Original Article

MEDICATION-RELATED OSTEONECROSIS OF THE JAW: EVALUATION OF KNOWLEDGE AND ATTITUDE AMONG SAUDI DENTAL STUDENTS AND INTERNS

Maha Shawky[1], Esraa Aljahdali[2], Reem Alkhanbashi[2]*

[1]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, King Abdulaziz University, Jeddah, Saudi Arabia and Cairo University, Cairo, Egypt.
[2]Faculty of Dentistry, King Abdulaziz University, Jeddah, Saudi Arabia. ReemAlkhnbshi@gmail.com

https://doi.org/10.51847/bBLGSuis16

ABSTRACT

The jaw (ONJ) Osteonecrosis is the most common hurdle in patients taking anti-resorptive, antiangiogenic, immunosuppressive, and chemotherapeutic drugs. Knowledge of these medications is essential for dental practitioners. There are no studies on this subject conducted in Saudi Arabia. This study aims to raise awareness and assess the knowledge and attitude of dental practitioners toward MRONJ. This cross-sectional descriptive observation was conducted through an analysis targeting the 5th and 6th-year dental students and interns randomly selected during the oral surgery session in KAUDH. The Total sample population included 219 students and interns; 73 participants in each level. The questionnaire totals 16 questions applied by one single researcher. A total of 72.1% of participants recognized which dental procedures might be risky for the development of MRONJ, while 40.6% were aware of the other factors associated with increasing MRONJ. Management of MRONJ included 32.4% positive response, and only 36.5% of participants were able to identify all medications other than Bisphosphonates which constituted 49.3% of the total sample. Concerning staging, severity, clinical, radiographic findings, and preoperative referral, the difference among the 3 groups was statistically significant. Many of the interviewees were unaware of the prevention and management of MRONJ, and 79.5% were seeking further information. We recommend that effective initiatives are needed to expand, reinforce and integrate the knowledge for better care of the patients.

Key words: Awareness, Bisphosphonate, Medication-related osteonecrosis, Jaw bone, Dental students.

Introduction

The jaw (BRONJ) bisphosphonate-related osteonecrosis is jaw bone-related necrosis or disparate to dental techniques. BRONJ may persist for more than 42 to 56 days and is obstinate to conservative therapy occurring in patients having no history of prior radiotherapy in the affected area and who are treated intravenously with amino-encompassing bisphosphonates for a smallest of 365 days or orally for a much more extended interval for a widespread disease causing bone resorption. Bisphosphonates (BPs) Have become a milestone in treating osteoclast-mediated bone loss due to osteoporosis, Paget's disease, multiple bone metastases, multiple myeloma, cancer breast, and prostate, as well as hypercalcemia malignancy [1, 2].

ONJ is the most common complication in patients on biologic/ target medication therapy, glucocorticoids, Rank-ligand inhibitors, and anti-cancer drugs used to treat fibromyalgia and rheumatoid arthritis. It could progress in the presence of other comorbid factors.

In dental practice, the majority are unaware of this complication. Prevention is the only evidence-based method of reducing it. The intravenous administration of BPs caused most published cases. Woo *et al*. stated that 94% of patients were hospitalized using intravenous pamidronate or Zoledronate, as well as 6% received oral bisphosphonates for osteoporosis and Paget's disease [3]. The first case report describing BRONJ was published in 2003 by Marx [4]. The occurrence of ONJ in the maxilla is less than in the mandible and the areas with thin mucosa, as the mylohyoid ridge and torus mandibularis are the most common sites for ONJ in the mandible [5]. Females, old, and Caucasians are riskier than blacks [6, 7]. Oncologic patients under a high IV dose of bisphosphonate treatment are more vulnerable to ONJ development (92%).

In contrast, in osteoporotic patients on oral Bisphosphonate, the risk for ONJ is low or rare [8, 9]. Bisphosphonates (BPs) are anti-resorptive drugs utilized to treat cancer-correlated bone metastases in case of breast, prostate, lung cancers, and lytic lesions in multiple myeloma. Even though the controversy remains related to possible BPs to mend cancer-specific subsistence, these medicines have had a substantial affirmative outcome on the quality of patients' life with progressive cancer encompassing the skeleton. Oral and intravenous BPs, such as infusion of Zoledronate and parenteral formulation of ibandronate administered every 3 months; have FDA approval for managing osteoporosis and osteopenia. They have been utilized in minor regular

illnesses, such as Paget disease of bone and osteogenesis imperfecta.

Bisphosphonate therapy can lead to adverse effects such as kidney failure, arthralgia, fever, muscle pain, and hypocalcemia [10]. The Receptor Activator of Nuclear factor-kB Ligand (RANKL) inhibitor (Denosumab) is an antiresorptive agent that subsists as an entirely humanized antibody contrary to RANKL along with inhibits osteoclast role as well as related bone resorption. When Denosumab is administered subcutaneously every single six months, a decrease in the risk of vertebral, non-vertebral, and hip fractures occurs in osteoporotic patients. However, it is not indicated for the treatment of multiple myeloma. On the other hand, the binding of RANKL inhibitors to bone did not occur, as well as their impacts on bone remodeling are regularly reduced in the six months of cessation treatment [10]. In vitro and in vivo tests reported an antiangiogenic effect of Zoledronic acid by inhibiting endothelial cell proliferation and induction of apoptosis [11]. MRONJ probably results from suppression of bone metabolism and accumulation of physiologic micro-traumas to the jawbones cooperating biomechanical properties. Trauma along with infection raises the necessity for bone reclamation, which may exceed the bone dimensions turnover, hence ensuing in local bone necrosis [11].

Clinically intraoral lesions in BRONJ appearance similar zones of yellow-white hard bone, using soft or indurated borders. Extra-or intraoral fistulas may be found, and some cases of pathological mandible fracture have been described [12]. Danneman *et al*. suggest that, unlike osteoradionecrosis, ONJ has no preference for the mandible, affecting both mandible and maxilla [13]. Woo *et al*. [3], the reported overview of 368 cases comprises 65% of the mandibular cases, 26% of the maxilla, and 9% of cases in both jaws at a 3:2 female to male ratio. They added that the maximum of the lesions was in the mandibular posterior regions, near the mylohyoid ridge, and that multifocal/bilateral lesions were a little bit supplementary recurrent in the maxilla (31%) paralleled to the mandible (23%). The symptoms of ONJ are pain and loss of functions, oral mucosa swelling along with ulceration, painful bone exposure, purulent discharge, teeth loosening at the site of necrosis, numbness, feeling, heaviness, or dysesthesia. Nevertheless, pain may be merely a sign without any radiological abnormality [13].

Risk factors accountable for the jaw necrosis improvement include type, regimen (cumulative dose, frequency, and route of administration), therapy length along with drug half-life, dental diseases then procedures, local anatomical comorbidity, dental infection, bad oral hygiene, osteoporosis, chemotherapy, and immunosuppressive drugs; added to major local trauma, dentoalveolar procedures, IV exposure and dental extraction [14-16]. Alendronic acid is the most common drug of bisphosphonates that induces ONJ. The theory that may well elucidate the localization exclusively to the jaws is micro-trauma, soft tissue BPs toxicity, infections, the biofilm of the oral cavity, high bony turnover, terminal vascularization of the mandible, bone exposition during oral treatments, and alterations medicament-dependent factors (bone remodeling, angiogenesis inhibition) [17]. The specific oral cavity environment permits easy exposure to infection sources. Local dental diseases demanding surgical processes, combined with the thin mucosal barrier covering the jaw, could also be the BRONJ explanation for an apparent condition in the jaws. Accordingly, BRONJ's several cases may perhaps be precluded through continued physical disinfection as well as proper dental care. It was stated that to lessen the risk in managing patients taking BP, the drug type must be cognizant by the clinicians, dose, effectiveness, as well as the use of BP length, and should confront these patients through regulating the balance of the oral along with systematic circumstances [18]. Regardless of the existing guidelines, students, together with dental practitioners, are hesitant about managing invasive dental procedures in patients taking BPs. The general strategies recognized for ONJ comprise managing the pain, secondary infection treatment, along with necrotic debris elimination, though aggressive debridement is contra-indicated. The fact that the use of any of the above medicines is mentioned in the patient's clinical history should be an alert for the application of all of the diagnostic as well as prophylactic measures correlated to ONJ.

The staging system is necessary to ensure the disease reflection presentation then contributes to patient stratification. The addition of the stage 0 category was in 2009 to comprise patients with non-specific signs or clinical as well as radiographic abnormalities because of exposure to an antiresorptive agent. Several studies have reported that 50% of patients with stage 0 have advanced to stage I, II, or III. Consequently, stage 0 appears to be an effective disease class that captures patients with prodromal signs of the disease (unexposed variant). Similarly, the description of exposed bone was broadened to comprise the cutaneous attendance or mucosal fistulas that probe to the bone stage I, II, and III categories [19]. Radiographic findings are variable plus could comprise: transformed bony trabeculae using mottled osteosclerotic modifications, bone sequestra along with osteolytic alterations, lamina dura congelation, narrowed periodontal ligament space, and insistent rarefaction at the site of dental extractions (≥6 months after extraction) [20].

This study aims to raise awareness of junior, senior dental students, and dental interns toward MRONJ by assessing their knowledge and attitude in terms of recognition of potential risk factors, prevention, diagnosis, and multidisciplinary management of patients on current medication or having a history of anti-resorptive, antiangiogenic, immunosuppressive and chemotherapeutic drug intake.

Materials and Methods

This research was led in King Abdulaziz University, Faculty of Dentistry/ Jeddah, using a survey targeting the dental students and interns selected randomly to assess their knowledge and attitude regarding MRONJ. The research proposal was revised then accepted by the institutional ethics committee. This survey evaluated the awareness of MRONJ amongst the participants, namely 5th-year junior students (JS), 6th-year senior students (SS), and dental interns (IN). They were approached and consented to participate in the study by signing a term of informed consent. The Total sample included 219 students and interns; 73 participants in each level. The study was conducted from November 2019 to March 2020. The Inclusion criteria were: clinical stage junior and senior students and dental interns; while exclusion criteria included: general dentists, preclinical stage dental students, residents, specialists, consultants, and faculty staff.

The data collection instrument used included a self-designed questionnaire which is structured according to the main strategies recommended by The American Association of Oral Maxillofacial Surgeons [21] about MRONJ and the risk factors associated with its development. The questionnaire was revised before distribution; instrument revision included modifications to the item's wording and format based on the recommendations to ensure feasibility, practicability, validity, and interpretation of the results. The questionnaire included sample characterization, demographic data, and general knowledge items. Core objective questions focused on assessing the knowledge and attitude of interviewees and their interest in receiving more information. All the core questions were self-explanatory and contained alternatives to be checked, totaling 16 questions. The participants were invited to answer the structured questionnaire elaborated on knowledge, attitude, and practice regarding aspects of the different drugs commercial names, staging, severity, clinical and radiographic presentation, diagnosis, predisposing factors, encounter, prevention, and management of the various drugs medication-associated ONJ. The questionnaire was accomplished on an individualized basis. The total time taken to respond to the questionnaire was about 10mins. One single researcher applied the questionnaires, and interviewees were not allowed to consult any source of information at the time of the study. Each questionnaire question was required to be answered, and the replies were marked as correct or incorrect. Only the correct answers were summed up to give the total outcome.

Data collected were analyzed by descriptive and frequency statistics. The Data entry, together with statistical evaluates done with SPSS version 23.00. A descriptive statistical study was made of each variable. The relations amongst the diverse qualitative variables were studied with one way ANOVA test. A significance level of 5 % was considered in fundamental analyses: the P-value = to or < 0.05 ($P \leq 0.05$) was acknowledged as substantial.

Results and Discussion

In this study, the self-structured questionnaire was used, and a number of 219 responses were acknowledged from the participants, which included positive answers to the following core data:

- Knowledge of changing from BRONJ to MRONJ
- Identification of all medications and their commercial brand names
- Determination of the drug-related risk factors
- Recognizing the dental procedures as a local predisposing risk factor
- Recognition of the stages of MRONJ
- Awareness of the severity of MRONJ
- Ability to identify the clinical manifestation presenting in the oral cavity
- identifying the radiographic findings
- Knowledge of procedures performed to prevent MRONJ
- History taking of MRONJ or other relevant medications
- Mentioning the risk of MRONJ to patients on relevant drugs
- Referral to their physician for pre-treatment assessment
- Awareness of BRONJ guidelines suggested by AAOMFS
- MRONJ encounter under their care
- Management of MRONJ
- Interest in receiving further information and Training

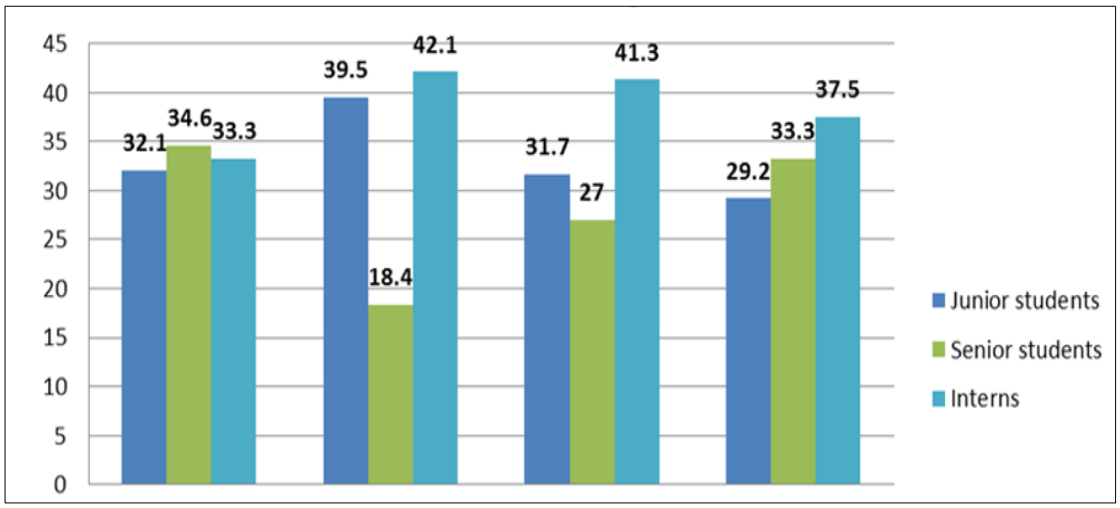
The total of participants who are familiar with the change of BRONJ to the term MRONJ was 74%: JS (32.1%), SS (34.6%), IN (33.3%). On the other hand, only 36.5% of the total participants were able to identify all medications associated with necrosis of the jawbone and their commercial product, other than Bisphosphonates, JS (28.7%), SS (35%), IN (36.3%). Most of them did not identify any drug or recognize their commercial brand names. Results revealed that 12.3% of the total sample were able to determine the drug-related risk factors, namely the duration of treatment, dosage, and route of administration, as the most crucial factors in producing MRONJ: JS (48.1%), SS (14.8%), IN (37%). A total of 72.1% of participants recognized which dental processes along with oral diseases might be risk factors for the MRONJ progression: JS (32.9%), SS (34.2%), IN (32.9%). As for staging, only 34.7% of total groups recognized the stages of MRONJ: JS (39.5%), SS (18.4%), IN (42.1%), and a total of 28.8%, can identify the severity of MRONJ: JS (31.7%), SS (27%), IN (41.3%). The difference in determining staging and severity of MRONJ among the three groups was statistically significant. Furthermore, 28.3% of participants were able to identify the clinical manifestation of MRONJ presenting in jaw bone depending on stage: JS (20.3%), SS (33.9%), IN (45.8%), and concerning radiographic findings identification; 54.8% were aware of bone changes associated with MRONJ: JS (29.2%), SS (33.3%), IN (37.5%). The difference among the groups for both clinical and

radiographic findings was statistically significant **(Table 1; Figures 1 and 2)**.

Table 1. Level of knowledge of students and Interns about medications, risk factors, staging, severity, and diagnosis

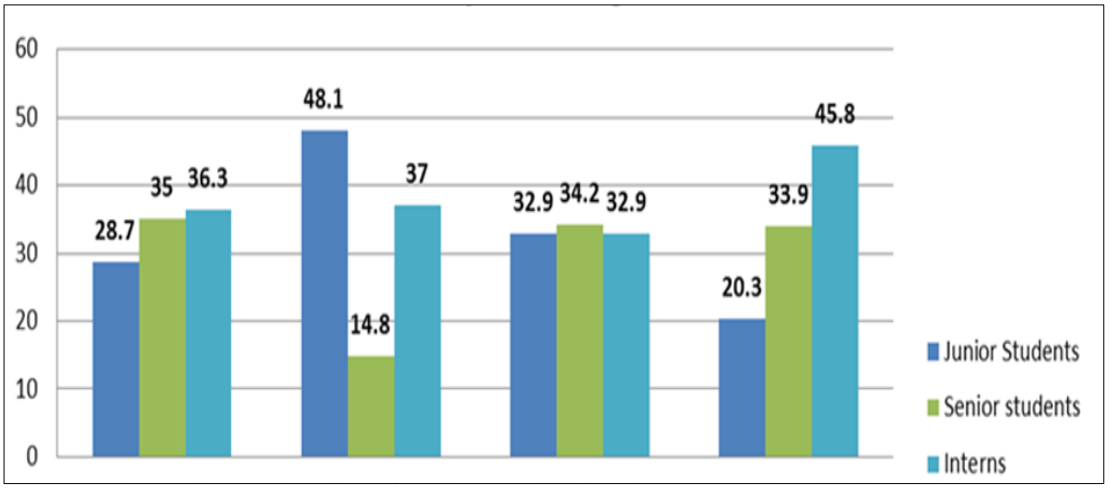
Items related to general knowledge of MRONJ	JS *n(%)*	SS *n(%)*	IN *n(%)*	Total *n(%)*	P value
Knowledge of changing from BRONJ to MRON	52 (32.1)	56(34.6)	54(33.3)	162(74)	0.013
Identification of all medications, and their commercial names	23(28.7)	28 (35)	29(36.3)	80(36.5)	0.547
Determination of the drug-related risk factors	13(48.1)	4(14.8)	10(37)	27(12.3)	0.070
Recognizing the dental procedures predisposing risk factor	52 (32.9)	54(34.2)	52(32.9)	158(72.1)	0.914
Recognition of the stages of MRONJ	30(39.5)	14(18.4)	32(42.1)	76(34.7)	0.000*
Awareness of the severity of MRONJ	20(31.7)	17(27)	26(41.3)	60 (28.8)	0.021*
Ability to identify the clinical manifestation	12(20.3)	20(33.9)	27(45.8)	59(28.3)	0.000*
identifying the radiographic findings	35(29.2)	40(33.3)	45(37.5)	120(54.8)	0.026*

*Statistically significant



a) b) c) d)

Figure 1. Bar chart representing the percentage of the correct answers of the following among the three groups: a) Knowledge of changing from BRONJ to MRONJ, b) Recognition of the stages of MRONJ (P-value 0.000) *, c) Awareness of the severity of MRONJ (P-value 0.021) *, d) Identifying the radiographic findings (P-value 0.026) *



a) b) c) d)

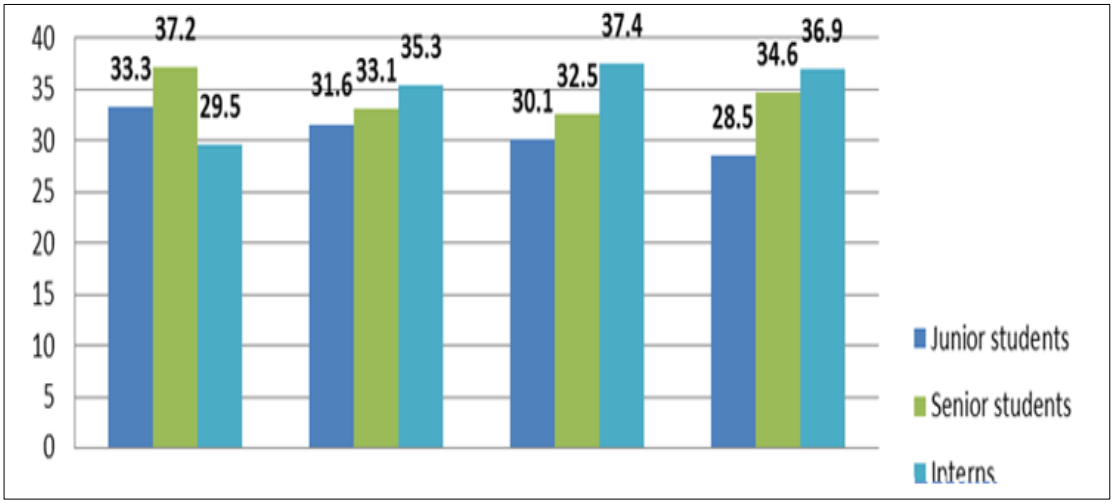
Figure 2. Bar chart representing the percentage of the correct answers of the following among the three groups: a) Identification of all medications and their commercial brand names, b) Determination of the drug-related risk factors, c) Recognizing the dental procedures as a local predisposing risk factor, d) Ability to identify the clinical manifestation presenting in the oral cavity (P-value 0.000) *

According to the clinical guidelines of AAOMFS, only 35.6% were knowledgeable of it: JS (33.3%), SS (37.2%), IN (29.5%), and 60.7% used to have a history of patient's medication upon treatment planning: JS (31.6%), SS (33.1%), IN (35.3%). Furthermore, though 56.2% mention the risk of appropriate medications to the patients: JS (30.1%), SS (32.5%), IN (37.4%); only 81.7% do consider a referral to their physicians for Pre-treatment assessment: JS (28.5%), SS (34.6%), IN (36.9%); the difference among the three groups was statistically significant. The study revealed that 7.8% reported patients developed MRONJ under their care: JS (52.9%), SS (29.4%), IN (17.6%), and only 69.4% knew the procedures performed to prevent the side effect of drugs: JS (29.6%), SS (33.6%), IN (36.8%) such as the use of a minimally invasive dental therapy. Management of MRONJ included 32.4% positive response JS (29.6%), SS (23.9%), IN (46.5%), and 79.5% are interested in receiving further information about prevention and management of MRONJ: JS (31.6%), SS (36.2%), IN (32.2%) **(Table 2; Figures 3 and 4)**.

Table 2. Level of knowledge, attitude, and practice in students and Interns referred to awareness, encounter, prevention, and management

Items related to prevention, awareness of guidelines and management	JS *n (%)*	SS *n (%)*	IN *n (%)*	Total *n (%)*	P value
Awareness the BRONJ guidelines suggested by AAOMFS	26(33.3)	23(37.2)	29(29.5)	78(35.6)	0.588
Taking the history of MRONJ or other relevant medications	42(31.6)	44(33.1)	47(35.3)	133(60.7)	0.698
Mentioning the risk of MRONJ to patients on such drugs	37(30.1)	40(32.5)	46(37.4)	123(56.2)	0.314
Referral to their physician for pre-treatment assessment	51(28.5)	62(34.6)	66(36.9)	179(81.7)	0.004*
MRONJ encounter under their care	9(52.9)	5(29.4)	3(17.6)	17(7.8)	0.169
Knowledge of procedures performed to prevent MRONJ	45(29.6)	51(33.6)	56(36.8)	152(69.4)	0.213
Management of MRONJ	21(29.6)	17(23.9)	33(46.5)	71(32.4)	0.323
Interest in receiving further information and Training	55(31.6)	63(36.2)	56(32.2)	174(79.5)	0.205

*Statistically significant



a) b) c) d)

Figure 3. Bar chart representing the percentage of the correct answers of the following among the three groups: a) The BRONJ Awareness strategies recommended by AAOMFS, b) Taking the history of MRONJ or other relevant medications, c) Mentioning the risk of MRONJ to patients on relevant drugs, d) Referral to their physician for pre-treatment assessment (P-value 0.004) *

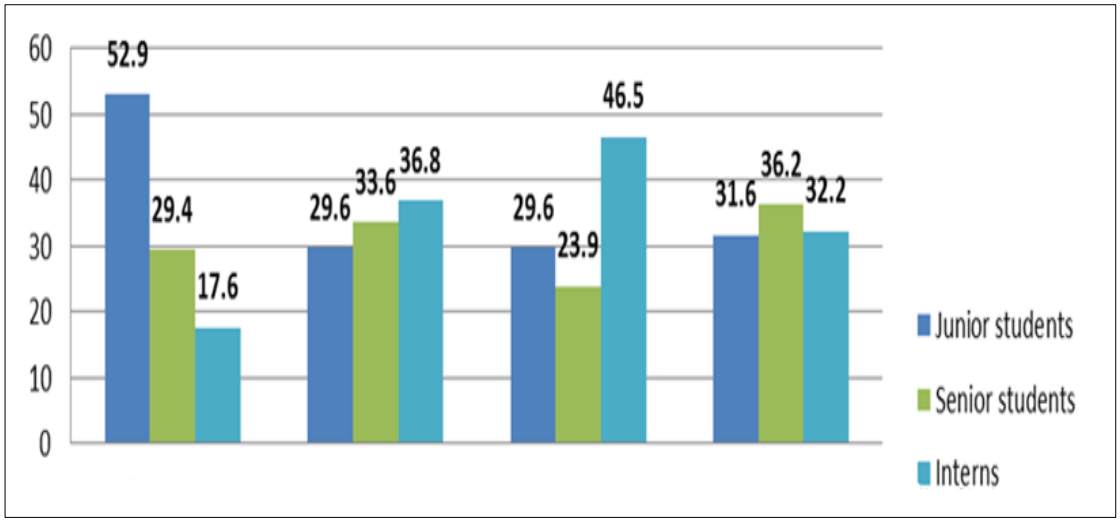


Figure 4. Bar chart representing the percentage of the correct answers of the following among the three groups: a) MRONJ encounter under their care, b) Knowledge of procedures performed to prevent MRONJ, c) Management of MRONJ, d) Interest in receiving further information and Training

This study aimed to investigate the understanding and approach of dental students along with interns toward MRONJ to raise awareness toward multidisciplinary management of patients having a history of anti-resorptive, antiangiogenic, immunosuppressive, and chemotherapeutic drug intake. Considering that such drugs are widely used in the general population, these findings indicate a risk of developing osteonecrosis in individuals subject to oral surgical procedures. Most of the group is aware of the terminology change from BRONJ to MRONJ from textbooks, articles, as well as continuing education programs. Most of our sample did not identify any of these drugs and did not recognize their commercial product names. These findings are alarming, as dental providers must recognize which medications belong to the class of BP to evaluate the patient's risk for developing MRONJ. On the other hand, the lack of history taking of relevant medications makes it difficult to evaluate the risk for MRONJ adequately.

Among the risk factors for MRONJ are related to the type of drug, duration of therapy, and form of administration. Long-term BP administered intravenously is considered a significant risk factor for the development of BRONJ. Dental extraction and dentoalveolar surgeries are significant comorbidities and risk developing osteonecrosis. Walter *et al*. [22] lately stated that 63% of BRONJ patients had a dental extraction history, which was the primary BRONJ occurrence trigger among the study patients. In this study, the highest percentage of participants knowing the potential drug-related risk factors of MRONJ were the junior student's JS (48.1%) compared to SS (14.8%), and IN (37%) were uninformed that BRONJ may be activated through invasive dental treatment in patients with treated BP. Juniors with shorter clinical experience have more excellent responsiveness to MRONJ since they have followed a more recent dental syllabus as well as have had more access to the Internet along with other resources. These numbers describe the state of urgency in educating students and interns about MRONJ.

The dental IN presented the highest percentage (36.8%) of knowing which procedures may be performed to prevent the side effect, added to the highest ability in managing MRONJ (46.5%), learning how MRONJ is clinically present in the oral cavity depending on the stage (45%), and identifying radiographic findings (37.5%), which could be due to the more extensive clinical exposure of dental interns compared to undergraduates. This finding eventually reflects the importance of awareness and recognition for students to perform treatments in patients who require special care. In a study, El Osta *et al*. [23] showed that only 22.1 % of a sample of physicians correctly stated that MRONJ could be asymptomatic or presented with non-specific clinical findings and no apparent necrotic bone. Accordingly, physicians ignore the early stages of the disease, which is a misinterpretation that will negatively affect the ability to detect the bisphosphonate-related ONJ earlier to prevent the disease from progressing from an initial stage to more progressive and devastating stages where the treatment becomes difficult to achieve. In the same context, Aghaloo *et al*. [24] reported no specific characteristics differentiating between BRONJ patients and osteonecrosis patients due to trauma, infection, steroids, chemotherapy, radiotherapy, and coagulation disorders which are rarely reported in the literature.

Concerning the MRONJ encounter, the junior students reported the highest patients developing MRONJ under their care as they have heard of BRONJ. Still, their application in the clinical setting was low. Fascinating surveillance in our research is that all three groups relatively claimed their willingness to receive information and Training about

MRONJ, which reflects that more tremendous educational efforts should be made to promote knowledge of this pathology at both undergraduate and postgraduate levels.

The SS awareness of the AAOMS guidelines was high, compared to JS and IN, having read the literature or attended some conferences on the continuous updates of the guidelines. They were more responsive than the BRONJ strategies recommended through the AAOMS sustenance of this opportunity. On the contrary, dental interns showed a higher percentage of awareness of staging (42.1%), the severity of MRONJ (41.3%), and considering referrals of patients (36.9%) to their physicians for pre-treatment assessment compared to JS and SS owing to their relatively vast experience and keeping updated. Our outcomes are in the treaty by De Lima *et al*. [25] and Lopez-Jornet *et al*. [26]. This research outcomes indication that most participants have not been presented to MRONJ thru the unvarying dental college syllabus or essential academic opportunities until recently when this complication is encountered. According to the findings, it has become necessary to prepare dental students for the osteonecrosis severity as well as urge them to respond properly thru drug history taking to prevent or reduce the risk of MRONJ in susceptible individuals. Dental extractions are widely performed in clinical Training.

Conclusion

In the present study, we conclude that many of the interviewees had an idea about MRONJ but did not know the fundamental concepts of prevention of MRONJ. Although the sample studied is limited, the data are sufficient to affirm that identifying patients who are users of antiresorptive and antiangiogenic medication does not form part of the dental student's routine because of history-taking negligence and lack of basic information about these medications. Despite this, the majority of participants were interested in knowing more about MRONJ. It is recommended that practical initiative must be considered to expand and integrate the knowledge of dental providers about MRONJ for better decision making and development of improved strategies and protocols for the prevention, risk reduction, treatment selection, prognosis, and outcome, thereby preventing or minimizing the occurrence of medication-related jaw necrosis in dental practice.

Acknowledgments: The Authors thank Ms. Huda Bashmail for her valuable help in the statistical analysis of the results.

Conflict of interest: None

Financial support: None

Ethics statement: The research was approved by the Faculty Research Ethics committee no 28-12-19. King Abdulaziz University Faculty of Dentistry Research Ethical Committee.

References

1. Coleman RE. Risks and benefits of bisphosphonates. Br J Cancer. 2008;98(11):1736-40.
2. Hess LM, Jeter JM, Benham-Hutchins M, Alberts DS. Factors associated with osteonecrosis of the jaw among bisphosphonate users. Am J Med. 2008;121(6):475-83.
3. Woo SB, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med. 2006;144(10):753-61.
4. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg. 2003;61(9):1115-7.
5. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg. 2005;63(11):1567-75.
6. Jadu F, Lee L, Pharoah M, Reece D, Wang L. A retrospective study assessing the incidence, risk factors and comorbidities of pamidronate-related necrosis of the jaws in multiple myeloma patients. Ann Oncol. 2007;18(12):2015-9.
7. Badros A, Weikel D, Salama A, Goloubeva O, Schneider A, Rapoport A, et al. Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. J Clin Oncol. 2006;24(6):945-52.
8. Favus MJ. Diabetes and the risk of osteonecrosis of the jaw. J Clin Endocrinol Metab. 2007;92(3):817-8.
9. Bamias A, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol. 2005;23(34):8580-7.
10. Ruggiero SL, Dodson TH, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American association of oral and maxillofacial surgeons. Position paper on medication-related osteonecrosis of the jaw–2014 update. J Oral Maxillofac Surg. 2014;72(10):1938-56.
11. Mehrotra B, Ruggiero S. Bisphosphonate complications including osteonecrosis of the jaw. ASH Education Program Book. 2006;2006(1):356-60.
12. Agrillo A, Petrucci MT, Tedaldi M, Mustazza MC, Marino SM, Gallucci C, et al. New therapeutic protocol in the treatment of avascular necrosis of the jaws. J Craniofac Surg. 2006;17(6):1080-3.
13. Bamias A, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol. 2005;23(34):8580-7.
14. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg. 2007;65:369-76.

15. Dimopoulos MA, Kastritis E, Anagnostopoulos A, Melakopoulos I, Gika D, Moulopoulos LA, et al. Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. Haematologica. 2006;91(7):968-71.
16. Hoff AO, Toth BB, Altundag K, Johnson MM, Warneke CL, Hu M, et al. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Miner Res. 2008;23(6):826-36.
17. Dannemann C, Zwahlen R. Clinical experiences with bisphopsphonate induced osteochemonecrosis of the jaws. Swiss Med Wkly. 2006;136(3132):504-9.
18. Hajmohammadi E, Sattarzadeh S, Amani F. Knowledge rate of dentists regarding dental consideration of bisphosphonate drug user patients. J Res Med Den Sci. 2015;3(3):194-8.
19. Rosella D, Papi P, Giardino R, Cicalini E, Piccoli L, Pompa G. Medication-related osteonecrosis of the jaw: Clinical and practical guidelines. J Int Soc Prev Community Dent. 2016;6(2):97-104. doi:10.4103/2231-0762.178742
20. Dental Guidelines for Patients Who Have or are at Risk for Medication-Related Osteonecrosis of the Jaw (MRONJ).Cancer Center. Developed by Brigham and Women's Hospital and Dana-Farber. Last revised 7/2018 Page 2-6.
21. Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaw–2022 Update. J Oral Maxillofac Surg. 2022;80:920-43.
22. Walter C, Grötz KA, Kunkel M, Al-Nawas B. Prevalence of bisphosphonate associated osteonecrosis of the jaw within the field of osteonecrosis. Support Care Cancer. 2007;15(2):197-202.
23. El Osta L, El Osta B, Lakiss S, Hennequin M, El Osta N. Bisphosphonate-related osteonecrosis of the jaw: awareness and level of knowledge of Lebanese physicians. Support Care Cancer. 2015;23(9):2825-31. doi:10.1007/s00520-015-2649-1
24. Aghaloo TL, Tetradis S. Osteonecrosis of the jaw in the absence of antiresorptive or antiangiogenic exposure: a series of 6 cases. J Oral Maxillofac Surg. 2017;75(1):129-42.
25. de Lima PB, Brasil VL, de Castro JF, de Moraes Ramos-Perez FM, Alves FA, dos Anjos Pontual ML, et al. Knowledge and attitudes of Brazilian dental students and dentists regarding bisphosphonate-related osteonecrosis of the jaw. Support Care Cancer. 2015;23(12):3421-6. doi:10.1007/s00520-015-2689-6
26. López-Jornet P, Camacho-Alonso F, Molina-Miñano F, Gomez-Garcia F. Bisphosphonate-associated osteonecrosis of the jaw. Knowledge and attitudes of dentists and dental students: a preliminary study. J Eval Clin Pract. 2010;16(5):878-82.