

The Awareness and Knowledge of Dentists of Medication-Related Osteonecrosis of the Jaw

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ABSTRACT

Objective: Medication-related osteonecrosis of the jaw (MRONJ) is a serious condition affecting the quality of life of patients taking antiresorptive and anti-angiogenic drugs. The main purpose of this study was to evaluate dentists' awareness of MRONJ.

Methods: A questionnaire was administered to dentists. The questionnaire contained 20 questions on the demographic data of the participants and their awareness of MRONJ and the complications of antiresorptive or anti-angiogenic drugs. The responses were analyzed using Pearson's chi-square test and Fisher's exact test.

Results: In total, 141 dentists participated in the survey. Of these, 42.6% did not know about MRONJ. There was a statistically significant difference between specialist dentists and general dentists on the questions about the complications, effects, and usage of antiresorptive and anti-angiogenic drugs on necrosis formation ($p < 0.05$). Dentists with less experience (seven years' <) were more knowledgeable about MRONJ (86.7%); compared to those with more than seven years' clinical experience.

Conclusions: This study showed that the knowledge level of dentists regarding the side effects of antiresorptive and anti-angiogenic medications is weak. Overall, MRONJ awareness among general dentists was poor.

Keywords: Antiresorptive, anti-angiogenic, medications, medication-related osteonecrosis of the jaw

1. INTRODUCTION

Bisphosphonates are antiresorptive agents and are widely used for the treatment of various pathologies, such as osteoporosis, Paget's disease, or hypercalcemia associated with some malignant tumors (as breast, prostate, and lung cancers, multiple myeloma) (1-3). Bisphosphonates and other antiresorptive drugs suppress osteoclastic bone resorption. However, these drugs may cause undesirable adverse effects, such as osteonecrosis (2).

Osteonecrosis of the jaw is a problem in patients taking bisphosphonates (3). Initially, avascular necrosis of the jaw was termed bisphosphonate-related osteonecrosis of the jaw (BRONJ). Recently, except for bisphosphonate drugs, other antiresorptive (denosumab) and anti-angiogenic drugs (bevacizumab and sunitinib) have been observed to cause the development of osteonecrosis in the jaw. The American Association of Oral and Maxillofacial Surgery (AAOMS) has suggested the use of the term medication-related osteonecrosis of the jaw (MRONJ) due to an increase in the number of osteonecrosis cases related to other antiresorptive and antiangiogenic drugs (4). The use of intravenous bisphosphonates represents an important part

of osteonecrosis cases. The diagnosis of MRONJ in the current guidelines is defined as the presence of exposed bone in individuals with a history of treatment with antiresorptive or anti-angiogenic agents that occurs clinically with an intraoral or extraoral fistula lasting longer than eight weeks in the maxillofacial area, independent of radiotherapy or metastatic diseases (5-7).

MRONJ affects quality of life and causes serious morbidity. Patients with MRONJ may experience swelling, mucosal ulceration, pain, paresthesia, extra – and intra-oral fistula, suppuration, and deformity of the jaw. Although the pathophysiology of MRONJ has not yet been fully elucidated, several mechanisms are suggested: inhibition of angiogenesis, impaired remodeling, infection, trauma, suppression of immunity, and local toxicity (4,8-10). Dentoalveolar surgery, periodontal diseases, and dental prostheses are the most important risk factors for MRONJ (4,11). In addition, the duration of treatment and usage method (intravascular or oral) of antiresorptive and anti-angiogenic drugs are among the risk factors related to MRONJ (8, 10,12). Vescovi et al. found that 63.8% of 567 patients with BRONJ were related

to preceding dentoalveolar procedures (13). Marx et al. reported that periodontitis was in 84% and dental caries was in 29% of patients with BRONJ (14).

It is important for dentists, clinicians, and patients to be aware of the potential adverse effects of antiresorptive and anti-angiogenic drugs (11). A few studies have evaluated the levels of knowledge and awareness of dentists regarding BRONJ (11, 15-17). The purpose of this study was to evaluate the awareness and knowledge of dentists regarding MRONJ.

2. METHODS

The cross-sectional study was approved by the Gazi University Ethics Committee (No: 2018-62) and was carried out by the Declaration of Helsinki. A questionnaire was administered to dentists working in oral and dental health centres. In this study, the principles of the AAOMS regarding MRONJ were followed (1,4). Validated questionnaires from previous studies were prepared and given to participants (11,16,18). Detailed information about the study was given to participants, and their consent was obtained. Participation in the survey was voluntary. The questionnaire was administered by two researchers (GA: an oral and maxillofacial radiologist with experience 6 years, AE: a maxillofacial surgeon with experience 6 years). Also, approval and permission for the study were obtained from the relevant institutions.

2.1. Survey

The survey contained 20 questions and two parts. In the first part, demographic information including age, gender, years of professional experience, and field of specialty was recorded. In the second part, we asked questions about experiences treating patients using antiresorptive and anti-angiogenic drugs, risk factors, indications of drugs, diagnostic criteria, awareness of MRONJ.

2.2. Statistical analysis

All statistical analyses were performed with IBM SPSS Statistics 23.0 (Armonk, New York). The number and percentage of dentists according to demographic factors (gender, age, years of professional experience, and field of specialty) were calculated and the descriptive statistics were reported. Pearson's chi-square test was used to determine if there is a significant relationship between the answers to questions and the properties of dentists. Fisher's exact test as an alternative to Pearson's chi-square test is used to examine the relation of two different binary properties. The level of significance was set at 0.05.

3. RESULTS

A total of 196 dentists was asked to participate in the survey. Twenty-three dentists have refused to participate,

and thirty-two dentists were excluded from the study due to incomplete questions. Among participants, 90 (63.9%) were females, 51 (36.1%) were males. The distribution of the demographic characteristics of the participants is shown in Table 1. Hundred and five dentists were general dentists, thirty-six dentists were specialists.

Table 1. Demographic features of dentists

	Male	Female	Total
Age			
24-34 age	9(17.3%)	43(82.7%)	52 (36.8%)
35-44 age	31(49.2%)	32(50.8%)	63(44.7%)
45+ age	11(42.3%)	15(57.7%)	26(18.5%)
Total	51 (36.1%)	90 (63.9%)	141 (100%)
Clinical experience			
1-3 years	0(0.0%)	3(100.0%)	3(2.2%)
4-7 years	5(18.6%)	22(81.4%)	27(19.4%)
8-11 years	4(18.1%)	18(81.9%)	22(15.8%)
12-16 years	15(48.4%)	16(51.6%)	31(22.4%)
17-20 years	12(44.4%)	15(55.6%)	27(19.4%)
20 + years	13(44.8%)	16(55.2%)	29(20.8%)
Specialty education			
Yes	6(16.6%)	30(83.4%)	36(25.5%)
No	45(42.8%)	60(57.2%)	105(74.5%)
Field of specialty			
Oral and Max. Radiology	2(40.0%)	3(60.0%)	5(13.9%)
Oral and Max. Surgery	0(0.0%)	6(100.0%)	6(16.7%)
Restorative Dentistry	0(0.0%)	5(100.0%)	5(13.9%)
Endodontics	0(0.0%)	2(100.0%)	2(5.5%)
Orthodontics	1(100.0%)	0(0.0%)	1(2.8%)
Pediatric Dentistry	0(0.0%)	10(100.0%)	10(27.8%)
Periodontology	1(50.0%)	1(50.0%)	2(5.5%)
Prosthodontics	2(40.0%)	3(60.0%)	5(13.9%)
Total	6 (16.7%)	30 (83.3%)	36 (100.0%)

The sources of information about MRONJ were summarized in Table 2. This knowledge about MRONJ had been acquired primarily from a university education (n:27, 33.3%), postgraduate training (n:17, 20.1%), or journal/literature (n:24, 29.7%). Alendronate (n:45, 31.9%) and Zoledronate (n:45, 31.9%) were the most frequently known drugs among dentists. However, fifty-six (39.7%) dentists did not know of any of these drugs. Specialists were more knowledgeable about antiresorptive and anti-angiogenic drugs, compared to general dentists (p<0.05) (Table 3).

Sixty (42.6%) dentists did not know about MRONJ. Most of the specialists knew MRONJ (91.7 %). Only 42% of participants reported taking a medication history from patients before dental treatment. Similarly, specialist dentists (88.9%) were more aware of complications of the antiresorptive and anti-angiogenic drugs than general dentists. According to the results of the analysis summarized

in Table 4, statistically, significant differences were found between specialists and general dentists in the questions about complications of drugs and the effect of usage method of drugs on necrosis formation ($p < 0.05$). There were also statistically significant differences between specialists and general dentists in the questions about the diseases using antiresorptive and anti-angiogenic drugs ($p < 0.05$). The most stated diseases were osteoporosis (27.6%) and bone metastases (30.4%). A total of 42.9% of general dentists did no comment about the diseases using antiresorptive and anti-angiogenic drugs. When comparing responses about treatment options in patients using these drugs, there were no statistically significant differences between specialists and general dentists ($p > 0.05$). Bone sequestrate (n:58, 41.1%) and expose bone areas (n:65, 46.1%) were the most known symptoms in the MRONJ diagnosis, whereas thickening of lamina dura was the rare answer (n:10, 7.1%). Statistically

significant differences were detected ($p < 0.05$) for all of the findings, except halitosis and enlargement in periodontal space. The findings showed that specialist dentists were more aware, compared to general dentists (Table 4).

The clinical experiences influenced the answers to some of the questions such as knowledge about MRONJ and complications of drugs (Table 5) ($p < 0.05$). Less experienced dentists had more knowledgeable about MRONJ (86.7%). Moreover, less experienced dentists (66.7%) had more knowledgeable about the effect of drugs on necrosis formation, compared to medium experienced and the most experienced dentists. Also, there were statistically significant differences among three experience levels on the questions about clinical and radiological findings of MRONJ (for changes in the structure of bone and expose bone regions) ($p < 0.05$). Expose bone regions (46.1%) were the most known symptoms or signs for MRONJ among participants.

Table 2. Information sources of dentists about MRONJ

	Specialist dentists	General dentists	Total
University education	10(30.3%)	17(35.4%)	27(33.3%)
PhD/postgraduate training	17(51.5%)	0(0.0%)	17(20.1%)
Journals and literature	10(30.3%)	14(29.1%)	24(29.6%)
Congress/Seminar	4(12.1%)	2(4.1%)	6(7.4%)
Internet/Television	5(15.1%)	11(22.9%)	16(19.7%)
Patient anamnesis	3(9.1%)	0(0.0%)	3(3.7%)
Drug experiences	0(0.0%)	3(6.2%)	3(3.7%)

Table 3. Table showing the knowledge about antiresorptive and anti-angiogenic drugs of specialist dentists and general dentists

Drugs	Specialist dentists	General dentists	Total	P-value
Alendronate (Fosamax®)	20(55.6%)	25(23.8)	45(31.9%)	0.001*
Risedronate (Actonel®)	8(22.2%)	4(3.8%)	12(8.5%)	0.002*
Ibandronate (Boniva®)	4(11.1%)	1(1.0%)	5(3.5%)	0.015*
Pamidronate (Aredia®)	5(13.9%)	3(2.9%)	8(5.6%)	0.026*
Denosumab (Xgeva, Prolia®)	9(25.0%)	17(16.2%)	26(18.4%)	0.318
Zoledronate (Zometa, Reclast®)	21(58.3%)	24(22.9%)	45(31.9%)	0.000*
Sunitinib (Sutent®)	7(19.4%)	2(1.9%)	9(6.3%)	0.001*
Sorafenib (Nexavar®)	3(8.3%)	0(0.0%)	3(2.1%)	0.016*
Bevacizumab (Avastin®)	8(22.2%)	2(1.9%)	10(7.1%)	0.000*
Sirolimus (Rapamune®)	-	-	-	-
None	4(11.1%)	52(49.5%)	56(39.7%)	0.000*

* significant at 0.05

Table 4. Knowledge of specialist and general dentists regarding complications, risk factors, and the treatment options of patients taking antiresorptive and anti-angiogenic medication

Variables	Specialist dentists	General dentists	Total	P-value
Knowledge about MRONJ? (Yes)	33(91.7%)	48 (45.7%)	81(57.4%)	0.000*
Do you take a medication history from patients before an invasive dental procedure? (Yes)	21(58.3%)	39(37.1%)	60(42.6%)	0.032*
Do you know the complications of these drugs? (Yes)	32(88.9%)	43(41.0%)	75(53.1%)	0.000*
Are there any effect duration and usage method (oral, intravenous, intramuscular) of drugs on necrosis formation? (Yes)	29(80.6%)	35(33.3%)	64(45.3%)	0.000*
Diseases using antiresorptive and anti-angiogenic drugs (Most)?				
Prostate CA	9(25.0%)	11(10.5%)	20(14.1%)	0.050*
Breast CA	17(47.2%)	13(12.4%)	30(21.2%)	0.000*
Multiple Myeloma	9(25.0%)	10(9.5%)	19(13.4%)	0.026*
Osteoporosis	16(44.4%)	23(21.9%)	39(27.6%)	0.016*
Bone Metastases	17(47.2%)	26(24.7%)	43(30.4%)	0.011*
Paget's Disease	8(22.2%)	12(11.4%)	20(14.1%)	0.163
Malign Hypercalcemia	10(27.8%)	7(6.7%)	17(12.1%)	0.002*
Lung CA	9(25.2%)	5(4.8%)	14(9.9%)	0.001*
None	8(22.2%)	45(42.9%)	53(37.5%)	0.030*
The treatment options in patients using these drugs?				
I make no treatment.	11(30.6%)	40(38.1%)	51(36.1%)	0.547
I perform all dental treatments without surgery.	4(11.1%)	13(12.4%)	17(12.1%)	1.000
I make simple surgical treatments (such as tooth extraction).	4(11.1%)	5(4.8%)	9(6.3%)	0.233
I perform all surgical treatments, including the implant.	-	-	-	-
I make all dental treatments after consulting the medical physician.	22(61.1%)	49(46.7%)	71(50.3%)	0.176
What are the clinical and radiological findings of the MRONJ?				
Halitosis	5(13.9%)	8(7.6%)	13(9.2%)	0.317
Ulceration of mucosa	12(33.3%)	14(13.3%)	26(18.4%)	0.010*
Drainage (inflammation)	13(36.1%)	13(12.4%)	26(18.4%)	0.003*
Mobility and sensitive teeth	13(36.1%)	13(12.4%)	26(18.4%)	0.003*
Expose bone regions	26(72.2%)	39(37.1%)	65(46.1%)	0.000*
Thickening of lamina dura	7(19.4%)	3(2.9%)	10(7.1%)	0.003*
Enlargement in periodontal space	4(11.1%)	7(6.7%)	11(7.8%)	0.472
Changes in the structure of bone trabecula	17(47.2%)	26(24.8%)	43(30.4%)	0.020*
Sequestration areas	21(58.3%)	37(35.6%)	58(41.1%)	0.020*

* significant at 0.05; MRONJ: Medication-related osteonecrosis of the jaw

Table 5. Correlation between clinical experience and responses

Variables	Clinical experience			Total	P-value
	Less exp. (1-7 years)	Medium exp. (8-16 years)	Experienced (17 + years)		
Knowledge about MRONJ? (Yes)	26(86.7%)	26(49.1%)	28(50.0%)	81(57.4%)	0.001*
Do you take a medication history from patients before an invasive dental procedure? (Yes)	17(56.7%)	24(45.3%)	19(33.9%)	60(42.6%)	0.118
Do you know the complications of these drugs? (Yes)	24(80.0%)	23(43.4%)	28(48.2%)	75(53.1%)	0.004*
Are there any effect duration and usage method (oral, intravenous, intramuscular) of drugs on necrosis formation? (Yes)	20(66.7%)	17(32.1%)	27(46.4%)	64(45.3%)	0.010*
Diseases using antiresorptive and anti-angiogenic drugs (Most)					
Prostate CA	6(20.0%)	6(11.3%)	8(14.3%)	20(14.1%)	0.555
Breast CA	7(23.3%)	11(20.8%)	12(21.4%)	30(21.5%)	0.962
Multiple Myeloma	7(23.3%)	3(5.7%)	9(16.1%)	19(13.6%)	0.063
Osteoporosis	10(33.3%)	12(22.6%)	17(30.4%)	39(28.1%)	0.514
Bone Metastases	14(46.7%)	13(22.6%)	16(28.6%)	43(30.4%)	0.068
Paget's Disease	7(23.3%)	6(11.3%)	7(10.7%)	20(13.6%)	0.219
Malign Hypercalcemia	6(20.0%)	4(7.5%)	7(12.5%)	17(12.2%)	0.250
Lung CA	3(10.0%)	3(5.7%)	8(14.3%)	14(10.1%)	0.327
None	9(30.0%)	26(47.2%)	18(32.1%)	53(37.5%)	0.172
The treatment options in patients using these drugs?					
I make no treatment.	10(33.3%)	20(35.8%)	21(37.5%)	51(36.1%)	0.929
I perform all dental treatments without surgery.	2(6.7%)	5(9.4%)	10(17.9%)	17(12.2%)	0.234
I make simple surgical treatments (such as tooth extraction).	2(6.7%)	3(5.7%)	4(7.1%)	9(6.4%)	0.951
I perform all surgical treatments, including the implant.	-	-	-	-	-
I make all dental treatments after consulting the medical physician.	16(53.3%)	31(56.6%)	24(42.9%)	71(50.3%)	0.334
What are the clinical and radiological findings of the MRONJ?					
Halitosis	5(16.7%)	6(11.3%)	2(3.6%)	13(9.2%)	0.114
Ulceration of mucosa	6(20.0%)	10(17.0%)	10(17.9%)	26(18.4%)	0.942
Drainage (inflammation)	8(30.8%)	8(30.8%)	10(38.5%)	26(18.4%)	0.421
Mobility and sensitive teeth	6(20.0%)	10(18.9%)	10(17.9%)	26(18.4%)	0.970
Expose bone regions	20(66.7%)	21(39.6%)	24(42.9%)	65(46.1%)	0.045*
Thickening of lamina dura	3(10.0%)	3(5.7%)	4(7.1%)	10(7.1%)	0.763
Enlargement in periodontal space	3(10.0%)	5(7.5%)	3(5.4%)	11(7.8%)	0.724
Changes in the structure of bone trabecula	15(50.0%)	13(24.5%)	15(26.8%)	43(30.4%)	0.037*
Sequestration areas	16(21.7%)	22(42.3%)	20(35.7%)	58(41.1%)	0.288

* significant at 0.05; MRONJ: Medication-related osteonecrosis of the jaw

4. DISCUSSION

Osteonecrosis of the jaw in patients using antiresorptive (bisphosphonate, denosumab) and anti-angiogenic drugs (Sunitinib, Sorafenib, Bevacizumab, Sirolimus) may develop after simple surgical procedures such as tooth extraction (4,18). In recent years, the incidence of this complication has increased due to the frequent prescription of these drugs by

oncologists and physicians (4). To the best of our knowledge, there are a few limited numbers of studies that assess the knowledge, opinions, and awareness of dentists about MRONJ (7,18). In the study in the United Kingdom, 90% of dentists were uninformed of the effect of antiresorptive and antiangiogenic drugs excluding bisphosphonates on MRONJ (7). Escobedo et al. evaluated the capabilities in the decision of clinical problems in patients using different medications

among dentists. The question regarding implant surgery in patients using oral amino-bisphosphonates had the lowest percentage of correct responses among participants (18). De Lima et al. reported that 72.1% of dentists and 75% of dental students did not know the bisphosphonates (11). In Mexico, Vinitzky-Brener et al. revealed that 99.7% of dentists were not found enough knowledge about the prevention, diagnosis, and treatment of BRONJ (16). In this study, the awareness, opinion, and knowledge of dentists regarding MRONJ were evaluated. The results showed that only 57.4% of dentists were knowledgeable about MRONJ.

Distinct committees have improved various consensus documents to guide the clinical management of patients treated with antiresorptive medication. In the literature, there is consensus that the education of dentists on the prevention and management of MRONJ should be increased (4,19,20). In 2014, the AAOMS published a position paper that highlighted the low risk of developing MRONJ in patients taking oral bisphosphonate therapy for less than four years and confirmed that these patients may be treated successfully in primary care (4). Patients taking intravenous bisphosphonate or denosumab have an increased risk of developing MRONJ and surgical procedures should be avoided in these patients (4). Previous studies have reported that dentists must be aware of the type, dosage, and usage duration of bisphosphonates to minimize the risk in patients taking them (8,15,21). In the study of Tanna et al., only 2% of general dental practitioners were aware that denosumab could cause osteonecrosis of the jaw other than bisphosphonates (7). Escobedo et al. (18) reported that Alendronate was the most known drug among dentists (77.2%), while Zoledronic acid was the most recognized drug among dental students (97.3%). In a study by De Lima et al., commercial brand names of bisphosphonates were only recognized by around 15% of dentists and dental students (11). In the present study, Alendronate and Zoledronate were the most known medications among dentists (31.9%), but 39.7% of dentists did not recognize anyone of antiresorptive and anti-angiogenic drugs.

Antiresorptive drugs are used to control cancer-related situations, including hypercalcemia of malignancy and bone metastases of solid tumors such as breast, prostate, and lung cancers. Anti-angiogenic agents have displayed effectiveness in the treatment of renal cell carcinomas, gastrointestinal tumors, and neuroendocrine tumors (4,7,22). Lopez – Jornet et al. reported that 51.6% of dentists have the correct information for bisphosphonate indications (17). The study results of De Lima et al. showed that 65.4% of dentists did not know the medical indication of bisphosphonates (11). In the present study, osteoporosis (27.6%) and bone metastases (30.4%) were the most known diseases on the question regarding the medical indications of bisphosphonates and anti-angiogenic drugs. 37.6% of dentists did not know any of the diseases regarding the indication of antiresorptive and anti-angiogenic medication.

Patients taking antiresorptive and anti-angiogenic medications should be informed about oral hygiene to prevent osteonecrosis (23). Dentists should have sufficient knowledge of these novel medications and MRONJ. Routine dental care containing prophylaxis, non-operative periodontal treatments, restorative applications, and fixed and removable prosthodontics is not contraindicated in these patients. Because advanced oral surgery, apical surgery, and dental implants can create a risk in this group of patients, dentists should exercise caution against the possibility of necrosis (21,23). Yoo et al. reported that only 33.3% of Korean dentists taken the medication anamnesis of patients before oral surgery or treatment (15). The results of our study showed that 57.4% of the dentists reported taking medication anamneses from patients (antiresorptive and anti-angiogenic drug history) before dental treatment.

In our study, we asked participants regarding the treatment protocol of patients using antiresorptive or anti-angiogenic drugs and 31.6% of the dentists reported that they would not perform any dental treatment. In the study of Lopez – Jornet et al. (17), 73.3% of dentists correctly marked the question about treatment procedures, including surgical procedures, which can be performed in patients using oral bisphosphonates for less than three years. The early findings of MRONJ can be difficult to distinguish clinically and radiographically, this complicates the treatment process of the disease (21). In the current study, bone sequestrate (n:58, 41.1%) and expose bone areas (n:65, 46.1%) were the most known symptoms regarding MRONJ diagnosis.

In previous studies, while dentists with more professional experience (> 5 years) had greater clinical experience in the treatment of patients with osteonecrosis, dentists with more professional experience had a lower knowledge about possible complications (11,15). Escoba et al. showed that dentists with professional experience (20 years>) obtained significantly lower results in the interpretation of clinical cases (18). In Brazil, De Lima et al. stated that 59.6% of dentists and 58% of dental students did not know the oral adverse effect of bisphosphonates in BRONJ (11). In our study, statistically significant differences were observed between clinically experienced dentists and less experienced dentists about MRONJ. Less experienced dentists (< 7 years) knew more about MRONJ. We investigated the correlation between postgraduation training and knowledge levels about MRONJ. There were statistically significant differences between specialist and general dentists regarding MRONJ awareness, drug complications, and drug effects on necrosis formation. The results of our study showed that dentists with postgraduate training had more information about MRONJ than general dentists. Education about the risks and adverse effects of antiresorptive and anti-angiogenic medication usage needs to be improved in many areas. Knowledge of the risk of MRONJ for dentists and patients should be increased through explanatory brochures, guideline booklets, and, of course, communication between doctors and patients (23).

5. CONCLUSION

The results of this study showed that the knowledge level of dentists on the side effects of antiresorptive and anti-angiogenic medications is weak. However, specialist dentists had more information about MRONJ, compared to general dentists. Overall, MRONJ awareness among general dentists was poor.

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