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Dental Care Awareness of Oral Complications among Patients Receiving Denosumab and Zoledronic Acid Therapy at KAMC Oncology Department

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Received: September 06, 2021; **Published:** September 24, 2021

Abstract

Background: Many risk factors for developing medication-related osteonecrosis of the jaw (MRONJ) have been reported in the literature, and patients' awareness is an important factor for developing MRONJ. We aim to evaluate patients' awareness about oral complications regarding these drugs. We also aim to assess the frequency of complications and the attitudes to these complications.

Methods: A cross-sectional questionnaire-based study was conducted at King Abdullah Medical City in Saudi Arabia to assess the relevant outcomes, after obtaining ethical approval from the included patients.

Results: We have finally included 183 participants, including 23 (12.6%) males, and 160 (87.4%) females. Five patients (2.7%) were in the 15 - 35 years old group, while the rest (97.3%) were > 35 years old. Most patients (97.3%) were familiar with drugs through doctors, and 153 patients (83.6%) used the prescribed drugs for more than 3 months. Pain in teeth/jaw (28.45), dry mouth (27.3%), and gingival sensitivity (19.7%) were the commonest oral manifestations. Besides, 73.8% did not know about the side effects of the drugs, while only 46 (25.1%) were aware of the oral complications of the drugs. Age, gender, and the frequency of brushing teeth might significantly impact some important awareness domains.

Conclusion: Our results indicate the low awareness levels among our population, indicating the need to apply proper interventional approaches and educational campaigns.

Keywords: *Dental Care; Awareness; Oral Complications; Denosumab; Zoledronic Acid Therapy*

Introduction

Evidence shows that several medications can be administered to prevent bone loss, however, these modalities should be cautiously used under adequate supervision to prevent the development of medication-related osteonecrosis of the jaw (MRONJ), in addition to other bone-related complications. The study conducted by Marx., *et al*. [1] was the first to report a case of MRONJ in 2003. Following this report, many investigations were published to report multiple cases of MRONJ that resulted from the administration of bone resorption inhibitors (as denosumab) and angiogenesis inhibitors.

Estimates from the United States show that the prevalence of MRONJ ranges between 0.8 - 12% among patients receiving intravenous bisphosphonate [2]. A lower prevalence rate was estimated in Europe, being 0.001%, and 0.095% for patients receiving oral and intravenous administrations, respectively [3]. Another investigation in Scotland reported a rate of 0.004%, and Leo., *et al*. showed that following the administration of bisphosphonate for more than 4 years, the prevalence of MRONJ ranged between 0.04 - 0.21% [4]. Papapoulos., *et*

al. [5] estimated a rate of 0.085% for patients receiving denosumab for five years for dealing with postmenopausal osteoporosis. These findings indicate the low prevalence of MRONJ across the different populations. However, it has been indicated that MRONJ significantly impacts the quality of life of the affected patients, with a variety of symptoms and complications as pain, paraesthesia, swelling, soft tissue ulcerations, suppurations, jaw deformities, and loosening of teeth [6-9].

Many risk factors for developing MRONJ have been reported in the literature, including the underlying disease or the presence of co-morbidities, the duration of administration of the drug modalities, the presence of associated dental diseases, teeth extraction, denture use, and the anatomical structure where the lesion takes places [10,11]. In addition to these factors, patients' awareness is another important risk factor for developing MRONJ. Identifying these patients is an essential process to adequately apply adequate interventional approaches and enhance the outcomes, as previously indicated among studies in the literature [12,13]. Furthermore, clinical data about the drugs may differ from data in real life, and the oral complications will differ according to patients' awareness and preventive measures are taken, which is why we are going to design a study to evaluate patients' awareness about oral complications regarding these drugs. We aim to assess the frequency of complications and the attitudes to these complications.

Methods

Study design and settings

This is a cross-sectional questionnaire-based study that was conducted at King Abdullah Medical City (KAMC) Located in makkah, saudi arabia. which is a tertiary care center with a specialized oncology department that treats a huge number of cancer patients. The center was inaugurated in 2008, and upon this, it became a large place of care for a large percentage of cancer patients.

Study population

Oncology Patients at KAMC receiving Denosumab or Zoledronic acid. The inclusion criteria were all patients receiving more than two doses of Denosumab or zoledronic acid at the KAMC Oncology Department The exclusion criteria were 1- patients who have stopped taking either medication for 6 months, 2- patients who took less than the required doses, and 3- patients that refused to participate. Ethical approval was sought from KAMC Institutional Review Board. No study activities were inaugurated until the IRB approval was obtained. A Questioner was used, thus there will be no data linked to the patients' identities, accordingly, only verbal consent was taken and no written consent was required.

Study procedures and outcomes

The included patients will be approached and asked for permission to participate in our study. Interviewing patients and questioner filling were then conducted. Identification of patients is not a necessity in our study, thus complete privacy of subjects will be maintained. The distribution of a paper questionnaire and patient interview will provide data of the following: 1- Patients' recognition of the relationship between the use of the zoledronic acid or denosumab and its risk of developing oral complications, 2- assessing patients understanding about the importance of receiving periodical dentistry maintenance, and 3- to observe the oral guidance and measures provided by the doctors and dentists.

Statistical analysis

SPSS software, version 20 will be used for all statistical analyses. Numeric data will be presented as mean± SD, or as median and range according to the type of distribution of each variable. For categorical variables, percentages will be used. P-value < 0.05 is considered significant when studying the significance of an association.

Results

Patients' characteristics

We have finally included 183 participants, including 23 (12.6%) males, and 160 (87.4%) females. Five patients (2.7%) were in the 15 - 35 years old group, while the rest (97.3%) were > 35 years old. Most patients (97.3%) were familiar with drugs through doctors, and 153 patients (83.6%) used the prescribed drugs for more than 3 months. Pain in teeth/jaw (28.45), dry mouth (27.3%), and gingival sensitivity (19.7%) were the commonest oral manifestations, and 35 patients (19.1%) first noticed the symptoms after one month, while 27 (14.8%) noticed them after more than one year. More than half of the patients (54.1%) brushed their teeth at least two times per day, and 83 (45.4%) used oral hygiene supplements. The detailed characteristics are presented in table 1.

Responded characteristics	Number (n)	Percentage (%)
Gender		
• Male	23	12.6
• Female	160	87.4
Age		
• 15 - 35	5	2.7
• More than 35	178	97.3
Familiarity with the drugs through		
• Doctor	178	97.3
• Nurse	2	1.1
• Others	3	1.6
Drug Duration		
• Less than 3 months	30	16.4
• More than 3 months	153	83.6
Oral manifestation		
• Pain in teeth/jaw	52	28.4
• Numbness around the mouth	18	9.8
• Dry mouth	50	27.3
• Periodontitis	36	19.7
• Pus	18	9.8
• Teeth movement	19	10.4
• Others	28	15.3

Oral manifestation first noticed		
• One month	35	19.1
• 3 months	20	10.9
• 6 months	21	11.5
• More than a year	27	14.8
Response to oral manifestation		
• Doctor consultation	13	7.1
• Dentist consultation	6	3.3
• Others	16	8.6
• Nothing	68	37.2
Dental visits		
• Before starting treatment	67	36.6
• During treatment	52	28.4
• Both	37	20.2
Oral Hygiene		

• Brushing times per day:
  • Never
  • Once
  • Twice or more
	38	20.8

• Other hygiene supplements	46	25.1
	99	54.1
	83	45.4

Table 1: *Patient's characteristics.*

Population awareness

Among the included patients, 73 (39.9%) and 58 (31.7%) used the drugs for bone brittleness and strengthening, respectively, and most participants (73.8%) did not know about the side effects of the drugs, while only 46 (25.1%) were aware of the oral complications of the drugs. Our results showed that there was a significant difference between included male and females populations regarding awareness of the use of drugs, side effects of drugs, and oral complications to treatment (p-value = 0.077, 0.052, and 0.052, respectively) (Table 2). Regarding awareness of the different age groups, our results showed that awareness of the side effects and oral complications were the only two significant factors among the two groups (p-value = 0.006, and 0.015, respectively) (Table 3). Regarding awareness based on the brushing times per day, our results showed that awareness of the use of drugs, and oral complications were the only two significant factors among the two groups (p-value = 0.035, and 0.006, respectively) (Table 4).

	Total		Male		Female		P
	(n)	(%)	(n)	(%)	(n)	(%)	
Use of the drugs:							
• Bone strengthening	58	31.7	8	34.8	50	31.3	
• For bone brittleness	73	39.9	6	26.1	67	41.9	0.077
• I don't know	32	17.5	6	26.1	26	16.2	
• Others	20	10.9	3	13.0	17	10.5	
Side effects of the drugs:							
• Pain in bone/ joins	12	6.6	1	4.3	11	6.9	
• Pain teeth/jaw	5	2.7	0	0.0	5	3.1	
• Osteonecrosis of the jaw	4	2.2	0	0.0	4	2.5	
• interfere with oral problems	6	3.3	0	0.0	6	3.8	0.052
• High temperature	7	3.8	0	0.0	7	4.4	
• I don't know	135	73.8	18	78.3	117	73.1	
• Others	14	7.4	4	17.3	10	6.0	
Oral complications due to treatment	46	25.1	2	8.7	44	27.5	0.052
Familiarity with Medication related osteonecrosis of the jaw	9	4.9	0	0.0	9	5.6	0.378
MRONJ knowledge through							
• Doctor/Dentist	6	66.7	0	0.0	6	66.7	-
• Others	3	3.33	0	0.0	3	3.33	
Importance of periodical dental visits	35	19.1	3	13.0	32	20.0	0.576

Table 2: *Patient's awareness towards (use of drugs, side effect of drugs, oral complications, MRONJ).*

Awareness of	15 - 35		More than 35		P
	(n)	(%)	(n)	(%)	
Use of the drugs:					
• Bone strengthening	3	60.0	55	30.9	
• For bone brittleness	1	20.0	72	40.4	0.733
• I don't know	1	20.0	31	17.4	
• Others	0	0.0	20	11.1	

Side effects of the drugs:					
• Pain in bone/ joints	0	0.0	12	6.7	
• Pain teeth/jaw	0	0.0	5	2.8	
• Osteonecrosis of the jaw	2	40.0	2	1.1	
• interfere with oral problems	0	0.0	6	3.4	0.006*
• High temperature	1	20.0	6	3.4	
• I don't know	1	20.0	134	75.3	
• Others	1	20.0	13	7.4	
Oral complications due to treatment	4	80.0	42	23.6	0.015*
Familiarity with Medication related osteonecrosis of the jaw	1	20	8	4.5	0.225
MRONJ knowledge through					
• Doctor/Dentist	1	100	5	62.7	1.000
• Others	0	0.0	3	37.5	
Importance of periodical dental visits	2	40.0	33	18.5	0.244

Table 3: *Patient's awareness among different age's groups.*

**: Statistically significant.*

Brushing times per day					
Awareness of	**Twice or more**		**Others**		**P**
	(n)	**(%)**	**(n)**	**(%)**	
Use of the drugs:					
• Bone strengthening	28	28.3	30	35.7	
• For bone brittleness	46	46.5	27	32.1	0.035*
• I don't know	11	11.1	21	25.0	
• Others	14	14.0	6	7.2	
Side effects of the drugs:					
• Pain in bone/joints	7	7.1	5	6.0	
• Pain teeth/jaw	4	4.0	1	1.2	
• Osteonecrosis of the jaw	3	3.0	1	1.2	
• interfere with oral problems	6	6.1	0	0.0	0.247
• High temperature	5	5.1	2	2.4	
• I don't know	68	68.7	67	79.8	
• Others	6	6.0	8	9.6	
Oral complications due to treatment	33	33.3	13	15.5	0.006*
Familiarity with Medication related osteonecrosis of the jaw	5	5.1	4	4.8	1.000
MRONJ knowledge through					
• Doctor/Dentist	4	80.0	2	50.0	0.524
• Others	1	20.0	2	50.0	
Importance of periodical dental visits	23	23.2	12	14.3	0.125

Table 4: *Patient's awareness in association with oral hygiene.*

**: Statistically significant.*

Association between oral manifestations and other characteristics

There is a significant difference between patients that reported pain in teeth (n = 20) and others that did not (n = 32) during dental visits (p-value = 0.058). Significant differences were also noticed between patients that reported pus (n = 12) and others that did not (n = 6) before dental visits (p-value = 0.005) and between patients that reported it before and during the dental visits (n = 13), and others that never reported it (n = 5) (p-value = 0.014) (Table 5). The frequencies of all oral manifestations when first noticed were significantly different during the 1, 3, 6 months, and 1 year or more (Table 6). No significance was found between oral manifestations and duration of drug administration and the results are presented in table 7. On the other hand, all of the reported oral manifestations were significantly more frequent in patients that did not respond to either doctor or dentist consultation (Table 8). We did not find any significant differences in the frequencies of oral manifestations between patients that brushed their teeth once, twice, or never per day (Table 9).

Dental visits												
Oral manifestations	Before				During				Both		Never	
	Yes		No		Yes		No					
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Pain in teeth/jaw	`		33	63.5	20	38.5	32	61.5	27	51.9	25	48.1
P value	0.990				0.058				0.223			
Numbness around mouth	7	38.9	11	61.1	7	38.9	11	61.1	10	55.6	8	44.4
P value	0.833				0.299				0.334			
Dry mouth	21	42.0	29	58.0	17	43.0	33	66.0	27	54.0	23	46.0
P value	0.354				0.304				0.125			
Periodontitis	11	30.6	25	69.4	11	30.6	25	69.4	17	47.2	19	52.8
P value	0.400				0.751				0.745			
Pus	12	66.7	6	33.3	7	38.9	11	61.1	13	72.2	5	27.8
P value	0.005*				0.299				0.014*			
Teeth movement	10	52.6	9	47.4	8	42.1	11 57.9		12	63.2	7	36.8
P value	0.126				0.162				0.089			
Others	11	16.4	17	14.7	9	17.3	19	14.5				
P value	0.489				0.964							

Table 5: *Oral manifestation in relation to dental visits.*
**: Statistically significant.*

First noticed in									
Oral manifestations	1 month		3 months		6 months		A year or more		P
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	
Pain in teeth/jaw	20	38.5	9	17.3	9	17.3	14	26.9	0.000*
Numbness around mouth area	6	33.3	3	16.7	4	22.2	5	27.8	0.004*
Dry mouth	16	32.0	11	22.0	10	20.0	13	26.0	0.000*
Periodontitis	13	36.1	6	16.7	7	19.4	10	27.8	0.000*
Pus	5	27.8	5	27.8	4	22.2	4	22.2	0.002*
Teeth movement	6	31.6	4	21.1	1	5.3	8	42.1	0.000*
Others	7	20.0	8	30.0	6	28.6	7	25.9	-

Table 6: *Oral manifestations in relation to its first notice.*
**: Statistically significant.*

Drug duration					
Oral manifestations	Less than 3 months		More than 3 months		P
	(n)	(%)	(n)	(%)	
Pain in teeth/jaw	7	13.5	45	86.5	0.500
Numbness around mouth area	2	11.1	16	88.9	0.742
Dry mouth	8	16.0	42	84.0	0.930
Periodontitis	6	16.7	30	83.3	0.961
Pus	5	27.8	13	72.2	0.183
Teeth movement	2	10.5	17	89.5	0.543
Others	3	10.0	25	16.3	0.768

Table 7: *Oral manifestation in relation to the course of the drug.*

Patients response							
Oral manifestations	Doctor consultation		Dentist consultation		Other		p
	(n)	(%)	(n)	(%)	(n)	(%)	
Pain in teeth/jaw	5	9.6	6	11.5	41	78.8	0.000*
Numbness around mouth area	5	27.8	1	5.6	12	66.7	0.001*
Dry mouth	3	6.0	4	8.0	43	86.0	0.000*
Periodontitis	6	16.7	4	11.1	26	72.2	0.000*
Pus	3	16.7	0	0.0	15	83.3	0.002*
Teeth movement	0	0.0	2	10.5	17	89.5	0.000*
Others	4	30.8	1	16.7	22	26.5	0.194

Table 8: *Oral manifestations in relation to patient response towards them.*

**: Statistically significant.*

Brushing times per day							
Oral manifestations	Once		Twice or more		Never		P
	(n)	(%)	(n)	(%)	(n)	(%)	
Pain in teeth/jaw	9	17.3	29	55.8	14	26.9	0.209
Numbness around mouth area	4	22.2	11	61.1	3	16.7	0.844
Dry mouth	12	24.0	27	54.0	11	22.0	0.958
Periodontitis	7	19.4	18	50.0	11	30.6	0.248
Pus	4	22.2	11	61.1	3	16.7	0.844
Teeth movement	5	26.3	13	68.4	1	5.3	0.218
Others	6	13.0	16	16.2	6	15.8	0.717

Table 9: *Oral manifestations in relation to oral hygiene.*

**: Statistically significant.*

Discussion

Our primary objective in the present study was to evaluate the awareness of MRONJ and its risk factors among cancer patients who receive denosumab and zoledronic acid. Our results show that only a small proportion of the included population is aware of the oral complications of the drugs, although most of them were aware of the adverse events. These findings are also consistent with the results of a previous Saudi investigation by Al Abdullateef., *et al*. [14] showing that only 33.82% of their participants were aware of MRONJ. In the same context, Singh., *et al*. [15] also reported that 94.3% and 86.7% of their study population were not aware of the correct way to recognize the adverse events, and what were these events, respectively. Another investigation by Bauer., *et al*. [16] also indicated that most of their study population (76%) were not aware of the adverse events of bisphosphonate-related MRONJ.

In addition, we found that age, gender, and the frequency of brushing their teeth were all significant factors that can affect the awareness of these populations of the oral complications and adverse events of the drugs. Al Abdullateef., *et al*. [14] also indicated that gender and educational levels were significantly associated with the awareness levels. This is consistent with what has been previously reported in our study that female patients are keener on obtaining adequate drug-related information, particularly regarding the side effects of the drugs [17]. Although the study by Al Abdullateef., *et al*. [14] reported that they did not find a significant statistical correlation between age and awareness levels of MRONJ but they reported that older patients (over 60 years of age) tend to have high awareness levels. This has also been indicated in the literature as older populations have been reported to have higher levels of knowledge and experience about the use and adverse events of these medications [17]. Previous studies have also correlated the levels of awareness with the level of education and having a university degree. Therefore, these populations should be targeted to enhance awareness levels and obtain better outcomes.

Another important factor that should also be considered when assessing the awareness levels of MRONJ is the degree of awareness of the corresponding physicians and whether they provide adequate educational information to their patients or not. In the present study, most of the study participants did not respond to either of the doctor's or dentist's consultations, which was significantly associated with the presence of MRONJ-related oral symptoms and manifestations. On the other hand, Al Abdullateef., *et al*. [14]showed that doctors were the main sources of information, while another investigation by Bauer., *et al*. [16] reported that most patients obtained their information from the drug-package inserts. This indicates that physicians and dentists should be more aware of their potential roles in elevating the awareness levels of the patients towards the potential uses and adverse events of each drug. In this context, many previous investigations have been published to assess the levels of physicians' awareness towards MRONJ. These studies indicated that that most of the included dentists, and physicians did not have adequate acquaintance levels about the MRONJ and related medications [18-21]. This might be attributable to the fact that some medications have been recently introduced, and might also be due to improper ways of communication between the healthcare professionals and their patients [22,23].

It has been indicated that the prevalence of oral complications might be significant in patients receiving bisphosphonates [14]. A previous meta-analysis concluded that the prevalence of MRONJ among patients receiving intravenous bisphosphonates was 0.2% [24]. Another study by Papanikolaou and Ioannidis reported that the highest awareness levels about the medication's adverse events were amongst the patients that experienced at least one adverse event [25]. We also found that the frequency of oral complications did not have a significant correlation with any of the brushing teeth habits, indicating that further interventional approaches might be needed, in addition to the oral hygiene methods, to achieve better outcomes. For instance, advising the patients to early report their oral symptoms and manifestations when they are first noticed, and conducting early and frequent check-up visits might be beneficial in the early detection and management of these manifestations, as indicated by the findings of the present study.

Lanching educational campaigns to both the doctors or dentists and patients might be a huge advancement, especially about new modalities as denosumab, which is a relatively new drug [26]. A previous investigation by Suresh and Abrahamsen indicated that the prevalence of MRONJ was 2.3%/100,000 population, among their patients receiving denosumab [27]. thus,urging the patients to conduct

frequent dental visits is also important and might have a vital role in the early detection of adverse events and also in educating patients about the uses and complications of these drugs. Among the various studies in the literature, it has been indicated that the adequate application of the prevention measures might be significantly associated with favorable outcomes on the disease and the MRONJ frequency [12,28-30].

Our study was limited by the small sample size of the included population, and the significance between them in the baseline characteristics as age, gender, and others. Therefore, further investigations might be needed for further validation of these outcomes.

Conclusion

Our results show that only a small proportion of the included population is aware of the oral complications of the drugs, although most of them were aware of the adverse events. Age, gender, and the frequency of brushing teeth were all significant factors that can affect the awareness of these populations of the oral complications and adverse events of the drugs. Accordingly, intervention protocols and programs are needed to properly apply adequate prevention measures that might enhance the outcomes in these patients.

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