



## Original article

## Awareness among patient at risk of developing Medication Related Osteonecrosis of the Jaw (MRONJ) – A primary prevention strategy

Abdulrhman Al Abdullateef<sup>a,\*</sup>, Muhanad S. Alhareky<sup>a,b</sup><sup>a</sup> King Fahad Specialist Hospital, Dammam, Saudi Arabia<sup>b</sup> Department of Preventive Dentistry, College of Dentistry, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

## ARTICLE INFO

## Article history:

Received 13 February 2020

Accepted 6 May 2020

Available online 15 May 2020

## Keywords:

Bisphosphonate

Denosumab

Antiangiogenics

Medication Related Osteonecrosis of the Jaw (MRONJ)

Dental

Awareness

## ABSTRACT

The quality of life, in itself, in cancer patients or in osteoporotic individuals, without even considering the side effects of the medication in the first place, has a considerable negative impact on the clinical outcome. The Medication Related Osteonecrosis of the Jaw (MRONJ), in the maxillofacial region, although rare, needs to be addressed with the prime importance. One of the key components of any given preventive treatment strategy is to, create awareness about the medication related unwanted effects, among health care professionals and patients.

**Objective:** This study is aimed to explore and assess the awareness level among dental patients about MRONJ, the risk factors, and the high-risk category (who are prone to develop MRONJ).

**Material and methods:** This is a prospective interviewer administered research electronic data capture (REDCap) survey. The sample included 68 patients, who are currently taking or will be taking Bisphosphonate (BP), and/or Denosumab, and anti-Angiogenic agent. Data have been analyzed using IBM SPSS software,

**Results:** Sixty-eight patients (18 males and 50 females), participated in this study. Only 23 subjects (33.82%) were aware about the MRONJ. Females were more aware about the complications than males. The awareness among the subjects with education at college level appears to be higher than the subjects having education less than high school level. Even though, a dental check-up, is mandatory, prior to starting these medications, to see if any dental treatment is required, only slightly more than half of the patients (54.72%) had a dental checkup.

**Conclusion:** This is a novel study in the Middle- East, used to assess awareness about the MRONJ including three type of related medications. Low awareness of MRONJ is alarming. The results of the study will help to initiate the process of providing the education materials, about the side effects and importance of oral hygiene maintenance, giving priority to improve the quality of life in such patients. Awareness of patients regarding the complications must be an important part of health care practice guidelines.

© 2020 The Authors. Published by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Abbreviations:** MRONJ, Medication Related Osteonecrosis of Jaw; IV, Intravenous; BP, Bisphosphonate; ONJ, Osteonecrosis of Jaw; AAOMS, American Academy of Oral Medicine; REDCap, Research Electronic data capture; PI, Principal investigator; mTOR inhibitor, mammalian target of Rapamycin.

\* Corresponding author at: General Dentist, King Fahad Specialist Hospital, Dammam, Saudi Arabia.

E-mail addresses: [Abdulrhman.abdullateef@kfsh.med.sa](mailto:Abdulrhman.abdullateef@kfsh.med.sa) (A. Al Abdullateef), [malhareky@iau.edu.sa](mailto:malhareky@iau.edu.sa) (M.S. Alhareky).

Peer review under responsibility of King Saud University.



Production and hosting by Elsevier

## 1. Introduction

With the developments and advances in the treatment of several bone conditions; ranging from osteoporosis to malignancy of the bone, adverse or side effects/complications of medications, follows the disease. Unexpected bone fracture (Kohli and Siva, 2015), hypocalcemia (Kreutle et al., 2014), and osteonecrosis of the jaw are few examples of these unwanted effects.

Medication Related Osteonecrosis of the Jaw (MRONJ), is a necrotic bone exposure, in the maxillofacial region, that persists for more than two months, with a history of or current use of an anti-resorptive or anti-angiogenic agent and no history of radiation therapy or obvious metastatic lesion to the jaws (Ruggiero et al.,

2014) MRONJ has been reported for more than a decade and has an adverse effect on the patient's quality of life (Pickett, 2006; American Association of Oral and Maxillofacial Surgeon, 2007). Specifically, MRONJ may present with pain, swelling, paresthesia, suppuration, soft tissue ulceration, sinus tract, loosening of teeth<sup>6</sup>, and/or jaw deformity (Khosla et al., 2007; Campisi et al., 2014).

The first case of MRONJ was reported way back in 2003, in a patient using Intra venous (I.V.) bisphosphonate (BP) (Pickett, 2006) Since then, several cases have been published about bisphosphonate-associated osteonecrosis of the jaw (American Association of Oral and Maxillofacial Surgeons 2006). I.V. BP related osteonecrosis of the jaw has been reported up to 27.5% with a mean of 7% (Campisi et al., 2014). The condition which once called as avascular necrosis of the jaw (Pickett, 2006) renamed to bisphosphonate-associated osteonecrosis of the jaw, (Pickett, 2006) when more reports getting published linking BPs to the jaw necrosis. Though majority of these patients received I.V. BP (Campisi et al., 2007) a causal relation is not yet established (Campisi et al., 2007, Koka et al., 2007, Carey and Palomo, 2008, Drake et al., 2008, Russell, 2011, Bramati et al., 2015, Cremers and Papapoulos, 2011, Weiss et al., 2008, Ishtiaq et al., 2015). Further, with the report of osteonecrosis of the jaws in patients using anti-resorptive medications, the term anti-resorptive osteonecrosis of the jaw (ARONJ) was used (Lescaillie et al., 2014, Hellstein, 2011, and Zhang et al., 2016). Anti-angiogenic agent was first reported to be associated with MRONJ without concomitant BP in 2008 (Fusco et al., 2016, Estilo et al., 2008). Similarly, in 2010, Aghaloo et al. (Aghaloo et al., 2010) reported a case of MRONJ that was related to Denosumab, a relatively new anti-resorptive agent. Since then, many cases of Denosumab-related MRONJ has been reported (Aghaloo et al., 2010) though, reported prevalence rate was lesser compared to IV BPs (Aghaloo et al., 2010, Henry et al., 2011, Hanley et al., 2012, Scott, 2014, Zwolak and Dudek, 2013, Fantasia, 2015, Suresh and Abrahamsen, 2015, Khan et al., 2015, Sim et al., 2015). As a consequence, the American Association of Maxillofacial Surgeons (AAOMS) included all of the above mentioned class of medications as potential risk factors for Osteonecrosis of the jaw, expanding the risk factors and utilizing the currently accepted term of Medication-Related Osteonecrosis of the Jaw (MRONJ) (Ruggiero et al., 2014, Fusco et al., 2016).

Culmination of the reports, publications lead to formulations of the first clinical practice guidelines in 2005 by the American Academy of Oral Medicine to educate the health care community and patients in an effort to prevent and manage the condition (Pickett, 2006). In 2007, the AAOMS published updated clinical guidelines that included more detailed staging and broader risk factors (American Association of Oral and Maxillofacial Surgeons Position Paper, 2007).

Despite the need of significant supportive role of physicians and dentists in minimizing MRONJ by following and applying the recommendations that stresses the importance of oral hygiene (Sim et al., 2015), many health professionals including dentists, physicians, and nurses are not aware of the MRONJ as a risk of BPs (El Osta et al., 2015, Al-Mohaya et al., 2011, Yoo et al., 2010, Mah et al., 2015). This may adversely affect clinical outcome among high risk patients.

Numerous studies link MRONJ to infection as a primary risk factor (Katsarelis et al., 2015). It is a proven fact, that by multiple mechanisms, microorganisms could enhance bone destruction as well as facilitate BP release from bone by acid production. This hinders the ability of macrophages to attack the bacteria (Katsarelis et al., 2015). Since periodontal disease is an immunoinflammatory disease initiated by microorganisms, the grave importance of optimum oral hygiene among those patients at risk for MRONJ has to be prioritized (Mirza et al., and Hamadeh et al., 2015).

Patient's co-operation plays a significant role in the prevention of MRONJ. These patients must be educated and made aware of the potential complications (Mueller et al., 2009). A recent study done in Australia found a significant reduction in the incidence of MRONJ cases after having applied preventive measures that included patient education (Sim et al., 2015) in few other studies, it was concluded that, a monitoring program which included a patient education proved to have better MRONJ outcomes and reduced the need for aggressive treatments (La Verde et al., 2008).

There are many cross-sectional surveys assessed the level of knowledge and awareness of patients regarding the risk of anti-resorptive agents (Bauer et al., 2012, Migliorati et al., 2010). There is insufficient information regarding the side effects of BP use, including the severe complication of MRONJ, among the patients and there is a serious need of different methods of educating patients with MRONJ risk (Bauer et al., 2012). Similarly, patients on BP medications may be unfamiliar with the drug and its possible adverse oral side effects (Migliorati et al., 2010). Despite the fact that, drug information resources are widely accessible online or by personal digital assistant devices, patients rely primarily on their physicians for this information. Hence, all the clinical practice guidelines emphasize the preventive measures that begins with patient's awareness initiated by healthcare providers.

Literature review till date on patient awareness about the MRONJ are scarce. Further, there are no reports of studies being done in the middle-east to assess the status of awareness. Thus, this prospective study is undertaken, to determine if any, additional steps are needed to educate the patients, by evaluating their awareness level for risk for MRONJ, a key step in primary prevention. The information gained from this project, will provide a foundation for developing effective patient education materials for use in dental clinics.

To explore and assess the awareness level of MRONJ among the patients, who receive dental services in dental clinics and to understand the possible demographics of MRONJ population at risk.

## 2. Materials and methods (Fig. 1)

### 2.1. Methodology of recruiting participants

This is a prospective interviewer administered, research electronic data capture (REDCap) survey project. REDCap (Paul et al., 2009) is a secure, web-based application designed to support data capture for research studies.

The sample size was calculated by using this formula.

$$\text{Sample size} = \frac{\frac{z^2 \times p(1-p)}{e^2}}{1 + \left(\frac{z^2 \times p(1-p)}{e^2 N}\right)}$$

where, N = is the total number of patients attending hospital, who are taking drug at risk for MRONJ, e = margin of error. Z score is the number of standard deviations in each population is away from the mean.

Thus, the target number for this study was 80 patients and the study duration were 8 months. Potential subjects were informed about the study and asked if they were interested in participating in a survey where they would be asked questions regarding their awareness of MRONJ. A questionnaire including 21 questions (3–5 min completion time) was used by a primary investigator in a private dental room prior to receiving dental services. Protected Health information (PHI) was not collected and the survey results were reported as aggregate data. Patients were provided with a patient information sheet and allowed to ask questions prior to the survey. Participation involved a one-time interview that lasted approximately 3 to 5 min. A waiver of documentation of informed

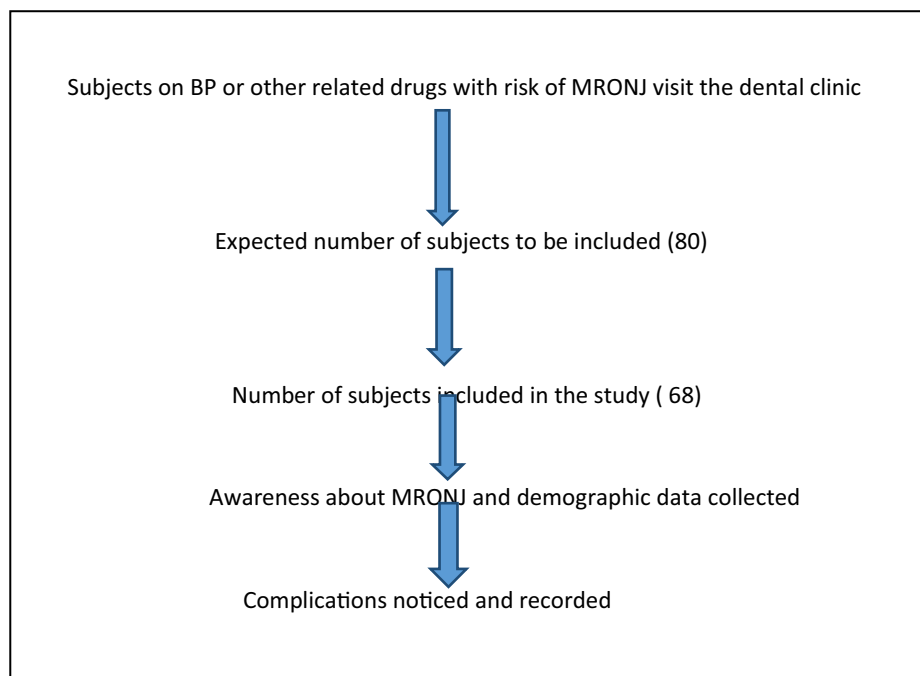


Fig. 1. Flow chart of materials and methods used.

consent was requested and approved. Data was analyzed directly from REDCap as an Excel spreadsheet. Analysis of identified information was completed, and data was maintained on a secure server at King Fahad Specialist Hospital-Dammam.

## 2.2. Questionnaire

Questionnaire was prepared and validated using a standard process. Face validation was done jointly by an expert in the field of the topic and by an expert in question construction. (Here we have taken the help of a community dentist who is expert in conducting survey). The Suggestions given by the expert has been added in improvising the questionnaire. Following which, a pilot study was done among 10 participants and collected data was analyzed. Principal component analysis was done and internal consistency for questionnaire was checked. At the end, by collecting all the information, a final draft of questionnaire was prepared and utilized for the survey.

Questionnaire consisted of demographic data like age, sex and educational background. This was followed by a single question on principal component of awareness about MRONJ. Third part consisted of series of 8 questions pertaining to each drug related with MRONJ and response was noted.

## 2.3. Subject selection

The principal investigator (PI) of this project, prescreened the dental patients for eligibility. All patients who were eligible were approached by the PI to determine voluntary participation.

### 2.3.1. Inclusion criteria

1. 18 years and above.
2. History of/current use of/future use of anti-resorptive (BPor Denosumab), and/or anti-angiogenic agent (Sunitinib or Bevacizumab).
3. Agree to participate in the survey.
4. Capability to answer without aid.

### 2.3.2. Exclusion criteria

1. Any patient who has been recently educated or patient who is enrolled in another study.
2. Does not speak and/or understand the common communicating language. (Arabic).

## 2.4. Statistical analysis

Data has been analyzed using IBM SPSS software. This study focused on descriptive analysis. The mean age and frequency distribution for all categorical variables have been calculated. Comparisons of MRONJ awareness question responses and education level have been done using chi-square test.

## 3. Result

Sixty-eight patients agreed to participate in this study with response rate of 77%. Among this, 50 of them being females. The participants ranged from 20 to 80 years of age. Most of the participants 67.64% (n = 46) were, in the age group of 41–60 years (Table 1). The patients have responded to the study questionnaire in the following manner:

Study population divided according to their education qualification as follows. College degree or above, 42.6% (n = 29); high school diploma 19.1% (n = 13) and less than high school, 38.2% (n = 26) (Table 1).

From the sixty-eight patients studied, only 33.82% (n = 23) patients were aware of osteonecrosis of jaw. Among this, majority of them were females. 66.18% (n = 45) of them were not aware of the condition, which is statistically significant (p value = 0.008). There appears to be a significant co-relation between education level and awareness, where patients with college education were found to be better aware than the high school and below high school patients (p value ≤ 0.001) (Table 1).

Regarding the use of BP, 16.18% (n = 11) were expected to take BP in the future, 51.47% (n = 35) were currently using BP, and

**Table 1**  
Demographical data of participated subjects.

Variables	Responses	Awareness		p-value
		Yes	No	
Age	20–40	2	9	<b>0.008</b>
	41–60	21	25	
	61–81	0	11	
Gender	Male	5	13	<b>0.573</b>
	Female	18	32	
Education Level	Less than high school	7	19	<b>&lt;0.001</b>
	High school	2	11	
	College degree or above	20	9	

17.65% (n = 12) have used it in the past. Similarly, regarding Denosumab, only 1.4% (n = 1) patient reported to have taken it in the past, 7.3% (n = 5) patients were currently taking the medication and 48.52% (n = 33) of them were expected to take in the future. There was no patient who was taking anti-angiogenesis in the study group and 66.17% (n = 45) of them would probably take the medication in future (Table 2)

Among the forty-seven patients who had a history of/currently using BP, 4.25% (n = 2) stated that, they are taking by mouth and 72.34% (n = 34) by infusion and the remaining 23.40% (n = 11) patients by injection. 100% (n = 6) patients who were on Denosumab were taking it by injection route (Table 3). 95.74% (n = 45) have taken BP for cancer and 4.26% (n = 2) patients for osteoporosis. All 6 (100%) patients who were on denosumab are cancer patients (Table 4).

In the present study, only 35.29% (n = 24) subjects (23 on BP medication and 1 on denosumab) received the information about the medication. Patient knowledge of BP was primarily received from one of the following sources: physicians 70.84% (n = 17), 4.17% (n = 1) from nurses, 25% (n = 6) from dentists (Tables 5 and 6).

In the BP medication group, twenty-nine patients did not have any oral side effects 61.70% (n = 29), 10.64% (n = 5) had an exposed bone, 19.15% (n = 9) patients had pain, 4.26% (n = 2) experienced swelling and another, 4.26% (n = 2) subjects have suffered from infection (Table 7). In Denosumab group, 16.67% (n = 1) patients experienced bone exposure and 83.34% (n = 5) of them did not have any unwanted effects.

#### 4. Discussion

In this study, the awareness level and the information source(s) of patients at risk with MRONJ was evaluated. With our knowledge and the literature reviewed till date, this pilot study is the first original study in assessing the awareness of the types of medications with risk for MRONJ in the Middle-East. Furthermore, this study is reported a first look at the correlation between MRONJ awareness and the academic background of the subject studied.

**Table 2**  
History of taking the medication.

Medication	Responses	Awareness		p-value
		Yes	No	
Bisphosphonate	I have taken in the past but not currently	6	6	<b>0.12</b>
	I am currently taking	14	21	
	I have never taken but I expect to take in future	3	8	
Denosumab	I have taken in the past but not currently	1	0	<b>0.246</b>
	I am currently taking	2	3	
	I have never taken but I expect to take in future	13	20	
Antiangiogenics	I have taken in the past but not currently	0	0	<b>0.575</b>
	I am currently taking	0	0	
	I have never taken but I expect to take in future	13	24	

Data was collected from sixty-eight patients over the course of 8 months. The small sample size of the present study is due to the narrow inclusion criteria alongside the difficulty of finding participants willing to join the study. The reasons for some patients' refusal to participate in the study were, questions of anonymity due to previous negative research experience, limited time for dental visits. Other reason is that the potential participants did not feel the need to disclose about their experience.

The study population comprised of 50 females and 18 males. Although a significant correlation between gender and MRONJ awareness was not found, women were found to be more aware of MRONJ. Studies revealed that women tend to search for additional drug information, specifically side effects, more so than the men (Ziegler et al., 2001).

The age of patients who participated in this study was ranged from 21 to 80 years. No significant relation between age and MRONJ awareness was found, however, patients under 60 years of age were likely to be unaware of MRONJ. This is explained by Ziegler DK et al., who stated that, younger individuals are more likely not to request for information on the adverse effects of drugs (Ziegler et al., 2001) Life experience of older individuals, may also be the possible reason for better awareness about the medication among them.

One of the crucial risk factors of MRONJ is patient knowledge and awareness. In our study, we observed that 66.12% of the patients were unaware of MRONJ. Likewise, study conducted by Bauer SJ et al., revealed that, among 56 study subjects, 76% of them were not aware of BP related MRONJ (Bauer et al., 2012). Another study by Singh J. et al., also found out that 86.7% of the individuals interviewed answered incorrectly to the question "which side effects may occur?" and 94.3% answered incorrectly to the question "how to recognize them?" in their survey (Singh et al., 2013).

In this study, eleven patients were aware that, they would be starting the BP medication relatively soon; however, some of them were unaware of MRONJ. Furthermore, nine patients knew nothing about BP, while in reality, some of them were currently using or about to start BP. Generally, one possible reason for the patients' lack of MRONJ awareness or even the type of medication could

**Table 3**  
Mode of delivery of the medication.

Medication	Responses	Awareness		p-value
		Yes	No	
Bisphosphonate	By injection	4	7	<b>0.38</b>
	By infusion	16	18	
	By mouth	0	2	
Denosumab	By injection	3	3	
	By infusion	0	0	
	By mouth	0	0	

**Table 4**  
Disease for medication taken.

Medication	Responses	Awareness		p-value
		Yes	No	
Bisphosphonate	Cancer	19	26	<b>0.657</b>
	Osteoporosis	1	1	
Denosumab	Cancer	3	3	–
	Osteoporosis	0	0	

**Table 5**  
Potential side effects information was given before administration of medication.

Medication	Responses	Awareness		p-value
		Yes	No	
Bisphosphonate	Yes	12	11	0.156
	No	8	16	
Denosumab	Yes	1	0	0.5
	No	2	3	

**Table 6**  
Source of unwanted effects of medication received.

Medication	Responses	Awareness		p-value
		Yes	No	
Bisphosphonate	Physician	9	8	<b>0.542</b>
	Nurse	0	1	
	Dentist	3	3	

**Table 7**  
Oral Side effect experienced after the medication.

Medication	Responses	Awareness		p-value
		Yes	No	
Bisphosphonate	Pain	1	8	<b>0.012</b>
	Swelling	0	2	
	Exposed bone	5	0	
	Infection	0	2	
	None	14	15	
Denosumab	Pain	1	0	<b>0.223</b>
	Exposed bone	1	0	
	None	2	3	

be the result of uninformed dentists or physicians. Many awareness studies among the physicians and dentists have revealed that, less acquaintance with the medications and have suggested modification in the curriculum regarding the medication related to MRONJ (Lopez-Jornet et al., 2010 Alhussain et al., 2015 El Osta et al., 2015, Al-Mohaya et al., 2011, Yoo et al., 2010). In fact, today's dentists are expected to be better aware of BP, since, it has been in use for decades. It is expected that lesser percentage of health professionals are aware of Denosumab-related MRONJ, because, Denosumab has been introduced only a few years ago. Possible other reason for unawareness, is the lack of written communication

(Morris, 1979, Savaş and Evcik, 2001). Our dental department in hospital is yet to provide the patients with the written instructions on MRONJ risk, but it is one of our future study goals and a step in preventive strategic plan.

Despite majority being unaware, those who were aware of MRONJ in this study were college graduates or individuals with good academic background. This observation is in comparable to the findings of Papanikolaou, PN et al., where they found out that, 67% of patients who were aware about the side effect of medications have completed university education (Papanikolaou and Ioannidis, 2003). However, Ziegler DK. results indicated that highly

educated individuals are less informed about drug side effects (Ziegler et al., 2001). One has to understand that, examining individual's desire for information is something different from examining their knowledge about the facts.

The source of patient information about the potential side effects of BP in this survey is mostly obtained from physicians. In contrast, Bauer JS et al., reported drug package inserts as the main source of drug information (Bauer et al., 2012). Interestingly, six of our subjects reported dentist / dental specialist as a source of information. It appears that though the unwanted effects are available in the drug package, it is the duty of the physician and/or the dentist to reinforce the same for the better compliance and lesser complications.

Among BP users, majority of them have experienced BP side effects, mainly, with exposed bone and pain. Based on a recent systematic review, MRONJ prevalence among oncology patients who received I.V. BP could reach up to 0.2% (Khan et al., 2015). Those who reported the side effects (pain and bone exposure) are probably aware of BP-related MRONJ. As claimed by Papanikolaou, PN et al, 76% of the patients experiencing at least one adverse event are aware of the side effects of their medication (Papanikolaou and Ioannidis, 2003). Two patients reported intra-oral swelling, however, no literature was found which associated BP with the oral tissue swelling. Thereby, we assume that oral tissue swelling reported in the present study may be due to other medications or mucosal trauma or infection or misinterpretation by the patient.

Low awareness about the unwanted effect of the Denosumab in the present study may be because, it is a relatively new medication unlike BP (Hanley et al., 2012). In the present study, only six patients had the medication or currently taking this medication. All the six users received their drug information from a physician prior to the drug course. One of the six patients noted bone exposure as a side effect. In fact, MRONJ in Denosumab users is considered rare. Though number of patients taking this medication is very small, there is possibility of the exposure to this drug in future among these patients. However due to small sample size of users of this medication in the present study, a definitive conclusion cannot be drawn. Aliya AK et al., mentioned that the prevalence of MRONJ among oncology patient who received Denosumab would reach up to 2.3% per 100,000 patients (Suresh and Abrahamsen, 2015). To the best of our knowledge, this is the first study that tests the patients' awareness of Denosumab.

Concerning the last drug of this survey, anti-angiogenics, none of the patient were taking or have a history of taking antiangiogenics. Our hospital protocol requires dental screening of any patient on a course to receive anti-resorptives rather than antiangiogenics, because all current evidence relates anti-resorptives to MRONJ more than any other drug class. It is also to be noted at this stage that, MRONJ cases associated with isolated antiangiogenics are considered to be rare. As stated by the Italian Safety Drug Agency, only 16 cases of Bevacizumab, 20 of Sunitinib, and 1 of sorafenib have been recorded to be related to MRONJ in 2015 over a span of 10 years (Fusco et al., 2016).

Out of the fifty-three who have reported to be using either of the medication, only twenty-nine received a dental examination before taking their medications and twenty-four received a dental examination after starting the medications. We consider a dental visit, for those who are going to receive BP or Denosumab, as a pre-medication clearance in our hospital. This allows them to take all MRONJ prevention measures and precautions. The dentist, during the visit will explain the importance of oral hygiene and educate the patient about the main MRONJ risk factors and symptoms. This will promote the importance of optimum oral health as well as the importance of follow-up in future. Indeed, every patient should know his/her medication plan and all information about possible adverse effects. Many different sources of

literature emphasize the preventative measures in order to avoid MRONJ and nearly all these sources include patient education as an essential step in the process (Vandone et al., 2012, Fraser and Adachi, 2009, Yamazaki et al., and Ascani et al., 2014). We believe that the patient education should not only be limited to oral hygiene instructions. MRONJ risk factors and MRONJ symptoms are also to be an integral aspect of the information, one must convey during patient education. Dental visits prior to taking anti-resorptives and/or antiangiogenics is highly recommended. Such visits have been shown to reduce MRONJ incidence significantly and expand the medication's benefit to the patient, especially if oral health measures are taken into consideration (Ruggiero et al., 2014). Sim et al., concluded in their study that MRONJ incidence was significantly less among oncology patients after dental preventive measures were observed, including educating the patient, before starting anti-resorptive therapy (Sim et al., 2015). Similarly, another study showed that the implementing preventive measures for multiple myeloma patients decreased the incidence of BP-related MRONJ by three-fold (Dimopoulos et al., 2009). Likewise, Ripamonti et al., reported a drop in the MRONJ incidence from 3.2% to 1.3% after application of pre-post preventive measures (Ripamonti et al., 2009). Repeated or follow-up dental visits, after starting anti-resorptives or antiangiogenics, are advised regardless of MRONJ diagnosis. Current AAOMS guidelines recommend close monitoring, not more than three months apart, to those with established MRONJ (Ruggiero et al., 2014).

We believe that the strength of our study is that, it is the first of its kind, that is considered all the MRONJ risk medications. Furthermore, majority of the study subjects were oncology patients, who categorically have a higher MRONJ risk. Finally, this study is the first reported study as per our knowledge reported in examining individuals planning to receive antiresorptive medication in the future, based on the treatment plans involved.

Though this study is unique and the first of its kind in the Middle East, and with results drawn which are useful to implement the preventive measures, the results are to be viewed with the caution. Small sample size, which is suitable for a pilot study. To conclude categorically, a larger sample size is desirable. Nevertheless, the outcome of this study definitely helps in initiating the educative aspect to increase the awareness among these patients. Since number of females were more in the study, a logic conclusion based on gender basis is difficult to interpret and implement, which warrants further continuation of study in different centers and with the inclusion of a large data base. Further, this would add a greater value to test the awareness level after the patient education session to compare their response to the baseline

Thus to improve upon and to conduct the future studies, the following recommendations are proposed. Aside from expanding the sample size, adding a socio-economic status as a variable, including new medications that have MRONJ risk, such as inhibitors of mammalian target of rapamycin (mTOR inhibitors)<sup>20</sup> and recording the number of individuals that refused to participate and noting their reasons, will add the greater value to this study.

## 5. Conclusion

This study shows that awareness of medication-related osteonecrosis of the jaw is poor amongst patients who are at risk of MRONJ. An effort to educate users of BP, Denosumab, Bevacizumab and Sunitinib about their medications and their potential side effects as well as including preventative measures must be added in the strategic treatment plan. Health care providers, especially dentists, must be aware of MRONJ and its risk factors. In addition, they should know the significance of their role in educating and preventing the condition by following their health practice

guidelines as well as applying the necessary preventive measures. A check list to be provided to the dentist and physicians when treating such patients to ensure that, information to the patients have been provided without failure. Written communication to the patient and patient's accompanist to be developed and made available. At each visit, dentists and physicians need to assure that, these written communications are understood by the patients and proper precautions are being taken by them to avoid the complications.

## References

- Ascani, G., Campisi, G., Junquera, G., et al., 2014. Current controversies in classification, management, and prevention of bisphosphonate-related osteonecrosis of the jaw. *Int. J. Dentistry* 565743. <https://doi.org/10.1155/2014/565743>.
- Aghaloo, T.L., Felsenfeld, A.L., Tetradis, S., 2010. Osteonecrosis of the jaw in a patient on Denosumab. *J. Oral Maxillofac. Surg.* 68, 959–963. <http://doi:10.1016/j.joms.2009.10.010>.
- Alhussain, A., Peel, S., Dempster, L., et al., 2015. Knowledge, practices, and opinions of Ontario dentists when treating patients receiving bisphosphonates. *J. Oral Maxillofac. Surg.* 73 (6), 1095–1105. <https://doi.org/10.1016/j.joms.2014.12.040>.
- Al-Mohaya, M.A., Al-Khashan, H.I., Mishriky, A.M., et al., 2011. Physicians' awareness of bisphosphonates-related osteonecrosis of the jaw. *Saudi Med. J.* 32, 830–835. PMID: 21858393.
- American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate Related Osteonecrosis of the Jaws, 2007. *J. Oral Maxillofac. Surg.* 3, 65369–376. <http://doi:10.1016/j.joms.2006.11.003>.
- Bauer, J.S., Beck, N., Kiefer, J., Stockmann, P., et al., 2012. Awareness and education of patients receiving bisphosphonates. *J. Craniomaxillofac. Surg.* 40, 277–282. <https://doi.org/10.1016/j.jcms.2011.04.011>.
- Bramati, A., Girelli, S., Farina, G., et al., 2015. Prospective, mono-institutional study of the impact of a systematic prevention program on incidence and outcome of osteonecrosis of the jaw in patients treated with bisphosphonates for bone metastases. *J. Bone Miner. Metab.* 33, 119–124. <https://doi.org/10.1007/s00774-014-0566-x>.
- Campisi, G., Fedele, S., Fusco, V., Pizzo, G., Di Fede, O., Bedogni, A., 2014. Epidemiology, clinical manifestations, risk reduction and treatment strategies of jaw osteonecrosis in cancer patients exposed to anti-resorptive agents. *Future Oncol.* 10, 257–275. <http://doi:10.2217/fon.13.211>.
- Campisi, G., Di Fede, O., Musciotto, A., et al., 2007. Bisphosphonate-related osteonecrosis of the jaw (BRONJ): dental management designs and issues in diagnosis. *Ann. Oncol.* 18, 168–172. <http://doi:10.1093/annonc/mdm250>.
- Carey, J.J., Palomo, L., 2008. Bisphosphonates and osteonecrosis of the jaw: innocent association or significant risk? *Cleve. Clin. J. Med.* 75, 871–879. <http://doi:10.3949/ccjm.75a.08014>.
- Cremers, S., Papapoulos, S., 2011. Pharmacology of bisphosphonates. *Bone* 49, 42–49. <https://doi.org/10.1016/j.bone.2011.01.014>.
- Dimopoulos, M.A., Kastritis, E., Bama, C., et al., 2009. Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. *Ann. Oncol.* 20, 117–120. <http://doi:10.1093/annonc/mdn554>.
- Drake, M.T., Clarke, B.L., Khosla, S., 2008. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin. Proc.* 83 (9), 1032–1045. <http://doi:10.4065/83.9.1032>.
- El Osta, L., El Osta, B., Lakiss, S., et al., 2015. Bisphosphonate-related osteonecrosis of the jaw: awareness and level of knowledge of Lebanese physicians. *Support Care Cancer.* 23, 2825–2831. <https://doi.org/10.1007/s00520-015-2649-1>.
- Estilo, C.L., Fournier, M., Farooki, A., et al., 2008. Osteonecrosis of the jaw related to bevacizumab. *J. Clin. Oncol.* 26, 4037–4038. <https://doi.org/10.1200/JCO.2007>.
- Fantasia, J.E., 2015. The role of antiangiogenic therapy in the development of osteonecrosis of the jaw. *Oral Maxillofac. Surg. Clin. North Am.* 27, 547–553. <https://doi.org/10.1016/j.coms.2015.06.004>.
- Fraser, L.A., Adachi, J.D., 2009. Glucocorticoid-induced osteoporosis: treatment update and review. *Ther. Adv. Musculoskelet.* 1, 71–85. <http://doi:10.1177/1759720X09343729>.
- Fusco, V., Santini, D., Armento, G., Tonini, G., et al., 2016. Campisi G. Osteonecrosis of jaw beyond antiresorptive (bone-targeted) agents: new horizons in oncology. *Expert Opin Drug Saf.* 3, 1–11. <http://doi:10.1080/14740338.2016.1177021>.
- Hanley, D.A., Adachi, J.D., Bell, A., Brown, V., 2012. Denosumab: mechanism of action and clinical outcomes. *Int. J. Clin. Pract.* 66, 1139–1146. <https://doi.org/10.1111/ijcp.12022>.
- Hamadeh, I.S., Ngwa, B.A., Gong, Y., 2015. Drug induced osteonecrosis of the jaw. *Cancer Treat. Rev.* 41, 455–464. <https://doi.org/10.1016/j.ctrv.2015.04.007>.
- Hellstein, J.W., Adler, R.A., Edwards, B., et al., 2011. Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: Executive summary of recommendations from the American Dental Association Council on Scientific Affairs. *J. Am. Dent. Assoc.* 111/ 2011; 142(11):1243–1251. <http://doi:10.14219/jada.archive.2011.0108>.
- Henry, D.H., Costa, L., Goldwasser, F., et al., 2011. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J. Clin. Oncol.* 29, 1125–1132. <https://doi.org/10.1200/JCO.2010.31.3304>.
- Ishtiaq, S., Edwards, S., Sankaralingam, A., et al., 2015. The effect of nitrogen containing bisphosphonates, zoledronate and alendronate, on the production of pro-angiogenic factors by osteoblastic cells. *Cytokine* 71, 154–160. <https://doi.org/10.1016/j.cyto.2014.10.025>.
- Katsarelis, H., Shah, N.P., Dhariwal, D.K., et al., 2015. Infection and medication-related osteonecrosis of the jaw. *J. Dent. Res.* 94, 534–539. [10.1177/0022034515572021](https://doi.org/10.1177/0022034515572021).
- Khan, A.A., Morrison, A., Hanley, D.A., et al., 2015. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J. Bone Miner. Res.* 30, 3–23. <https://doi.org/10.1002/jbmr.2405>.
- Khosla, S., Burr, D., Cauley, J., et al., 2007. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J. Bone Miner. Res.* 22, 1479–1491. <https://doi.org/10.1359/jbmr.07070nj>.
- Koka, S., Clarke, B.L., Amin, S., Gertz, M., Ruggiero, S.L., 2007. Oral bisphosphonate therapy and osteonecrosis of the jaw: what to tell the concerned patient. *Int. J. Prosthodont.* 20, 115.
- Kohli, R., Siva, C., 2015. Atypical femoral fractures can happen even with short duration bisphosphonate treatment. *Conn. Med.* 79, 419–422. PMID: 26411180.
- Kreutle, V., Blum, C., Meier, C., et al., 2014. Bisphosphonate induced hypocalcemia - report of six cases and review of the literature. *Swiss Med. Wkly.* 144, w13979.
- La Verde, N., Bareggi, C., Garassino, M., et al., 2008. Osteonecrosis of the jaw (ONJ) in cancer patients treated with Bisphosphonates: how the knowledge of a phenomenon can change its evolution. *Support. Care Cancer.* 16, 1311–1315 (23) <http://doi:10.1007/s00520-008-0484-3>.
- Lescaillie, G., Coudert, A.E., Baaroun, V., et al., 2014. Clinical study evaluating the effect of bevacizumab on the severity of zoledronic acid-related osteonecrosis of the jaw in cancer patients. *Bone* 58, 103–107. <https://doi.org/10.1016/j.bone.2013.10.002>.
- Lopez-Jornet, P., Camacho-Alonso, F., Molina-Minano, F., et al., 2010. Bisphosphonate-associated osteonecrosis of the jaw. Knowledge and attitudes of dentists and dental students: a preliminary study. *J. Eval. Clin. Pract.* 16, 878–882. <https://doi.org/10.1111/j.1365-2753.2009.01203.x>.
- Mah, Y.J., Kang, G.Y., Kim, S.J., 2015. Survey on awareness and perceptions of bisphosphonate-related osteonecrosis of the jaw in dental hygienists in Seoul. *Int. J. Dent. Hyg.* 13, 222–227. [10.1111/ijdh.12122](http://doi:10.1111/ijdh.12122).
- Migliorati, C.A., Mattos, K., Palazzolo, M.J., 2010. How patients' lack of knowledge about oral bisphosphonates can interfere with medical and dental care. *J. Am. Dent. Assoc.* 141, 562–566. <https://doi.org/10.14219/jada.archive.2010.0229>.
- Mirza, F., Canalis, E., Secondary osteoporosis: pathophysiology and management. *European Journal of Endocrinology.* 173, R131–R151. <http://doi:10.1530/EJE-15-0118>.
- Morris, L.A., Halperin, J.A., 1979. Effects of written drug information on patient knowledge and compliance: a literature review. *Am. J. Public Health.* 69, 47–52. <https://doi.org/10.2105/ajph.69.1.47>.
- Mueller, E.A., Kirch, W., 2009. Risks associated with drug therapy. What do patients need to know? What can they do?. *Med. Klin. (Munich).* 104, 846–850. <https://doi.org/10.1007/s00063-009-1181-9>.
- Papanikolaou, P.N., Ioannidis, J.P., 2003. Awareness of the side effects of possessed medications in a community setting. *Eur. J. Clin. Pharmacol.* 58, 821–827. <https://doi.org/10.1007/s003-0570-x>.
- Paul, A., Harris, R.T., Robert, T., et al., 2009. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J. Biomed. Inform.* 42 (377–381). <https://doi.org/10.1016/j.jbi.2008.08.010>.
- Pickett, F.A., 2006. Bisphosphonate-associated osteonecrosis of the jaw: a literature review and clinical practice guidelines. *J. Dent. Hyg.* 80, 10–10. PMID: 16953991.
- Ripamonti, C.I., Maniezzo, M., Campa, T., et al., 2009. Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumour patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milan. *Ann. Oncol.* Jan 20, 137–145. <http://doi:10.1093/annonc/mdn526>.
- Ruggiero, S.L., Dodson, T.B., Fantasia, J., et al., 2014. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw - update. *J. Oral Maxillofac. Surg.* 72, 1938–1956. <https://doi.org/10.1016/j.joms.2014.04.031>.
- Russell, R. Graham G., 2011. Bisphosphonates: The first 40 years. *Bone* 49 (1), 2–19. <https://doi.org/10.1016/j.bone.2011.04.022>.
- Savas, Serpil, Evcik, Deniz, 2001. Do undereducated patients read and understand written education materials?. *Scand. J. Rheumatol.* 30 (2), 99–102. <https://doi.org/10.1080/03009740151095385>.
- Scott, L.J., 2014. Denosumab: a review of its use in postmenopausal women with osteoporosis. *Drugs Aging* 31 (555–576). <https://doi.org/10.1007/s40266-014-0191-3>.
- Sim, I.W., Sanders, K.M., Borromeo, G.L., et al., 2015. Declining incidence of medication-related osteonecrosis of the jaw in patients with cancer. *J. Clin. Endocrinol. Metab.* 100, 3887–3893. <https://doi.org/10.1210/jc.2015-1794>.
- Singh, J., Singh, N., Kumar, R., et al., 2013. Awareness about prescribed drugs among patients attending Out-patient departments. *Int. J. Appl. Basic Med. Res.* 3, 48–51. <https://doi.org/10.4103/2229-516X.112240>.

- Suresh, E., Abrahamsen, B., 2015. Denosumab: a novel antiresorptive drug for osteoporosis. *Cleve. Clin. J. Med.* 82,105–114. <https://doi.org/10.3949/cjcm.82a.13173>.
- Vandone, A.M., Donadio, M., Mozzati, M., Ardine, M., Polimeni, M.A., Beatrice, S., Ciuffreda, L., Scoletta, M., 2012. Impact of dental care in the prevention of bisphosphonate-associated osteonecrosis of the jaw: a single-center clinical experience. *Ann. Oncol.* 23 (1), 193–200. <https://doi.org/10.1093/annonc/mdr039>.
- Weiss, H.M., Pfaar, U., Schweitzer, A., Wiegand, H., Skerjanec, A., Schran, H., 2008. Bio distribution and plasma protein binding of zoledronic acid. *Drug Metab. Dispos.* 36, 2043–2049. <https://doi.org/10.1124/dmd.108.021071>.
- Yamazaki, T., Takahashi, K., Bessho, K., Recent clinical evidence in bisphosphonate-related osteomyelitis of the jaw: focus on risk, prevention and treatment. *Rev. Recent Clin. Trials.* 9, 37–52. <http://doi:10.2174/1574887109666140423120614>.
- Yoo, J.Y., Park, Y.D., Kwon, Y.D., et al., 2010. Survey of Korean dentists on the awareness on bisphosphonate-related osteonecrosis of the jaws. *J. Investig. Clin. Dent.* 1, 90–95. <http://doi:10.1111/j.2041-1626.2010.00024.x>.
- Zhang, Xiaoyan, Hamadeh, Issam S, Song, Shuang, Katz, Joseph, Moreb, Jan S, Langae, Taimour Y, Lesko, Lawrence J, Gong, Yan, 2016. Osteonecrosis of the jaw in the united states food and drug administration's adverse event reporting system (FAERS): DRUG INDUCED ONJ AND FAERS DATABASE. *J. Bone Miner. Res.* 31 (2), 336–340. <https://doi.org/10.1002/jbmr.2693>.
- Ziegler, D.K., Mosier, M.C., Buenaver, M., et al., 2001. How much information about adverse effects of medication do patients want from physicians?. *Arch. Intern. Med.* 161,706–713 [10.1001/archinte.161.5.706](https://doi.org/10.1001/archinte.161.5.706).
- Zwolak, P., Dudek, A.Z., 2013. Antineoplastic activity of zoledronic acid and denosumab. *Anticancer Res.* 33, 2981–2988. PMID: 23898050.