, then to carry out the dental extraction (n=39, 20.7%) (Table 4).

**Table 4:** Dentists’ clinical management of patients taking medications that predispose to MRONJ in the dental clinic

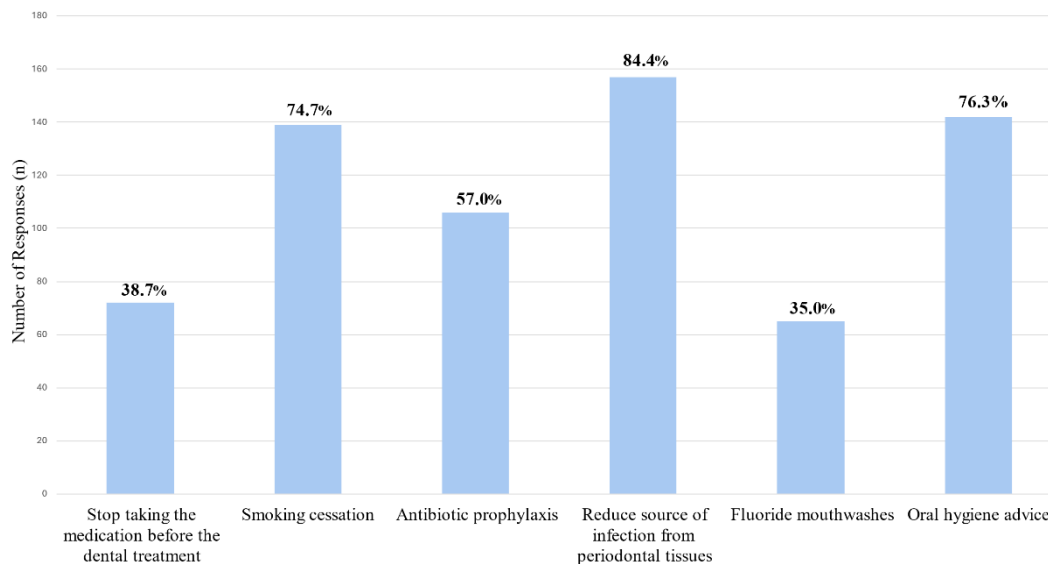
	do before exodontia in a patient taking IV bisphosphonates? N (%)	before exodontia in a patient taking oral bisphosphonates less than 3 years? N (%)	before exodontia in a patient taking oral bisphosphonates more than 3 years? N (%)
<b>I carry out the dental extraction</b>	7 (3.7)	54 (28.7)	18 (9.6)
<b>I don't extract the tooth</b>	60 (31.9)	14 (7.4)	27 (14.4)
<b>I am unsure, I refer the patient to a specialist</b>	86 (45.7)	89 (47.3)	102 (54.3)
<b>I suspend the bisphosphonate treatment for 3 months, then I carry out the dental extraction</b>	33 (17.6)	29 (15.4)	39 (20.7)

Among the study participants, only 11.8% were able to identify all 6 choices that might aid in the prevention

of MRONJ (n=22). 84.4% of the participants chose to reduce the source of infection as a prevention method

(n=157), 76.3% chose oral-hygiene instructions (n=142), followed by 74.7% who chose smoking cessation (n=139), while only 34.9% were able to identify fluoride mouthwash as a preventive measure (n=65). Upon comparison of the mean KS and the

prevention methods, it was noticed that as the mean KS increased for the participants, more preventative measures were correctly identified by the study participants ( $p < 0.001$ ) (Figure 1).



**Figure 1:** Dentists' responses to questions about methods that might aid in the prevention of MRONJ

The majority of the participants identified 5 correct treatment measures out of 6 options (n=64, 34.4%), and 22% were able to identify all correct treatment options (n=41). It was noticed that as the KS increased, the number of correctly identified treatment options increased as well ( $p = 0.004$ ).

#### 4. Discussion

Medication-related osteonecrosis of the jaws is a complication that arises in the oral and maxillofacial region in patients taking anti-angiogenic or anti-resorptive medications (15). Dentists' knowledge regarding the appropriate management is very imperative to avoid severe repercussions including jawbone resection and patient hospitalization (16). Consequently, sufficient knowledge and proper prevention are fundamental in patient management (12,17).

In this study, the knowledge, awareness and prevention practices of dentists were evaluated using a validated and pre-tested survey with minor modifications. The vast majority of the participants (91.4%) were aware of MRONJ as a disease related to the use of anti-resorptive and anti-angiogenic drugs.

This was higher than the results reported in other studies (75.4% to 87.5%) (13,18). Moreover, our study is in alignment with previous research conducted in Saudi Arabia, revealing a comparatively lower level of knowledge among dentists, with percentages ranging from 60.8% to 87.5% (18).

A mean knowledge score of 9.5 of the study participants reflects intermediate knowledge regarding MRONJ. The majority of participants recognized that anti-resorptive medications predispose to MRONJ (75.3%). However, only 33.3% correctly recognized the role of anti-angiogenic medications in MRONJ. This might be explained by the wide use of anti-resorptive medications, like bisphosphonates, in many common conditions, like osteoporosis. On the other hand, anti-angiogenic medications, like sunitinib and sorafenib, are rarely used and less commonly heard of (18). Additionally, only 38.7% of the study participants discerned that radiotherapy does not contribute to MRONJ, and this relatively low percentage can be explained by the notion that MRONJ is commonly mistaken for osteoradionecrosis due to the similarities in terms of imaging, risk factors, prevention, and treatment (19,20).

The vast majority of the participants knew that bisphosphonates are used in the management of osteoporosis (94.6%) (21), while only 40.9%, 56.5%, and 17.2% knew that bisphosphonates are used in the management of Multiple Myeloma, Bone Metastasis, and Osteogenesis Imperfecta, respectively (22,23).

The percentage of the participants who knew that Alendronate belongs to the bisphosphonate drug category was 75%, while a minority were able to correctly identify the drug category of Bevacizumab (21.0%), Denosumab (26.9%), Sirolimus (12.9%), and Sorafenib/ Sunitib (17.2%). This is likely, as bisphosphonates are more commonly heard of and used than the latter drugs (2, 18). A new Brazilian study found that a significant number of the participants (65.3%) did not recognize the bisphosphonates when presenting a sample of medication, from which a percentage of 66.5% also did not know how to treat patients on bisphosphonate in the clinical routine (24).

The exact mechanism of MRONJ development is not fully comprehended; however, there are numerous risk factors associated with the progression of the disease (25). These risk factors are divided into local, drug-related, and systemic-related factors (26,27). The most important risk factors contributing to the development of MRONJ are the route of drug administration, whether they are administered for osteoporosis or cancer treatment, and the length of therapy (2,28).

Most of the participants properly identified that patients taking IV bisphosphonate are at a higher risk to develop MRONJ than patients taking oral bisphosphonate (88.2%) and that patients taking oral bisphosphonate for cancer therapy are at a higher risk to develop MRONJ than patients taking oral bisphosphonate for osteoporosis therapy (90.9%). Conversely, only 47.8% answered correctly that patients taking IV bisphosphonate for cancer therapy are at a higher risk of developing MRONJ than patients taking IV bisphosphonate for osteoporosis therapy. This can be clarified by the assumption that IV bisphosphonates impose a high risk regardless of the condition it is used to treat. Finally, most of the participants recognized that oral bisphosphonate does not only cause MRONJ after 5 years of usage (29).

The mean KS regarding MRONJ among OMFS was 12.0, compared to 9.4 mean KS for the other combined specialties, which is anti-cipated, as OMFS typically manage and treat patients with MRONJ (30,31). Male

participants had a higher mean KS compared to female participants (9.7 vs. 9.4); this can be elucidated by the fact that all the participating OMFS are males (32).

Moreover, the lowest mean KS of 8.5 was found among general practitioner dentists. This is worrisome, since patients initially seek general dentists; thus, they should have adequate knowledge in order to correctly perform dental procedures and manage patients undergoing therapy with anti-angiogenic or anti-resorptive drugs (33). In addition to that, according to a study conducted in Jordan to evaluate the awareness among patients using bisphosphonates regarding the risk of developing MRONJ, the results indicated low awareness levels (34). Therefore, it is very imperative for general dentists to educate the patients and provide adequate preventative measures (11,35).

The highest mean KS of 12.4 was observed among participants who feel comfortable in treating patients with MRONJ with their current knowledge, while those who answered 'No, I would rather refer' and 'I don't know' had a mean KS of 8.8 and 7.0, respectively. Dentists with less knowledge will rather refer patients to an OMFS who in turn will appropriately manage the patient and avoid any complications (30,36).

Treatment options for patients at risk should exclude the extraction of teeth as much as feasible. Endodontic treatment, coronectomy, and splinting teeth with mobility grades 1 and 2 should be taken into account before exodontia (37). If extraction is unavoidable, then reinforcement of oral hygiene, smoking cessation, antibiotic prophylaxis, atraumatic procedures, and a 'drug holiday' should be considered before undergoing the extraction procedure (2,38). A large number of participants answered that they would rather refer the patient to a specialist if exodontia is required, while the second majority of the participants chose suspension of the bisphosphonate treatment for 3 months before carrying out the dental extraction (39).

Medication-related osteonecrosis of the jaw prevention hinges upon the dentist's ability to stabilize patients' oral health, in order to avoid any surgical procedures later on that may predispose to MRONJ (40). A considerable proportion of the study participants were able to correctly identify the preventative methods; reducing the source of infection (84.4%) oral hygiene instructions (76.3%), and smoking cessation (74.7%), while a few identified the use of fluoride mouthwash as a method to prevent MRONJ. Expectedly, as the KS

increased, more preventative measures and treatment options were correctly identified.

This study had several important limitations. First, a foreseeable limitation in all surveys is the propensity of some participants to respond in a way they believe to be apt for the researchers. Second, the inclination to participate in online-based surveys is often limited. Furthermore, the knowledge scoring system (KS) that was used to assess the level of knowledge among participants was devised by the authors and therefore, it might be considered subjective. The sample size was relatively small and limited to specific locations in Jordan. The outcomes reported may lack representativeness for dentists nationwide. Future studies should include larger sample sizes and broaden their sampling to include other regions in Jordan.

## 5. Conclusions

This study identified gaps in the knowledge regarding MRONJ, particularly among general practitioner dentists. Thus, it is essential to sustain and intensify the awareness and education of dental students with evidence-based knowledge and maintain

knowledge throughout their practice. It is essential to actively include this topic in the continuing medical education (CME) programs, in wide verse conferences and scientific days, in order to increase awareness and the recent updates and precautions about the topic to take effective measures of modifying the policies or curriculum emphasis. In regard to sample size, increasing participation of dentists by sharing through the dental association website, mobile applications, and more social media platforms, thus assuring more participants. Our findings of the relatively insufficient knowledge about MRONJ among practitioners suggest that increased emphasis should be placed on educating medical doctors, dentists, and students about this condition to improve the quality of care provided to patients.

## Conflict of Interests

The authors declare no conflict of interests.

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