Saudi Pharmaceutical Journal 29 (2021) 96–103

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Dental practitioners' and students' knowledge of medication related osteonecrosis of the jaw (MRONJ)

Mandlin Abdulaziz Almousa [a,c,*], Ghadah Khalid Alharbi [a,c], Amerah Saeed Alqahtani [a,c], Yusra Chachar [b,c], Lubna Alkadi [b,c,d], Ali Aboalela [b,c,d]

[a] Dental Interns, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[b] College of Dentistry, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[c] King Abdullah International Medical Research Center, Riyadh, Saudi Arabia
[d] National Guard Health-Affairs, Riyadh, Saudi Arabia

ARTICLE INFO

Article history:
Received 8 September 2020
Accepted 19 December 2020
Available online 29 December 2020

Keywords:
MRONJ
Knowledge
Bisphosphonates
Dental practitioners
Dental students
Cancer treatment
Side effects
Management

ABSTRACT

Background: Medication-related osteonecrosis of the jaw (MRONJ) is a complication affecting patients who are being treated with antiresorptive or antiangiogenic medication. These patients require meticulous treatment planning and management strategies. This research aimed to assess the knowledge of dental practitioners and students in their professional years regarding MRONJ.

Methods: A cross-sectional study was conducted among 345 dental practitioners and students in their professional years of both genders, in governmental and private dental schools. The data was collected using an electronic and paper-based self-administered structured questionnaire with six sections. The data was entered and analyzed using SPSS Version 23, and a P-value <0.05 was considered significant. A Chi-square test was used to compare the categorical variables.

Results: Though more than half of the sample 68% received information about antiresorptive and antiangiogenic drugs during their studies, the level of knowledge was low. The primary diseases targeted by antiresorptive and antiangiogenic medications were not known by the majority of the sample. Almost half of the sample could not identify any antiresorptive or antiangiogenic medication and only 28.1% knew the correct definition of MRONJ.

Conclusion: The level of knowledge regarding MRONJ is a concern, necessitating more educational courses and workshops.

1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is characterized by osteonecrosis associated with antiresorptive and antiangiogenic therapies (Ruggiero et al., 2014; Rosella et al., 2016). MRONJ most frequently occurs in the mandible (73%) and less frequently in the maxilla (22.5%) (Kang et al., 2018; Pazianas et al., 2007). Although the first MRONJ case was reported more than a decade ago, proper management strategies are still not fully outlined, highlighting the importance of further research and raising awareness. Osteonecrosis of the jaw as a consequence of Bisphosphonate (BP) treatment was first described as a pathological condition by Marx in 2003 and was later termed Bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Ruggiero et al., 2014; Marx, 2003). In 2009, the American Association of Oral and Maxillofacial Surgeons (AAOMS) defined BRONJ as exposed bone within the oral cavity of patients using BPs, lasting for more than eight weeks, without a history of radiation therapy. Later in 2014, AAOMS changed the term to medication-related osteonecrosis of the jaw (MRONJ) to cover the substantial number of osteonecrosis cases related to other antiresorptive and antiangiogenic therapies (Ruggiero et al., 2014).

Medications associated with MRONJ include BPs, Denosumab, and anti-angiogenics (Voss et al., 2017). BPs bind to

* Corresponding author at: Dental Interns, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.
E-mail addresses: mandalinalmousa@gmail.com (M.A. Almousa), Alhrbai133@ksau-hs.edu.sa (G.K. Alharbi), Alqahtani111@ksau-hs.edu.sa (A.S. Alqahtani), chachary@ksau-hs.edu.sa (Y. Chachar), kadil@ksau-hs.edu.sa (L. Alkadi), Ali_aboalela@alumni.harvard.edu (A. Aboalela).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2020.12.012
1319-0164/

hydroxyapatite, resulting in bone remodeling inhibition that may last for years after the treatment discontinuation. Denosumab, a RANK-L inhibitor, is an antiresorptive medication prescribed for patients with osteoporosis or to reduce the complications associated with bone metastases. Denosumab has a much shorter half-life than BPs. Drugs, with an antiangiogenic activity include tyrosine kinase inhibitors such as Sunitinib and Sorafenib. These drugs are mostly prescribed to treat malignant conditions such as gastrointestinal tumors and renal cell carcinomas. Tyrosine kinase inhibitors target multiple signaling proteins resulting in a reduction of new vessel formation. Other antiangiogenics include Bevacizumab, a monoclonal antibody, which acts by inhibiting new vessel formation by targeting the vascular endothelial growth factor (Ruggiero et al., 2014; Beth-Tasdogan et al., 2017).

Many hypotheses have been suggested to explain the pathophysiology of MRONJ, and the three most stated theories are described. The first hypothesis associates MRONJ with the suppression of bone remodeling by inhibiting osteoclastic activity and apoptosis due to the medication. As a consequence, the jaws will undergo micro-damage and eventually areas of necrosis will develop (Wat, 2016). The second hypothesis states that antiresorptive medication have a direct toxic effect on epithelial cells and macrophages by altering the integrity of the oral mucosa, resulting in infections and bone necrosis (Wat, 2016). This theory may explain the delayed healing of soft tissue, observed after trauma and tooth extractions (Voss et al., 2017). The premise of the final hypothesis is infection-induced excessive bone resorption, leading to osteonecrosis of the jaw. The production of lipopolysaccharides by bacteria, especially gram-negative species, stimulates cytokines which accelerate bone resorption. Patients with a history of periodontal disease, and other inflammatory dental diseases, are at a higher risk of developing MRONJ (Wat, 2016).

The risk factors for the development of MRONJ are mostly medication related, such as the dosage, route of administration, duration, and therapeutic indication (Beth-Tasdogan et al., 2017). Other risk factors associated with increasing the chance of developing MRONJ include operative procedures, especially extractions, patients with co-morbidities including diabetes, and concurrent corticosteroid usage. Patients at risk of MRONJ are classified in different risk categories. Low risk patients are treated for diseases unrelated to cancer, such as osteoporosis, osteopenia, Paget's disease, osteogenesis imperfecta. Patients in this risk category are usually prescribed medications in the form of oral or intravenous BPs (given once yearly) (Conte and Guarneri, 2004; Jeffcoat, 2006). Patients taking oral antiresorptives in a non-cancer setting for less than four years, with no other clinical risk factors, have a low risk of developing MRONJ. Dental treatment of any sort can be done without modification in low risk patients. However, patients treated for cancer such as multiple myeloma and bone metastases are at high risk (Rosella et al., 2016; Conte and Guarneri, 2004). In a cancer context, patients will receive antiresorptive medication more frequently (once a month) and as a result, receive high cumulative doses in a short period. Patients who have clinical risk factors, with BPs prescribed for more than four years, are considered as intermediate risk.

MRONJ susceptible patients require a multidisciplinary treatment approach involving an oncologist, maxillofacial surgeon, and a dentist, as evidence indicates that prevention provides the best outcome. Oncologists should refer patients to a dentist for dental screening and treatment prior to starting antiangiogenic or antiresorptive drug therapy. Early referral will reduce the incidence rate of MRONJ and avoid complications due to the treatment of susceptible patients. After therapy initiation, surgical intervention should be avoided as much as possible, but when deemed necessary, should be performed as atraumatically as possible in aseptic conditions. Drug discontinuation during the healing period has been advised if circumstances allow (Ruggiero et al., 2014).

Few studies assessed the level of knowledge related to MRONJ of dental students and dentists (Rosella et al., 2017; de Lima et al., 2015; López-Jornet et al., 2010). To the best of the authors knowledge, no study has assessed the level of MRONJ knowledge of dental students, interns, general practitioners, and specialists. By identifying and addressing knowledge deficiencies, complications in patients at risk of MRONJ may be avoided. The aim of this study was to quantify the level of MRONJ related knowledge in these groups.

2. Methods

This cross-sectional questionnaire-based study was conducted to assess the knowledge of dental practitioners and students in their professional years regarding MRONJ in Riyadh, Saudi Arabia. Ethical approval was obtained from the Institutional Review Board at King Abdullah International Medical Research Center. The sample included 345 participants, including dental students (in their professional years in governmental and private dental schools), interns, general practitioners, and specialists working in Riyadh. Participation in the study was voluntary and a written informed consent was obtained from the participants before completing the questionnaire. Participants were selected using a non-probability purposive sampling technique and the data was collected using a validated self-administered structured questionnaire. Approval to use the questionnaire was obtained from Rosella who published in 2017 (Rosella et al., 2017). The questionnaire was modified to meet the aims and objectives (Table 1). The questionnaire was divided in six sections. The first section included six items related to general demographic data (age, gender, college graduated from/enrolled in, years of experience since graduation and highest degree obtained). The second section had six items related to prior information received about antiresorptive and antiangiogenic medication and the participants' perception of the importance of the information. Section three had five items assessing the participants' knowledge about the therapeutic uses of antiresorptive and antiangiogenic medication. The fourth section included three items assessing the participants' knowledge about osteonecrosis of the jaw and the risk factors. The fifth section had four items related to knowledge about the dental management of patients taking BP therapy. The last section, with three items, explored the frequency of encountering patients with osteonecrosis of the jaw with or without BPs in their clinics. The data was entered and analyzed with SPSS Version 23 (IBM Corporation, Armonk, NY, USA). A Chi-square test was used to compare the categorical variables. P-value of less than 0.05 was considered statistically significant.

3. Results

Out of the 345 participants in the study, 203 were females (58.8%) and 142 were males (41.2%). Additionally, 109 (31.6%) were students while 236 (68.4%) were dentists including interns, general practitioners (GPs) and specialists. A small proportion, 68 (19.7%) were specialists with a post graduate degree (Master or PhD). Table 2 presents the frequency distribution of the baseline characteristics of the sample.

Table 3 displays the details of the sample's responses related to receiving prior information and the perception of the importance of the information. The majority of participants have encountered information regarding antiresorptive and antiangiogenic medications. The primary source of this information has been identified to be universities in both the students' and dentists' groups.

Table 1
The Questionnaire Distributed to the Participants.

Section 1: Demographic Profile:	Age:	19–20 21–22 23–24 25 or above
	Gender:	Male Female
	Dentistry college graduated/enrolled in:	a. King Saud University – College of Dentistry b. King Saud Bin Abdulaziz University for Health Science – College of Dentistry c. Prince Sultan Bin Abdulaziz University – College of Dentistry d. Riyadh College of Dentistry and Pharmacy e. Other: _____
	If you are a student what year are you enrolled in at your college?	a. First year (pre-professional year) b. Second year c. Third year d. Fourth year e. Fifth year f. Sixth year g. Intern
	What year did you graduate in _____	
	Highest degree obtained:	a. Bachelor b. Master c. Phd d. Specialty certificate in _____ e. Board specialty in _____
Section 2: Questions Related to General Knowledge of Antiresorptive/Antiangiogenic Medications:	Have you encountered any antiresorptive medications such as bisphosphonate related information during your study years?	a. Yes b. No
	Have you encountered any antiangiogenic medications related information during your study years?	a. Yes b. No
	Where have you heard about anti-resorptive medications?	a. Never heard of it b. University c. Mass media d. Scientific journals e. Medical meetings f. Other_____
	Where have you heard about antiangiogenic medications?	a. Never heard of it b. University c. Mass media d. Scientific journals e. Medical meetings f. Other_____
	Do you think it is important to ask if patients are using anti-resorptive medications?	a. Yes b. No
	Do you think it is important to ask if patients are using antiangiogenic medications?	a. Yes b. No
Section 3: Questions Related to the Knowledge of Therapeutic Uses of Anti-resorptive/ Anti-angiogenic Medications:	What diseases are targeted by antiresorptive therapy? (it is possible to mark more than one choice):	a. Bone metastases b. Osteomyelitis c. Multiple myeloma d. Hypercalcemia of malignancy e. Osteopetrosis f. Osteopenia g. Chondroblastoma h. Osteogenesis imperfecta i. Paget's disease of bone
	What diseases are targeted by anti-angiogenic therapy? (it is possible to mark more than one choice):	a. Elastofibromas b. Metastatic colorectal cancer c. Leiomyomas d. renal cell cancer e. Neuroendocrine tumor of the pancreas f. Multiple myeloma g. Granular cell tumors
	Mark the name of the antiresorptive drugs you are familiar with:	a. I don't know of any antiresorptive drug b. Alendronate (Fosamax) c. Risedronate (Actonel) d. Ibandronate (Boniva) e. Neridronate (Nerixia) f. Pamidronate (Aredia) g. Zolendronate (Zometa) h. Tiludronate (Skelid) i. Denosumab (Prolia)

	Mark the name of the anti-angiogenic drugs you are familiar with (it is possible to mark more than one choice):	a. I don't know of any anti-angiogenic drugs b. Sunitib (Sutent) c. Sorafenib (Nexavar) d. Bevacizumab (Avastin) e. Sirolimus (Rapamune)
	Do you know that anti-resorptive/antiangiogenic medications can lead to osteonecrosis of the jaw?	a. Yes b. No
Section 4: Questions Related to the Knowledge of Osteonecrosis of the Jaw and Its Risk Factors:	What is the correct definition of osteonecrosis of the jaw according to the American Association of Oral and Maxillofacial surgeons (AAOMS)?	a. Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region which has persisted for more than 8 weeks in patients in current or previous therapy with antiresorptive or antiangiogenic agents, and no history of radiation therapy to the jaws or obvious metastatic disease to the jaws. b. Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region which has persisted for more than 4 weeks in patients in current or previous therapy with antiresorptive or antiangiogenic agents, and no history of radiation therapy to the jaws or obvious metastatic disease to the jaws. c. Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region which has persisted for more than 8 weeks in patients in current or previous therapy with antiresorptive or antiangiogenic agents, and a medical history of radiation therapy to the jaws or obvious metastatic disease to the jaws. d. Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region which has persisted for more than 4 weeks in patients in current or previous therapy with antiresorptive or antiangiogenic agents and, a medical history of radiation therapy to the jaws or obvious metastatic disease to the jaws. e. I don't know.
	Which of the following are the risk factors related to osteonecrosis of the jaw? (it is possible to mark more than one choice)	a. Tobacco b. Antibiotic therapy c. Route of administration d. Alcohol e. Arterial hypertension f. Length of therapy g. Hyperlipidemia h. Steroid therapy i. Total amount of drug administered j. Micro-trauma
	Do you think patients should be checked by the dentist before starting an IV bisphosphonates treatment?	a. Yes b. No c. I don't know
Section 5: Questions Related to the Knowledge of Dental Management in Patients Undergoing Bisphosphonates Therapy:	Can invasive dental treatments be performed safely to patients during an intravenous bisphosphonate drug therapy?	a. Yes b. No c. I don't know
	Can invasive dental treatments be performed safely to patients using oral bisphosphonates for <4 years without risk factors?	a. Yes b. No c. I don't know
	Can invasive dental treatments be performed safely to patients using oral bisphosphonates for <4 years with risk factors?	a. Yes b. No c. I don't know
	Can invasive dental treatments be performed safely to patients using oral bisphosphonates for >4 years?	a. Yes b. No c. I don't know
Section 6: Questions related to the frequency of encountering patients with osteonecrosis of the jaw with or without bisphosphates in Riyadh clinics:	Have you treated patients with osteonecrosis of the jaw and are on antiresorptive therapy?	a. Yes b. no
	Have you treated patients with osteonecrosis of the jaw and are NOT on antiresorptive therapy?	a. Yes b. no
	Have you treated patients WITHOUT osteonecrosis of the jaw and are on anti-resorptive therapy?	a. Yes b. no

However, there was a higher tendency in the dentists' group to obtain such knowledge from variable additional sources (such as media, scientific journals and meetings) compared to the students' group. This difference was significant for both antiresorptive and antiangiogenic medications ($p = 0.026$ and 0.006 respectively). Almost all of the participants thought it was important to ask patients about their usage of antiresorptive/antiangiogenic medications.

Table 4 demonstrates the level of knowledge of the therapeutic uses of antiresorptive and antiangiogenic medications. Their knowledge was generally low in this section with no significant differences between dentists and students. Among the therapeutic

Table 2
Frequency Distribution of the Baseline Characteristics of the Sample.

Sample Characteristics	Frequency (n = 245)	Percentage %
Age (years)		
19–20	3	0.9
21–22	57	16.5
23–24	107	31
25 and above	178	51.6
Gender		
Male	142	41.2
Female	203	58.8
University		
King Saud University	75	21.7
King Saud bin Abdulaziz University for Health Sciences	116	33.6
Princess Nourah University	26	7.5
Riyadh Alelm University	42	12.2
Other Universities Within Saudi Arabia	64	18.6
Other Universities Outside Saudi Arabia	22	6.4
Level		
Students	109	31.6
Dentist (interns, GPs and specialists)	236	68.4
Experience (years)		
Less than 1	204	59.1
1–5	60	17.4
6–10	40	11.6
11–15	23	6.7
16–20	6	1.7
21 or more	12	3.5

uses of antiresorptive therapy, bone metastasis was the most commonly recognized among students 49 (45.0%) and dentists 110 (46.6%). Interestingly, 43 (39.4%) of students and 95 (40.3%) of dentists were not able to identify any antiresorptive medication while 53 (48.6%) of students and 129 (54.7%) of dentists were not able to identify any antiangiogenic medication. Out of all listed antiresorptive medications, Alendronate (Fosamax) was the most recognized followed by Zolendronate (Zometa). On the other hand, Bevacizumab (Avastin) was the most recognized among antiangiogenic medications. Students significantly outperformed dentists in the recognition of Denosumab (Prolia) from the antiresorptive medication list and Sirolimus (Rapamune) from the antiangiogenic medication list. Most of the participants 271 (78.6%) knew that antiresorptives/antiangiogenics could lead to osteonecrosis of the jaw.

In the fourth section, only a small proportion 97 (28.1%) knew the correct definition of MRONJ, according to the American Association of Oral and Maxillofacial surgeons (AAOMS). Regarding the risk factors of MRONJ, tobacco was the most recognized by over half of the participants 181 (52.5%) with a significantly higher rate of recognition among dentists in comparison to students (p = 0.001). This was followed by the factors related to length of therapy and the total amount of drugs administered which were recognized by 159 (46.1%) and 146 (42.3%) respectively (Table 5). The majority of participants 275 (79.1%), including significantly more students, thought that patients should be checked by a dentist before starting IV bisphosphonates treatment (p = 0.018).

Regarding the level of knowledge about the dental management of patients receiving bisphosphonate therapy, which was addressed in the fifth section of the survey, The majority of the participants 239 (69.3%) did not think invasive dental treatment could be performed safely on patients during intravenous bisphosphonate therapy, whereas 87 (25.2%) correctly indicated that invasive dental treatment could be performed safely on patients on oral bisphosphonate therapy for less than 4 years, provided they are without risk factors. 185 (53.6%) recognized that having risk factors associated with less than 4 years of oral bisphosphonate therapy will make invasive dental treatment unsafe for such patients. In addition, 138 (40.0%) indicated that invasive dental treatment could not be performed safely on patients on oral bisphosphonate therapy for more than 4 years (Table 6).

4. Discussion

MRONJ is a serious debilitating adverse drug event in patients receiving long-term antiresorptive or antiangiogenic therapies, which mainly affect the jaw bones. Adequate knowledge about MRONJ is a prerequisite to improve treatment outcomes and reduce the complications associated with these medications. To the best of our knowledge, only a few studies explored the level of knowledge related to MRONJ, in dental healthcare providers and dental students. The available studies focused mainly on BP (Rosella et al., 2017; de Lima et al., 2015; López-Jornet et al., 2010).

In the current study, approximately one third of the sample, received no information regarding antiresorptive or antiangiogenic

Table 3
General Knowledge of Antiresorptive/antiangiogenic Medications.

General Knowledge of Medications	Students (n = 109) n (%)	Dentists (n = 236) n (%)	Total (n = 345) n (%)	p-Value
Have you encountered any antiresorptive medications related information during your study years?	78 (71.6%)	157 (66.5%)	235 (68.1%)	0.351
Have you encountered any antiangiogenic medications related information during your study years?	75 (68.8%)	158 (66.9%)	233 (67.5%)	0.732
Where have you heard about antiresorptive medications?				
Never heard of it	16 (14.7%)	20 (8.5%)	36 (10.4%)	
University	88 (80.7%)	181 (76.7%)	269 (78.0%)	**0.026**
Mass media	2 (1.8%)	4 (1.7%)	6 (1.7%)	
Scientific journals	2 (1.8%)	20 (8.5%)	22 (6.4%)	
Medical meetings	1 (0.9%)	11 (4.7%)	12 (3.5%)	
Where have you heard about antiangiogenic medications?				
Never heard of it	19 (17.4%)	31 (13.1%)	50 (14.5%)	
University	88 (80.7%)	169 (71.6%)	257 (74.5%)	**0.006**
Mass media	0 (0.0%)	3 (1.3%)	3 (0.9%)	
Scientific journals	2 (1.8%)	19 (8.1%)	21 (6.1%)	
Medical meetings	0 (0.0%)	14 (5.9%)	14 (4.1%)	
Do you think it is important to ask if patients are using antiresorptive medications?	104 (95.4%)	224 (94.9%)	328 (95.1%)	0.843
Do you think it is important to ask if patients are using antiangiogenic medications?	105 (96.3%)	219 (92.8%)	324 (93.9%)	0.202

Table 4
Knowledge of the Therapeutic Uses of Antiresorptive/antiangiogenic Medication.

Knowledge of Therapeutic Uses of Antiresorptive/antiangiogenic Medications	Students (n = 109) n (%)	Dentists (n = 236) n (%)	Total (n = 345) n (%)	p-Value
What diseases are targeted by antiresorptive therapy?				
Bone metastases	49 (45.0%)	110 (46.6%)	159 (46.1%)	0.774
Multiple myeloma	37 (33.9%)	66 (28.0%)	103 (29.9%)	0.259
Hypercalcemia of malignancy	18 (16.5%)	49 (20.8%)	67 (19.4%)	0.354
Osteopenia	44 (40.4%)	71 (30.1%)	115 (33.3%)	0.060
Osteogenesis imperfecta	30 (27.5%)	51 (21.6%)	81 (23.5%)	0.228
Paget's disease	37 (33.9%)	79 (33.5%)	116 (33.6%)	0.931
What diseases are targeted by antiangiogenic therapy?				
Metastatic colorectal cancer	30 (27.5%)	71 (30.1%)	101 (29.3%)	0.627
Renal cell cancer	37 (33.9%)	60 (25.4%)	97 (28.1%)	0.067
Neuroendocrine tumor of pancreas	16 (14.7%)	51 (21.6%)	67 (19.4%)	0.084
Mark the name of antiresorptive drugs you are familiar with.				
Alendronate (Fosamax)	41 (37.6%)	83 (35.2%)	124 (35.9%)	0.660
Risedronate (Actonel)	24 (22.0%)	42 (17.8%)	66 (19.1%)	0.354
Ibandronate (Boniva)	21 (19.3%)	48 (20.3%)	69 (20.0%)	0.817
Neridronate (Nerixia)	5 (4.6%)	23 (9.7%)	28 (8.1%)	0.103
Pamidronate (Aredia)	18 (16.5%)	26 (11.0%)	44 (12.8%)	0.155
Zolendronate (Zometa)	33 (30.3%)	80 (33.9%)	113 (32.8%)	0.505
Tiludronate (Skelid)	8 (7.3%)	16 (6.8%)	24 (7.0%)	0.849
Denosumab (Prolia)	41 (37.6%)	44 (18.6%)	85 (24.6%)	**0.000**
I don't know any of them	43 (39.4%)	95 (40.3%)	138 (40.0%)	0.887
Mark the name of antiangiogenic drugs you are familiar with.				
Sunitib (Sutent)	29 (26.6%)	45 (19.1%)	74 (21.4%)	0.113
Sorafenib (Nexavar)	26 (23.9%)	38 (16.1%)	64 (18.6%)	0.085
Bevacizumab (Avastin)	29 (26.6%)	51 (21.6%)	80 (23.2%)	0.307
Sirolimus (Rapamune)	37 (33.9%)	38 (16.1%)	75 (21.7%)	**0.000**
I don't know any of them	53 (48.6%)	129 (54.7%)	182 (52.8%)	0.296
Do you know that antiresorptives/antiangiogenics can lead to osteonecrosis of the jaw?	82 (75.2%)	189 (80.1%)	271 (78.6%)	0.307

Table 5
Knowledge of Risk Factors Related to Osteonecrosis of the Jaw.

Knowledge of Risk Factors Related to Osteonecrosis of The Jaw	Students (n = 109) n (%)	Dentists (n = 236) n (%)	Total (n = 345) n (%)	p-Value
What of the following are risk factors related to osteonecrosis of the jaw?				
Tobacco	43 (39.4%)	138 (58.5%)	181 (52.5%)	**0.001**
Route of administration	39 (35.8%)	87 (36.9%)	126 (36.5%)	0.846
Length of therapy	47 (43.1%)	112 (47.5%)	159 (46.1%)	0.452
Steroid therapy	28 (25.7%)	85 (36.0%)	113 (32.8%)	0.057
Total amount of drugs administered	51 (46.8%)	95 (40.3%)	146 (42.3%)	0.253
Micro-truma	36 (33.0%)	61 (25.8%)	97 (28.1%)	0.168

Table 6
Knowledge of Dental Management in Patients Undergoing Bisphosphonate Therapy (frequency and percentage of correct answers).

Questions Related to Knowledge of Dental Management in Patients Undergoing Bisphosphonate Therapy	Students (n = 109) n (%)	Dentists (n = 236) n (%)	Total (n = 345) n (%)	p-Value
Can invasive dental treatment be performed safely to patients during an intravenous Bisphosphonate therapy?	73 (67.0%)	166 (70.3%)	239 (69.3%)	0.111
Can invasive dental treatments be performed safely to patients using oral Bisphosphonates for <4 years without risk factors?	29 (26.6%)	58 (24.6%)	87 (25.2%)	0.899
Can invasive dental treatments be performed safely to patients using oral Bisphosphonates for <4 years with risk factors?	61 (56.0%)	124 (52.5%)	185 (53.6%)	0.839
Can invasive dental treatments be performed safely to patients using oral Bisphosphonates for >4 years?	47 (43.1%)	91 (38.6%)	138 (40.0%)	0.103

medication during their undergraduate years. For the majority who received such information, the source was their respective universities. Generally, the dentist group tended to acquire knowledge from other sources such as the media, scientific journals, and meetings, compared to the student group. The reason may be that the dentist group is more likely to encounter patients at risk of MRONJ and/or participate in CME activities. MRONJ related education was recently introduced in dental curricula, though it is not consistently taught in the various institutions.

Though most of the participants knew it was important to ask patients about using antiresorptive and antiangiogenic medications, they were not able to identify major diseases treated with anti-resorptive medication, except for bone metastases, known by 49 (45.0%) in the student group and 110 (46.6%) of the dentist group. These findings were contradictory to the Rosella et al. study among Italian dental students, where most of the participants knew the main diseases targeted by anti-resorptive medication (Rosella et al., 2017). In the current study, the sample also lacked

knowledge regarding the diseases targeted by antiangiogenic medication. This knowledge deficit may cause the dentist to miss such information when taking the medication history. Reasons for not listing antiresorptives/antiangiogenics by the patient may include recently discontinued medication by the primary provider or forgetting to include medications that are not taken on a daily basis, such as IV BPs, taken once a year for osteoporosis. Discontinuing a medication does not mean the patient is no longer at risk in fact, the risk may continue for many more years. In this study, although the generic and brand names of the medications associated with MRONJ were provided, over half of the sample did not know any of the antiangiogenic or antiresorptive medications. Similar findings were reported by de Lima et al. in their study among Brazilian dental students and dentists, with the majority (86%) of the participants not recognizing the commercial brand names of BP medication (de Lima et al., 2015). In the current study, Alendronate (Fosamax) was the most frequently known antiresorptive medication (n = 124, 35.9%), followed by Zolendronate (Zometa) (n = 113, 32.8%), and Denosumab, a RANK-L monoclonal antibody, only by a small proportion (n = 85, 24.6%) of the sample. Comparing the student group (n = 41, 37.6%) to the dentist group (n = 44, 18.6%), the students recognized Denosumab more frequently (p-value = 0.00). This may be attributed to the inclusion of Denosumab in the dental curricula at a later date and the graduated dentists may not have been exposed to other medications than BPs. Similar results were reported by Roselle et al. with Zoledronate and Alendronate the best known BP medications (Rosella et al., 2017). Identification of medications is necessary to reduce the risk of inadvertently providing care without being aware of the risks involved. Antiangiogenic medications were less known compared to antiresorptive medications, with over half of the sample not knowing any. Bevacizumab (Avastin) was known by only 80 (23.2%) participants and Sirolimus (Rapamune) by only 75 (21.7%). These findings highlight that the level of knowledge is inadequate, and the sample may not be able to identify patients at an increased risk of MRONJ. Similar findings were reported by S. Franchi et al study among Italian medical students which showed that the majority of the sample lacked knowledge regarding antiangiogenic medications as drugs associated with MRONJ (Franchi et al., 2020). A compounding factor that may increase the risk of complications, is that the patients themselves may be unaware of side effects of the medication they are taking. The clinician has the responsibility of knowing the medications associated with MRONJ.

The majority of the sample did not know the AAOMS definition of MRONJ, which is "Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region which has persisted for more than eight weeks in patients currently or previously treated with antiresorptive or antiangiogenic agents with no history of radiation therapy to the jaws or obvious metastatic disease to the jaws" (Ruggiero et al., 2014). These results are comparable with Rosella et al. who highlighted the lack of knowledge regarding the clinical characteristics of MRONJ (Rosella et al., 2017). In contrast, according to Lopez et al., Spanish dental students and dentists had higher levels of knowledge as they were more familiar with the correct definition of MRONJ (López-Jornet et al., 2010). The lack of knowledge regarding the working definition of MRONJ may result in a late diagnosis and/or unnecessary procedures increasing the risk of more severe complications. With regards to the risk factors, the responses were insufficient as less than half of the participants were able to identify the correct risk factors. In comparison to the student group, the dentist group were more familiar with tobacco as a risk factor; however, the risk of tobacco is inconsistently reported in literature, with some studies reporting no association (Vahtsevanos et al., 2009; Tsao et al., 2013). Of concern is that the participants were not knowledgeable about well-established associations, such as the route of administration, total amount of drug administered, and length of therapy. The majority (n = 275, 79.1%), when asked "Patients should be checked by a dentist before starting IV Bisphosphonates treatment" answered yes, although only 126 (36.5%) knew that the route of administration was a risk factor. Similarly, in Franchi et al. study, medical students were aware of the fact that patients should be checked by a dentist before starting BP therapy; however, the majority of the sample did not know that the IV route of administration has a higher risk for MRONJ in comparison to the oral route (Franchi et al., 2020). An oral route is mainly used in the management of osteopenia and osteoporosis and has minimal risk of developing osteonecrosis, especially when taken for less than 4 years with no other risk factors (Ruggiero et al., 2014). In addition, the IV and subcutaneous delivery of medication in a cancer setting increase the risk of developing osteonecrosis compared to the oral route. In terms of knowing that the length of therapy and total amount of medication administered were risk factors, only 159 (46.1%) and 146 (42.3%), responded correctly. It is known that the risk of osteonecrosis increases as the cumulative doses and duration of therapy increase (Henry et al., 2011). Another interesting finding was that only 113 (32.8%) of the participants knew steroid therapy was a risk factor, associated with an increased risk of developing MRONJ (Ruggiero et al., 2014).

Despite the availability of current guidelines from the AAOMS and MRONJ related literature, 106 (30.7%) of the participants did not know that invasive dental treatment should not be performed on patients during IV BP therapy without precautions. Only 138 (40.0%) knew that it was preferable to not proceed with invasive dental treatment on patients who has been taking oral BP for more than 4 years, before contacting the prescribing provider and considering a drug holiday. A small proportion (n = 87, 25.2%) of the sample agreed when asked "Can invasive dental treatments be performed safely to patients using oral Bisphosphonates for <4 years without risk factors?" which indicates that the majority (75%) were not comfortable with managing a patient and may cause an unnecessary delay of treatment. Overall, the findings highlight a general deficiency in knowledge regarding how to correctly manage patients, ranging from avoiding necessary treatment when risk is minimal, to proceeding with treatment in high risk patients, without taking the necessary precautions.

5. Conclusion

The overall level of knowledge regarding MRONJ was inadequate in the students and practitioners for all the sections in the questionnaire. This knowledge deficit may result in withholding or delaying necessary surgeries when the risk is minimal. However, a greater concern is that clinicians are likely to be unaware of the risk when treating MRONJ susceptible patients and treat patients without providing the required precautions. These findings emphasize the need of continuous educational courses and workshops to improve patient care.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The authors would like to give a special thank you to Dr. Hussah Layl Alodwene, Dr. Abdulkareem Saad Alghamdi and Khaled Ajlan Alshahri for their assistance as data collectors. The authors would also like to thank all dental students and dental practitioners who participated in the research.

References

Beth-Tasdogan, N.H., Mayer, B., Hussein, H., Zolk, O., 2017. Interventions for managing medication-related osteonecrosis of the jaw. Cochrane Database Syst. Rev. 10 (10), CD012432. https://doi.org/10.1002/14651858.CD012432.pub2. PMID: 28983908; PMCID: PMC6485859.

Conte, P., Guarneri, V., 2004. Safety of intravenous and oral bisphosphonates and compliance with dosing regimens. Oncologist 9 (Suppl 4), 28–37. https://doi.org/10.1634/theoncologist.9-90004-28. PMID: 15459427.

de Lima, P.B., Brasil, V.L., de Castro, J.F., de Moraes Ramos-Perez, F.M., Alves, F.A., dos Anjos Pontual, M.L., da Cruz Perez, D.E., 2015. Knowledge and attitudes of Brazilian dental students and dentists regarding bisphosphonate-related osteonecrosis of the jaw. Support Care Cancer 23 (12), 3421–3426. https://doi.org/10.1007/s00520-015-2689-6. Epub 2015 Mar 11 PMID: 25757408.

Franchi, S., Brucoli, M., Boffano, P., Dosio, C., Benech, A., 2020. Medical students' knowledge of medication related osteonecrosis of the jaw. J. Stomatol. Oral Maxillofac. Surg. 121 (4), 344–346. https://doi.org/10.1016/j.jormas.2019.10.005. Epub 2019 Oct 28 PMID: 31672685.

Henry, D.H., Costa, L., Goldwasser, F., Hirsh, V., Hungria, V., Prausova, J., Scagliotti, G. V., Sleeboom, H., Spencer, A., Vadhan-Raj, S., von Moos, R., Willenbacher, W., Woll, P.J., Wang, J., Jiang, Q., Jun, S., Dansey, R., Yeh, H., 2011. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J. Clin. Oncol. 29 (9), 1125–1132. https://doi.org/10.1200/JCO.2010.31.3304. Epub 2011 Feb 22 PMID: 21343556.

Jeffcoat, M.K., 2006. Safety of oral bisphosphonates: controlled studies on alveolar bone. Int. J. Oral Maxillofac. Implants 21 (3), 349–353. PMID: 16796276.

Kang, M.H., Lee, D.K., Kim, C.W., Song, I.S., Jun, S.H., 2018. Clinical characteristics and recurrence-related factors of medication-related osteonecrosis of the jaw. J. Korean Assoc. Oral Maxillofac. Surg. 44 (5), 225–231. https://doi.org/10.5125/jkaoms.2018.44.5.225. Epub 2018 Oct 26. Erratum in: J Korean Assoc Oral Maxillofac Surg. 2018 Dec;44(6):302. PMID: 30402414; PMCID: PMC6209697.

López-Jornet, P., Camacho-Alonso, F., Molina-Miñano, F., Gomez-Garcia, F., 2010. Bisphosphonate-associated osteonecrosis of the jaw. Knowledge and attitudes of dentists and dental students: a preliminary study. J. Eval. Clin. Pract. 16 (5), 878–882. https://doi.org/10.1111/j.1365-2753.2009.01203.x. PMID: 20663005.

Marx, R.E., 2003. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J. Oral Maxillofac. Surg. 61 (9), 1115–1117. https://doi.org/10.1016/s0278-2391(03)00720-1. PMID: 12966493.

Pazianas, M., Miller, P., Blumentals, W.A., Bernal, M., Kothawala, P., 2007. A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates: prevalence, risk factors, and clinical characteristics. Clin. Ther. 29 (8), 1548–1558. https://doi.org/10.1016/j.clinthera.2007.08.008. PMID: 17919538.

Rosella, D., Papi, P., Giardino, R., Cicalini, E., Piccoli, L., Pompa, G., 2016. Medication-related osteonecrosis of the jaw: Clinical and practical guidelines. J. Int. Soc. Prev. Community Dent. 6 (2), 97–104. https://doi.org/10.4103/2231-0762.178742. PMID: 27114946; PMCID: PMC4820581.

Rosella, D., Papi, P., Pompa, G., Capogreco, M., De Angelis, F., Di Carlo, S., 2017. Dental students' knowledge of medication-related osteonecrosis of the jaw. Eur. J. Dent. 11 (4), 461–468. https://doi.org/10.4103/ejd.ejd_27_17. PMID: 29279671; PMCID: PMC5727730.

Ruggiero, S.L., Dodson, T.B., Fantasia, J., Goodday, R., Aghaloo, T., Mehrotra, B., O'Ryan, F., 2014. American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw–2014 update. J. Oral Maxillofac. Surg. 72 (10), 1938–1956. https://doi.org/10.1016/j.joms.2014.04.031. Epub 2014 May 5. Erratum in: J Oral Maxillofac Surg. 2015 Jul;73(7):1440. Erratum in: J Oral Maxillofac Surg. 2015 Sep;73(9):1879. PMID: 25234529.

Tsao, C., Darby, I., Ebeling, P.R., Walsh, K., O'Brien-Simpson, N., Reynolds, E., Borromeo, G., 2013. Oral health risk factors for bisphosphonate-associated jaw osteonecrosis. J. Oral Maxillofac. Surg. 71 (8), 1360–1366. https://doi.org/10.1016/j.joms.2013.02.016. Epub 2013 Apr 11 PMID: 23582590.

Vahtsevanos, K., Kyrgidis, A., Verrou, E., Katodritou, E., Triaridis, S., Andreadis, C.G., Boukovinas, I., Koloutsos, G.E., Teleioudis, Z., Kitikidou, K., Paraskevopoulos, P., Zervas, K., Antoniades, K., 2009. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. J. Clin. Oncol. 27 (32), 5356–5362. https://doi.org/10.1200/JCO.2009.21.9584. Epub 2009 Oct 5 PMID: 19805682.

Voss, P.J., Poxleitner, P., Schmelzeisen, R., Stricker, A., Semper-Hogg, W., 2017. Update MRONJ and perspectives of its treatment. J. Stomatol. Oral Maxillofac. Surg. 118 (4), 232–235. https://doi.org/10.1016/j.jormas.2017.06.012. Epub 2017 Jul 8 PMID: 28697987.

Wat, W.Z.M., 2016. Current controversies on the pathogenesis of medication-related osteonecrosis of the jaw. Dent. J. (Basel) 4 (4), 38. https://doi.org/10.3390/dj4040038. PMID: 29563480; PMCID: PMC5806951.