

Cross-Sectional Study

Awareness and Preparedness of Saudi Dental Trainees on Medication-Related Osteonecrosis of the Jaw

Diana Heimes^{1*}, Nicolas Alexander Mark², Robert Kuchen³, Andreas Pabst⁴, Philipp Becker⁴, Solomiya Kyyak¹, Daniel G. E. Thiem¹, Ralf Schulze⁵, Peer W. Kämmerer¹

¹Department of Oral- and Maxillofacial Surgery, University Medical Center Mainz, Augustusplatz 2, 55131 Mainz, Germany.

²Private Praxis Dr. Kühnöl, Bayreuther Straße 30, 01187 Dresden, Germany.

³Institute for Medical Statistics, Epidemiology and Informatics, University Medical Center of the Johannes-Gutenberg-University Mainz, 55131 Mainz, Germany.

⁴Department of Oral and Maxillofacial Surgery, Federal Armed Forces Hospital, Rübenacherstraße 170, 56072 Koblenz, Germany.

⁵Department of Oral Surgery and Stomatology, Division of Oral Diagnostic Science, University of Bern, Freiburgstrasse 7, 3010 Bern, Switzerland.

*E-mail ✉ diana.heimes@unimedizin-mainz.de

Received: 02 June 2022; Revised: 20 September 2022; Accepted: 07 October 2022

ABSTRACT

Osteonecrosis of the jaw (ONJ) is the most common side effect among individuals receiving immunosuppressive, anti-resorptive, antiangiogenic, and chemotherapeutic medications. Dental professionals must be knowledgeable about these drugs. Saudi Arabia has not conducted any research on this topic. This study aimed to increase awareness about MRONJ and evaluate the attitude and knowledge of dental professionals about it. This cross-sectional descriptive observation was conducted targeting fifth and sixth-year dental students and interns who were randomly selected during the oral surgery session at KAUDH. 219 students and interns made up the entire sample group, with 70 participants at each level. There are a total of 16 items and only one researcher used the questionnaire. Of the participants, 72.1% knew which dental operations could increase the risk of developing MRONJ, and 40.6% knew about the other factors that could increase MRONJ. Only 36.5% of the subjects were able to identify all drugs besides bisphosphonates, which made up 49.3% of the sample overall, and 32.4% of the participants had a favorable reaction when managing MRONJ. There were statistically significant differences between the three groups in terms of staging, severity, clinical, radiological, and preoperative referral results. 79.5% of the interviewees wanted more knowledge, and many were ignorant of the management and prevention of MRONJ. We recommend that to improve patient care, efficient measures are required to increase, strengthen, and incorporate the information.

Keywords: Awareness, Bisphosphonate, Medication-related osteonecrosis, Jaw bone, Dental students

How to Cite This Article: Heimes D, Mark NA, Kuchen R, Pabst A, Becker P, Kyyak S, et al. Awareness and Preparedness of Saudi Dental Trainees on Medication-Related Osteonecrosis of the Jaw. *Ann J Dent Med Assist.* 2022;2:26-34.

Introduction

According to dental procedures, osteonecrosis associated with bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a necrosis of the jaw bone. When patients with no history of previous radiation therapy in the affected area receive intravenous amino-

encompassing bisphosphonates (BPs) for a minimum of 365 days or oral treatment for a longer period for widespread disease-causing bone resorption, BRONJ may persist for more than 42 to 56 days and is resistant to conservative therapy. BPs have emerged as a key treatment for osteoporosis, Paget's disease, multiple

bone metastases, multiple myeloma, breast and prostate cancer, hypercalcemia malignancy, and osteoclast-mediated bone loss [1, 2].

The most frequent side effect in individuals using glucocorticoids, rank-ligand inhibitors, biologic/target pharmaceutical therapy, and anti-cancer medications used to treat rheumatoid arthritis and fibromyalgia is ONJ. If there are additional comorbid issues, it can worsen.

Most dental professionals are not aware of this problem. The only evidence-based strategy to lower it is prevention. The majority of reported instances were brought on by intravenous BP injection. According to Woo *et al.* [3], 6% of patients received oral BPs for osteoporosis and Paget's disease, and 94% of patients were admitted with intravenous pamidronate or Zoledronate. Marx released the first case report outlining BRONJ in 2003 [4]. Since the mylohyoid ridge and torus mandibularis are the most prevalent locations for ONJ in the lower jaw, the upper jaw has a lower incidence of ONJ than the mandible and areas with thin mucosa [5]. Black people are less dangerous than women, the elderly, and Caucasians [6, 7]. 92% of oncologic patients receiving high IV doses of BPs are at increased risk of developing ONJ.

On the other hand, ONJ is uncommon or of low risk in osteoporotic patients taking oral BPs [8, 9]. Anti-resorptive medications called BPs are used to treat lytic lesions in multiple myeloma and cancer-related bone metastases in cases of lung, breast, and prostate malignancies. These medications have significantly improved the quality of life for individuals with progressing cancer that has spread to the skeleton, notwithstanding the ongoing debate about their potential to treat cancer-specific symptoms. The FDA has approved oral and intravenous BPs for the treatment of osteoporosis and osteopenia, including parenteral formulations of ibandronate given every three months and infusions of Zoledronate. They have been used to treat mild, common conditions such as osteogenesis imperfecta and Paget disease of the bone. Bisphosphonate therapy can lead to adverse effects such as kidney failure, arthralgia, fever, muscle pain, and hypocalcemia [10]. The antiresorptive drug denosumab, also known as the receptor activator of nuclear factor- κ B ligand (RANKL) inhibitor, functions as a fully humanized antibody that opposes RANKL and also prevents osteoclast function and associated bone resorption. Patients with osteoporosis have a lower incidence of hip, non-vertebral, and vertebral fractures when denosumab is given subcutaneously every six months. It is not recommended for the treatment of multiple myeloma, though. However, RANKL inhibitors did not attach to bone, and during

the six months of treatment termination, their effects on bone remodeling were consistently diminished [10]. Zoledronic acid has been shown to have an antiangiogenic impact in both in vitro and in vivo experiments by preventing the proliferation of endothelial cells and causing apoptosis [11]. MRONJ is most likely caused by a combination of physiologic microtraumas to the jawbones and a reduction of bone metabolism, which work together to affect biomechanical qualities. Local bone necrosis results from trauma and infection because they increase the need for bone reclamation, which may be more than the turnover of bone dimensions [11].

Clinically, BRONJ intraoral lesions resemble yellow-white hard bone zones with indurated or soft margins. There may be intraoral or extraoral fistulas, and there have been reports of pathological mandibular fractures [12]. According to researchers ONJ affects both the mandible and the maxilla and does not prefer the mandible as osteoradionecrosis does [9]. According to Woo *et al.* [3], the 368 cases that were recorded included 65% of lower jaw cases, 26% of maxilla cases, and 9% of cases in both jaws, with a 3:2 female-to-male ratio. They also mentioned that multifocal/bilateral lesions were somewhat recurring in the upper jaw (31%) parallel to the lower jaw (23%) and that the majority of the lesions were in the mandibular posterior regions, close to the mylohyoid ridge. ONJ is characterized by pain and loss of function, swelling, and ulceration of the oral mucosa, painful bone exposure, purulent discharge, loosening of the teeth at the necrosis site, numbness, sensation, heaviness, or dysesthesia. However, discomfort can only be a symptom and not a radiological anomaly [9]. In addition to major local trauma, dentoalveolar procedures, IV exposure, and dental removal, risk factors responsible for an enhancement in jaw necrosis include type, regimen (cumulative dose, frequency, and route of administration), therapy length and drug half-life, dental diseases and procedures, local anatomical comorbidity, dental infection, poor oral hygiene, osteoporosis, chemotherapy, and immunosuppressive drugs [13-15]. The majority frequent bisphosphonate that causes ONJ is alendronic acid. Microtrauma, soft tissue blood pressure toxicity, infections, oral cavity biofilm, high bone turnover, terminal vascularization of the mandible, bone exposition during oral treatments, and changes in medication-dependent factors (bone remodeling, angiogenesis inhibition) are some of the theories that could explain the localization solely to the jaws [16]. The environment of the oral cavity makes it simple to expose oneself to infection sources. An apparent condition in the jaws could also be explained by

BRONJ because of the thin mucosal barrier protecting the jaw and local dental problems that require surgical procedures. Therefore, ongoing physical disinfection and appropriate dental care may help prevent BRONJ's multiple cases. It was said that to reduce the danger of treating patients who take blood pressure medication, physicians should be aware of the drug type, dosage, effectiveness, and duration of use. They should also address these patients by controlling the balance between oral medication and systematic conditions [17]. Despite the current standards, dental professionals and students are reluctant to perform invasive dental operations on patients who are taking blood pressure medications. Although severe debridement is contraindicated, the general techniques known for ONJ include managing the pain, treating the secondary infection, and removing necrotic material. The administration of all diagnostic and preventative procedures associated with ONJ should be prompted if the patient's clinical history mentions the usage of any of the aforementioned medications.

To ensure that the disease reflection presentation contributes to patient classification, the staging system is required. To include those who have non-specific symptoms or clinical and radiographic abnormalities as a result of exposure to an antiresorptive drug, the stage 0 category was added in 2009. 50% of patients with stage 0 have progressed to stages I, II, or III, according to several studies. In light of this, stage 0 seems to be a useful disease class for identifying people who exhibit prodromal symptoms of the illness (unexposed variety). Likewise, the definition of exposed bone was expanded to include mucosal fistulas or cutaneous attendance that pertain to the bone stage I, II, and III categories [18]. Bony trabeculae that have been transformed using mottled osteosclerotic modifications, bone sequences with osteolytic alterations, lamina dura congelation, narrowed periodontal ligament space, and persistent rarefaction at the site of dental extractions (≥ 6 months after extraction) are among the variable radiographic findings [19].

By evaluating their knowledge and attitudes regarding the identification of potential risk factors, prevention, diagnosis, and multidisciplinary management of patients on current medication or with a history of anti-resorptive, antiangiogenic, immunosuppressive, and chemotherapeutic drug intake, this study seeks to increase awareness of MRONJ among junior, senior, and dental interns.

Materials and Methods

This research was led at 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 and 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; with 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 [20] 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 10 minutes. 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 evaluations done with SPSS version 23.00. A descriptive statistical study was made of each variable. The relations among the diverse qualitative variables were studied with a one-way ANOVA test. A significance level of 5% was considered a significant level.

Results and Discussion

- The self-structured questionnaire utilized in the present research received 219 replies from participants, including affirmative responses to the following key questions:
- Understanding how to switch from BRONJ to MRONJ
- Identification of all medications and their commercial brand names
- Determining the risk factors of drug
- Identifying dental operations as a risk factor that predisposes people locally to recognition of the stages of MRONJ
- Awareness of the severity of MRONJ
- The capacity to recognize the clinical signs that appear 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 encounters under their care
- Management of MRONJ
- Interest in receiving further information and training

74% of interviewees were aware that BRONJ had changed to MRONJ: JS (32.1%), SS (34.6%), and IN (33.3%). However, only 36.5% of all participants could name all drugs linked to jawbone necrosis and their brand names, except BPs, JS (28.7%), SS (35%), and IN (36.3%). The majority of them were unable to identify any medications or know their commercial brand names. The findings showed that 12.3% of the entire sample could identify the drug-related risk factors—specifically, the length of therapy, dosage, and delivery method—as the most important elements in causing MRONJ: JS (48.1%), SS (14.8%), and IN (37%). 72% of participants identified oral disorders and dental procedures that could be risk factors for the advancement of MRONJ: JS (32.9%), SS (34.2%), and 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%), and IN (41.3%). The 3 groups' differences in MRONJ stage and intensity were statistically significant. In addition, 54.8% of participants were aware of bone changes linked to MRONJ, including JS (29.2%), SS (33.3%), and IN (37.5%). Based on the stage, 28.3% of respondents could identify clinical signs of MRONJ illustrating in the jaw bone, including JS (20.3%), SS (33.9%), and IN (45.8%). For both clinical and radiographic data, there was a statistically substantial distinction between the groups (**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

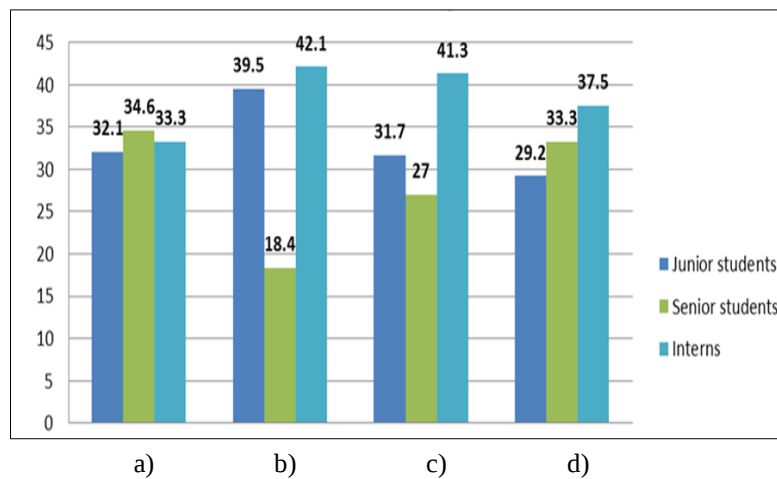


Figure 1. Bar graph showing the three groups' respective percentages of right responses for the following questions: Understanding the transition from BRONJ to MRONJ, recognizing the stages of MRONJ (P-value = 0.000)*, being cognizant of the severity of MRONJ (P-value = 0.021)*, and recognizing the radiographic findings (P-value = 0.026)*

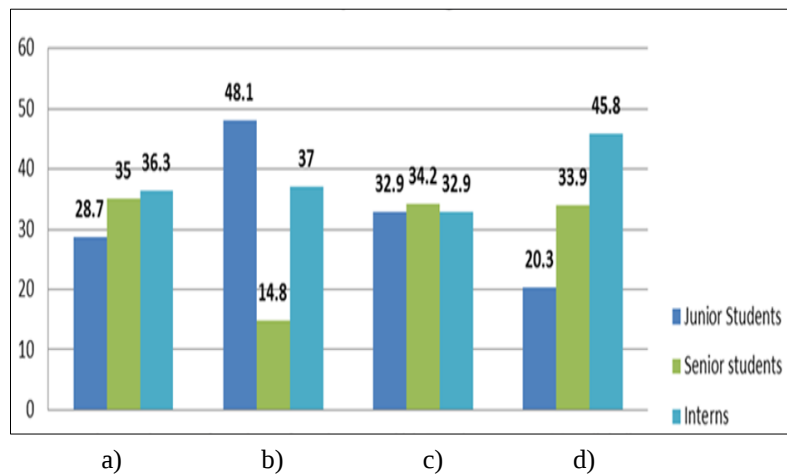


Figure 2. The subsequent bar chart shows the percentage of each of the 3 groups' correct answers; a) identify all medications and their commercial brand names, b) identify drug-related risk factors, c) identify dental procedures as a local predisposing risk factor, and d) identify the clinical manifestation presenting in the oral cavity (P-value = 0.000)*

Just 35.6% of respondents were aware of it, as per the AAOMFS clinical guidelines: JS (33.3%), SS (37.2%), IN (29.5%), and 60.7% previously had a patient's medication history while planning a course of treatment: JS (31.6%), SS (33.1%), IN (35.3%). Additionally, only 81.7% of respondents consider referring patients to their doctors for a preliminary management assessment: JS (28.5%), SS (34.6%), and IN (36.9%); the difference between the 3 groups was statistically significant, even though 56.2% of respondents discuss the risk of appropriate medications to the patients: JS (30.1%), SS (32.5%), and IN

(37.4%). Only 69.4% of respondents were aware of the measures used to prevent drug side effects like the application of dental therapy that is subtle, and 7.8% of respondents indicated that patients they treated developed MRONJ: JS (52.9%), SS (29.4%), and IN (17.6%). MRONJ management includes a 32.4% positive response rate. JS (31.6%), SS (36.2%), and IN (32.2%) are interested in learning more about MRONJ management and prevention, followed by JS (29.6%), SS (23.9%), and IN (46.5%) (**Table 2; Figures 3 and 4**).

Table 2. Students and interns' level of awareness, encounter, preventive, and management-related knowledge, attitude, and practice

Items related to prevention, awareness of guidelines, and management	JS (n (%))	SS (n (%))	IN (n (%))	Total (n (%))	P-value
Awareness of 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 encounters 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

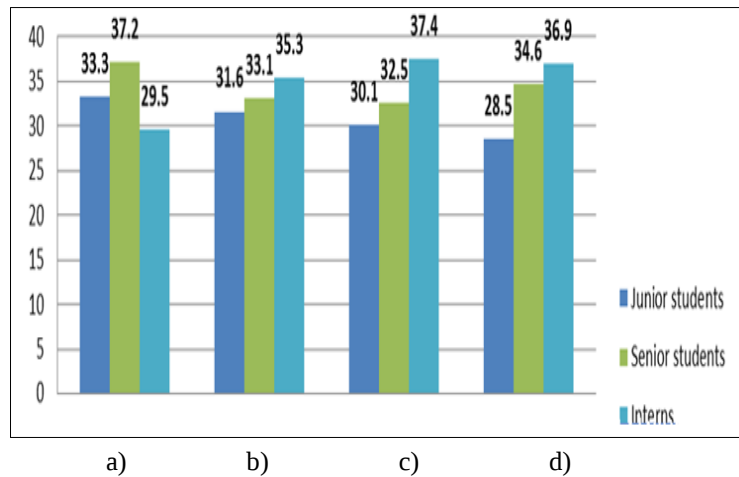


Figure 3. Bar graph showing the three groups' respective percentages of right responses for the following questions;

- a) The AAOMFS-recommended BRONJ Awareness techniques, b) Asking about MRONJ or other pertinent medication histories, c) Bringing up the danger of MRONJ to patients taking pertinent medications, and d) Sending them to their doctor for a pre-treatment evaluation (P-value = 0.004).

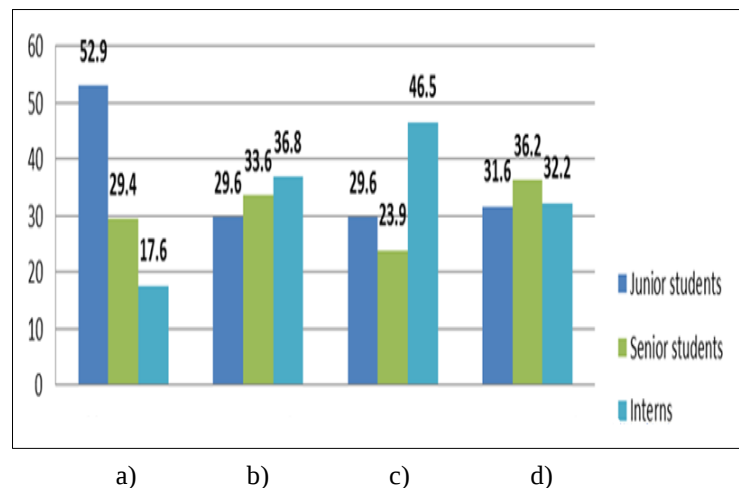


Figure 4. Bar graph showing the three groups' respective percentages of right responses for the following questions; a) MRONJ cases they handle, b) awareness of the preventative measures used, c) MRONJ management, and d) desire for additional training and information

To increase awareness of multidisciplinary therapy of patients with a history of anti-resorptive, antiangiogenic, immunosuppressive, and chemotherapeutic medication intake, this study sought to understand how dental students and interns understood and approached MRONJ. Given the

prevalence of these medications in the general community, these results suggest that patients undergoing oral surgery may be at risk for osteonecrosis. The majority of the group is aware that the term “MRONJ” has replaced “BRONJ” in textbooks, papers, and continuing education courses.

The majority of our sample was unable to name any of these medications or their brand names. These results are concerning because dental professionals need to know which drugs are in the BP class to assess a patient's risk of developing MRONJ. However, it's challenging to properly assess the risk for MRONJ when pertinent drug histories aren't taken.

The kind of medication, length of treatment, and mode of administration are among the risk factors for MRONJ. An important risk factor for the development of BRONJ is long-term intravenous blood pressure. Dentoalveolar surgery and dental extractions are major comorbidities that increase the risk of osteonecrosis. According to recent findings by Walter *et al.* [21], the main factor contributing to BRONJ occurrence among the study participants was a history of tooth extractions, which was present in 63% of BRONJ patients. Junior students' JS (48.1%) and SS (14.8%) had the highest percentage of those involved in this study who were aware of the possible drug-related risk factors of MRONJ, whereas IN (37%) were unaware that invasive dental procedures could trigger BRONJ in individuals with controlled blood pressure. Because they have more recent dental curriculums and have had greater access to the Internet and other information, juniors with less clinical experience are more susceptible to MRONJ. These figures illustrate how urgent it is to inform interns and students about MRONJ.

This can occur simply because dental interns obtain greater clinical exposure than undergraduates. The dental IN demonstrated the highest percentage (36.8%) of comprehending treatment modality could be carried out to avoid this side effect, along with the highest ability to manage MRONJ (46.5%), understand how MRONJ is clinically found in the mouth subject to the stage (45%), and recognize radiographic findings (37.5%). The significance of understanding and recognition for students to provide therapies to individuals who need particular care is ultimately reflected in this finding. Only 22.1% of a sample of doctors accurately identified that MRONJ could be asymptomatic or present with non-specific clinical signs and no evident necrotic bone, according to a study by El Osta *et al.* [22]. As a result, doctors overlook the disease's early stages, a misconception that will make it more difficult to identify bisphosphonate-related ONJ early and stop it from developing into more severe and debilitating stages where treatment is challenging. Aghaloo *et al.* [23] did not describe any particular characteristics that would distinguish BRONJ patients from those who had osteonecrosis as a result of trauma, infection, steroids,

chemotherapy, radiotherapy, and coagulation disorders—disorders that are rarely documented in the literature.

Due to their familiarity with BRONJ, junior students stated that the majority of patients in their care developed MRONJ. Nevertheless, they were not widely used in clinical settings. Our research's intriguing observation is that all three groups comparatively expressed a desire to learn more about and receive training on MRONJ. This implies that to raise knowledge of this illness at the undergraduate and graduate levels, more comprehensive educational programs had to be implemented.

In comparison to JS and IN, SS had a higher level of awareness of the AAOMS recommendations because they had read the literature or gone to conferences on the guidelines' ongoing modifications. Compared to the BRONJ techniques suggested by the AAOMS for this possibility, they were quicker to respond to. Conversely, due to their relatively extensive experience and up-to-date knowledge, dental interns demonstrated a greater percentage of awareness regarding staging (42.1%), the severity of MRONJ (41.3%), and taking into consideration the referral of individuals to medical professionals for pre-treatment assessment (36.9%) than JS and SS. The treaties by De Lima *et al.* [24] and López-Jornet *et al.* [25] contain our findings. The results of this study show that, until recently, when this issue arose, the majority of participants had not been familiarized with MRONJ through the consistent dentistry college curriculum or necessary educational opportunities. The results indicate that to avoid or lower the risk of MRONJ in vulnerable persons, dentistry students must now be prepared for the severity of osteonecrosis and encouraged to react appropriately by drug history taking. In clinical training, dental extractions are frequently performed.

Conclusion

According to the current study, a large number of interviewees knew something about MRONJ but were unaware of the basic principles of MRONJ prevention. Despite the small sample size, the data are enough to confirm that dental students do not routinely detect individuals who use antiresorptive and antiangiogenic treatments due to careless history-taking and their dearth of basic knowledge about these drugs. The vast majority of participants were nevertheless curious about MRONJ. To prevent or minimize the occurrence of medication-related jaw necrosis in dental practice, it is advised that practical initiatives be taken to increase and integrate dental providers' knowledge of MRONJ.

For prevention, risk reduction, treatment selection, prognosis, and result, this will assist them in making better decisions and creating better plans and protocols.

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, Kastiris 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. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons. American association of oral and maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg*. 2007;65(3):369-76.
14. Dimopoulos MA, Kastiris 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.
15. 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.
16. Dannemann C, Zwahlen R. Clinical experiences with bisphosphonate induced osteonecrosis of the jaws. *Swiss Med Wkly*. 2006;136(3132):504-9.
17. 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.
18. 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
19. 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.

20. 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(5):920-43.
21. 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.
22. 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
23. 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.
24. 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
25. 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.