

Knowledge and clinical behavior on antiresorptive medications and osteonecrosis of the jaws: a cross-sectional study

Conhecimento e conduta clínica sobre medicamentos anti-reabsortivos e osteonecrose dos maxilares: um estudo transversal

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ABSTRACT

Objective: This present study assessed the knowledge and clinical behaviors of dentists on antiresorptive medications (AM) and osteonecrosis of the jaws (ONJ). **Methods:** A cross-sectional study was performed by a questionnaire applied to a sample of 101 dentists. It inquired about general information, knowledge on AM and ONJ, behaviors regarding clinical cases of patients, and knowledge acquisition sources. Kappa coefficient (κ) checked the questionnaire's reliability. Descriptive statistics were computed, Fisher's test assessed the association between behaviors and knowledge. Logistic regression analysis to estimate propensity score. Statistical significance was set at $p \leq 0.05$. **Results:** The reliability showed good agreement ($\kappa = 0.8$). 59% of the dentists reporting to know AM, 83% believing it is important to know whether patients took AM during anamnesis and 53% indicating that they knew that ONJ was a side effect of AM. However, 5% of the dentists informed that they could fully recognize brand name of AM, and that 50% would not perform any dental invasive treatment, with 73% acquiring knowledge on AM and ONJ from scientific articles. **Conclusion:** dentists recognized AM, but they would not be comfortable treating patients who had taken AM or developed ONJ. Educational efforts might be made to promote the knowledge of dentists.

Keywords: Knowledge. Health behavior. Bisphosphonate. Antiresorptive drugs. Osteonecrosis of the jaw.

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RESUMO

Objetivo: Avaliar o conhecimento e conduta clínica de dentistas sobre medicamentos anti-reabsortivos (AM) e osteonecrose dos maxilares (ONJ). **Métodos:** um estudo transversal foi realizado por meio de um questionário aplicado a uma amostra de 101 dentistas. Este instrumento questionou sobre informações gerais, conhecimento sobre AM e ONJ, condutas em relação a casos clínicos de pacientes e fontes de aquisição de conhecimento. A viabilidade do questionário foi verificada pelo coeficiente Kappa (κ). Análises descritivas foram calculadas, teste exato de Fisher avaliou a associação entre conhecimento e condutas. Análises de regressão logística estimaram escores de propensão. Nível de significância estatística foi de $p \leq 0.05$. **Resultados:** a viabilidade demonstrou boa concordância ($\kappa = 0.8$). 59% dos dentistas relataram conhecer AM, 83% afirmaram que acreditam ser importante saber se o paciente utilizou AM durante a anamnese e 53% indicaram que sabiam que osteonecrose dos maxilares era um efeito colateral dos medicamentos anti-reabsortivos. No entanto, 5% dos dentistas informaram que poderiam reconhecer completamente os medicamentos anti-reabsortivos, 50% dos dentistas não realizariam nenhum tratamento dental invasivo, 73% adquiriram conhecimento sobre medicamentos anti-reabsortivos e osteonecrose dos maxilares através de artigos científicos. **Conclusão:** dentistas reconheceram AM, mas eles não se sentiriam confortáveis em tratar pacientes que tomaram medicamentos anti-reabsortivos ou desenvolveram osteonecrose dos maxilares. Esforços educacionais poderiam ser realizados para promoverem o conhecimento dos dentistas.

Termos de indexação: Conhecimento. Conduta. Bisfosfonatos. Medicamentos anti-reabsortivos. Osteonecrose dos maxilares.

INTRODUCTION

Synthetic drugs for inhibition of osteoclastic action were developed 20 years ago in order to decrease bone resorption [1,2]. Initially, those medications were called bisphosphonates (BP) and became effective in preventing and treating bone metabolic diseases (i.e. osteoporosis, bone metastatic neoplasm, Paget's disease, multiple myeloma) [3-5]. Despite the efficacy of the treatments used, Marx reported a series of 36 cases of side effects related to the use of these medications, which were termed as osteonecrosis of jaws (ONJ) [6]. ONJ consists of one or more areas of exposure in the maxilla or mandible where there was no repair within eight weeks, affecting patients who undergo or underwent treatments with BP [7,8].

Later, there were other case reports of ONJ related to non-bisphosphonate medications. Malan et al. [9], Pichardo et al. [10] and Pova et al. [11] described cases of ONJ in patients treated with denosumab (i.e. anti-resorptive drug) to prevent bone metastasis in prostatic neoplasms. Based on the reports on BP-related ONJ, the American Association of Oral and Maxillofacial Surgeons (AAOMS) recommended that the term "bisphosphonate-related osteonecrosis of the jaws" (BRONJ) should be changed to "medication-related osteonecrosis of the jaws" (MRONJ) because there were an increasing number of cases involving other drugs rather than BP [12].

In 2014, Rugiero et al. published an updated position paper from the AAOMS on MRONJ, which enabled the dissemination of scientific evidence-based

guidelines [12]. This allowed the healthcare professionals to improve their knowledge, thus suggesting changes in dental diagnostic practices and providing guidelines on the recognition of risk factors and prevention [13]. However, it is questionable whether dentists would have knowledge on antiresorptive medications (AM) and ONJ.

With the objective to assess the awareness and knowledge of dentists, Yoo et al. and Lima et al. conducted cross-sectional studies and found that dentists had no adequate knowledge on BRONJ. The authors showed that changes in educational patterns are needed to allow clinical practice to be supported by scientific evidence in order to widen knowledge and mainly to assist prevention of ONJ [3,14]. Alhussain et al. assessed the knowledge of dentists and found that 60% showed a good level of knowledge on BP as they considered ONJ as a side effect, although they opted for referring the BP-treated patients. The authors concluded that although dentists demonstrated a good knowledge, the majority did not feel comfortable treating patients with ONJ [15].

Despite the guidelines produced by the AAOMS categorizing the patients according to developmental risk factors, clinical stages and recommended treatment of ONJ [7,12], dentists usually refuse to treat patients who take or took AM [15]. Some studies assessed the knowledge of oral surgeons on BP and BRONJ. However, they did not outline behaviors based on the adherence or non-adherence of oral surgeons to the AAOMS position paper [12], thus not assessing knowledge more broadly. Therefore, the objective of this study was to assess the knowledge and clinical behavior of dentists on AM and ONJ.

METHODS

The cross-sectional study was approved by the Research Ethics Committee of the Federal University of Juiz de Fora and was carried out to comply with ethical principles and the Declaration of Helsinki. Our study was conducted in the city of Juiz de Fora, State of Minas Gerais, from June 2017 to January 2018. A self-applicable questionnaire was formulated based on the AAOMS updated position paper [12] and on the adapted questionnaire used by Alhussain et al. [15]. Prior to data collection, the questionnaire was applied to two oral-maxillofacial surgeons for calibration in order to provide clarity and reliability to the collected data. Next, the questionnaires were applied to 101 dentists who signed a free informed consent form. The questionnaire structure used is shown in figure 1.

As inclusion criteria, all dentists have been attending post-graduate courses (such as Orthodontic, Endodontic, Dental Implantology). They were approached during their clinical activities at the institutes of Juiz de Fora and asked to answer the survey instrument without acquiring any information during its application. Dentists not enrolled in the aforementioned post-graduate courses and not accepting to take part in the study were the exclusion criteria. No gift or remuneration was offered to them.

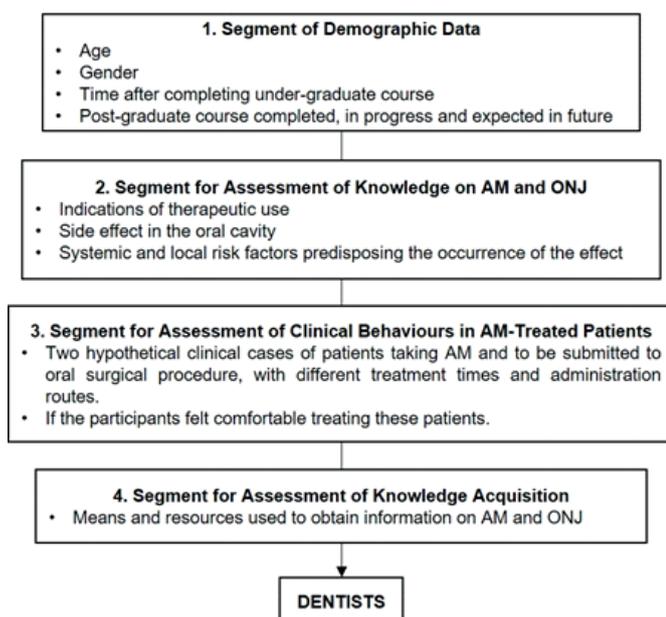


Figure 1. Scheme of the segments addressed in the questionnaire for dentists.

Statistical analysis

Statistical analysis was performed by using the R Core Team software, version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). The questionnaire was calibrated by using Cohen’s kappa coefficient (κ) for obtaining inter-rater reliability between both oral-maxillofacial surgeons.

The answers of the dentists were transformed into binary categorical variables (i.e. multiple and numerical categories), which were submitted to descriptive analysis for estimation of proportion with respective 95-percent confidence intervals and normal distributions.

In order to evaluate the hypothesis of independence or absence of association between clinical behaviour and the answers given, Fisher’s exact test was used at nominal level of $\alpha = 0.05$ and significance level of $P = 0.05$ as well.

Logistic regression analysis was used to estimate the propensity score for questions related to the knowledge on AM and ONJ (dependent variables) as well as to assume a given association value with other answers (explicative variable). Those answers considered as explicative and dependent variables were submitted to regression models, with estimated predictive value or propensity score (F value) being found and test z providing P value at significant level of 0.05.

RESULTS

The Cohen’s kappa coefficient was considered excellent ($\kappa = 0.8$), demonstrating the reliability of the questionnaire regarding the agreement between the raters (i.e. oral surgeons).

The sample of 101 dentists had a variable distribution (i.e. abnormal) regarding the age groups, with minimum and maximum ages of 21 and 66 years old, respectively, for a median value of 24 years old.

The majority of dentists were female (73.27%) and with regard to their professional formation, 57% completed undergraduate courses at public higher education institutions, 72.25% completed undergraduate courses within 5 years, 66.34% did not complete any post-graduate dental course, 55.45% were post-graduate students and 58.42% reported no intention of having other post-graduate course in the future. Table 1 shows the descriptive results of the above-mentioned data.

Table 1. Distribution of the descriptive analysis results of the dentists regarding gender and dental education.

Variable	Category	n (%)
Gender	Male	27 (26.73)
	Female	74 (73.27)
Dental school*	Public	57 (57)
	Private	43 (43)
Time after completing undergraduate course	Until 5 years	76 (75.25)
	5 to 10 years	6 (5.94)
	10 to 20 years	13 (12.87)
	More than 20 years	6 (5.94)
Post-graduate course completed	Yes	34 (33.66)
	No	67 (66.34)
Post-graduate course in progress	Yes	56 (55.45)
	No	45 (44.55)
Post-graduate course in the future	Yes	42 (41.58)
	No	59 (58.42)

Note: *Missing data: 01 participant did not answer.

In Table 2, it is possible to demonstrate that the answers given by dentists regarding some questions had different estimated proportions at a confidence interval of 95%. It was found that the majority of the dentists knew about AM (59.18%) as they believed it is important to know whether the patient takes or took these medications (83%). For the answers to question Q3b, which depended on the results of Q3a, it was found that most of the dentists reported to know AM partially or fully, they also identified at least one brand name of AM if their patient had been using these medications (table 2). The proportion of dentists recognizing at most four risk factors correctly was higher than those recognizing at least five local risk factors (i.e. oral cavity).

Table 3 shows the estimated proportions for the dentist's behavior in hypothetical clinical cases of patients treated with AM at different moments. The results indicated that the proportion of dentists who would refer the patient was higher than those who would perform surgical procedures and, consequently, than those who would request discontinuation of the treatment with AM prior to surgical procedures, resuming the drug treatment after three months. In addition, 72% of the dentists reported feeling uncomfortable when treating patients who developed ONJ.

Table 4 shows the results of the answers on how dentists acquire their knowledge and which resources

they use to keep up with general dentistry, particularly within the context of AM and ONJ. It was found that the proportion of dentists who read scientific articles to stay informed was higher compared to those who use Internet research or attend continuing education courses for the same objective (respectively, 73%, 52% and 63%). The highest proportion of dentists had learned on AM and ONJ during their undergraduate courses (49%).

In Table 5, one can observe statistically significant results ($P < 0.05$) demonstrating that the hypothesis of independence was rejected due to the evidence of association between the dentists' behavior and their answers to questions Q11 and Q12 regarding clinical cases. Most of the participants reported that, regardless of whether they acquired their knowledge on AM and ONJ during post-graduate or undergraduate courses, or even never, they would refer the patient rather than performing surgical procedures (e.g. tooth extraction, dental implant). Dentists who reported on the importance of knowing whether the patient takes or took AM during anamnesis also referred their patients rather than performing any oral cavity surgery.

Of the results found by using logistic regression analysis, only the statistically significant ones were shown ($P < 0.05$). Based on the coefficients shown in Table 6, it is possible to suggest that dentists who reported to know about AM in their post-graduate courses were more likely (80%) to recognize at least three brand names of AM

Table 2. Descriptive analysis results of the dentists regarding answers on knowledge on AM and ONJ.

	Questions	Answers	n (%)	Inferior – superior*
Q1.	Knowledge on the class of AM [§]	Yes No	58 (59.18) 40 (40.82)	0.49 – 0.67 0.31 – 0.50
Q2.	In the anamnesis, do you think it is important to know whether the patient takes or took AM? [§]	Yes No	83 (83) 17 (17)	0.75 – 0.90 0.09 – 0.24
Q3	a. Recognition of AM [§]	None	48 (48.98)	0.39 – 0.60
		Partially Fully	45 (45.92) 5 (5.10)	0.36 – 0.56 0 – 0.16
Q4	b. Identification of brand names of AM in a list of 10 medications**	Up to 2 At least 3	30 (56.60) 23 (43.40)	0.43 – 0.69 0.30 – 0.56
		a. Recognition of the indication for use of AM	Yes No	64 (63.37) 37 (36.63)
Q5	b. Identification of alternatives representing indications for use of AM***	Up 1 At least 2	41 (64.06) 23 (35.94)	0.52 – 0.75 0.24 – 0.47
		a. Recognition of some side effect of AM in the oral cavity [§]	Yes No	53 (53) 47 (47)
Q6	b. Identification of the side effect in the oral cavity	Correctly Incorrectly	34 (69.39) 15 (30.61)	0.56 – 0.82 0.17 – 0.43
		a. Recognition of systemic risk factors related to AM, which would increase the likelihood of occurrence of side effects in the oral cavity [§]	Yes No	50 (50) 50 (50)
Q7	b. Identification of alternatives you think that represent systemic risk factors****	Upto 4 At least 5	22 (43.14) 29 (56.86)	0.29 – 0.56 0.43 – 0.70
		a. Recognition of local risk factors related to AM, which would increase the likelihood of development of side effects in the oral cavity ^{§§}	Yes No	65 (65.00) 35 (35.00)
	b. Identification of alternatives you think that represent local risk factors****	Upto 4 At least 5	41 (62.12) 25 (37.88)	0.50 – 0.73 0.26 – 0.49

*Confidence interval limits; **Alendronate, pamidronate, denosumab, zoledronate; ***Osteoporosis, Paget's disease, osteogenesis imperfecta, bone metastasis, multiple myeloma; ****Diabetes, chronic use of corticosteroid, use of immune-suppressors, smoking, osteoporosis, intravenous AM; ***** bone exostosis, periodontal disease, odontogenic abscess, para-endodontic surgery, dental implants, tooth extraction, bone grafting; §Missing data: 03 participants did not answer.

Table 3. Descriptive analysis results of the dentists regarding their clinical behavior for patients under treatment with AM.

Clinical cases	Behavior	n (%)
Q8. A 62-year-old woman with osteoporosis and under treatment with oral BP presented indication for dental intervention to be performed according to the medication usage time [§]	a. Simple tooth extraction: use of BP < 3 years	18 (19.35)
	Performing the procedure	18 (19.35)
	Discontinuing BP, performing the procedure and resuming BP	28 (30.11)
Q9. A 65-year-old man diagnosed with non-surgical adenocarcinoma of the prostate taking intravenous BP regularly to prevent bone metastasis [§]	b. Simple tooth extraction: use of BP > 3 years	47 (50.54)
	Performing the procedure	13 (14.29)
	Discontinuing BP, performing the procedure and resuming BP	27 (29.67)
Q10. Would you feel comfortable treating patients who developed ONJ ^{§§}	Performing no procedure (i.e. referral of the patient)	51 (56.04)
	Performing the procedure	6 (6.32)
	Discontinuing BP, performing the procedure and resuming BP	17 (17.89)
Q9. A 65-year-old man diagnosed with non-surgical adenocarcinoma of the prostate taking intravenous BP regularly to prevent bone metastasis [§]	a. Dental implant: use of BP < 3 years	72 (75.79)
	Performing the procedure	4 (4.17)
	Discontinuing BP, performing the procedure and resuming BP	10 (10.42)
Q10. Would you feel comfortable treating patients who developed ONJ ^{§§}	b. Dental implant: use of BP < 3 years	82 (85.42)
	Performing the procedure	27 (27.27)
	Performing no procedure (i.e. referral of the patient)	72 (72.73)

BP: Bisphosphonate; §Missing data: until 10 did not answer.

Table 4. Descriptive analysis results of the dentists regarding acquisition of knowledge.

Question	Answers	n (%)	
Q11. Which resources would you use to keep up with dentistry? [§]	Research on Internet	Yes	52 (52.53)
		No	47 (47.47)
	Scientific articles	Yes	73 (73.74)
		No	26 (26.26)
Q12. Where did you learn about AM and its side effects in the oral cavity? [§]	Continued education courses	Yes	63 (63.64)
		No	36 (36.36)
	Undergraduate dental courses	Yes	49 (49.49)
		No	50 (50.51)
Q13. Which would be your preference for acquiring knowledge on AM and ONJ? [§]	Postgraduate dental courses	Yes	10 (10.10)
		No	89 (89.90)
	Continued education courses	Yes	10 (10.10)
		No	89 (89.89)
Q13. Which would be your preference for acquiring knowledge on AM and ONJ? [§]	Scientific articles	Yes	21 (21.21)
		No	78 (78.79)
	Neverbefore	Yes	32 (32.32)
		No	67 (67.68)
Q13. Which would be your preference for acquiring knowledge on AM and ONJ? [§]	On-line courses	Yes	12 (12.12)
		No	87 (87.88)
	Short courses	Yes	37 (37.37)
		No	62 (62.63)
Q13. Which would be your preference for acquiring knowledge on AM and ONJ? [§]	Scientific articles	Yes	52 (52.53)
		No	47 (47.47)
	Continued education courses	Yes	50 (50.51)
		No	49 (49.49)

[§] Missing data: 2 participants did not answer.

(F =0.80). Table 6 shows coefficients indicating evidence that younger participants (age group close to the median) who reported to learn about systemic risk factors (which can increase the possibility of occurrence of ONJ) and AM in their post-graduate courses were more likely (91%) to correctly identify two or more indications for the use of such medications (F = 0.91). Moreover, those younger participants who completed their undergraduate courses at public institutions and learned about AM and ONJ by reading scientific articles were more likely (91%) to correctly recognize ONJ in the oral cavity as a side effect (F = 0.91). These results also evidenced that dentists who reported to identify some indications for the use of AM were more likely (66%) to correctly recognize five or more systemic risk factors.

DISCUSSION

Despite the almost 10 years, an increasing number of cases of BP-related ONJ have been published [16-19]

since the last publication of the AAOMS position paper on BRONJ, which was based on multicentric evidence from specialists and approved by the AAOMS Board of Trustees [7]. According to Rosella et al., a high level of knowledge is needed to reduce the incidence of BP-related ONJ by preventing it and improving its treatment [5]. Saad et al. also highlighted that a higher level of knowledge on AM among oral surgeons provides a better quality treatment [20]. In this way, the use of a cross-sectional study design with questionnaires would allow the knowledge and behavior of professionals to be assessed, possibly supporting collaborations for educational adequacy and improvement.

According to the results, one can observe that the majority of the dentists (59%) learned about AM and believed it is important to know whether the patient takes or took such medications during anamnesis (83%). For Alhussain et al. [15] 60% of the oral surgeons recognized that there is a relationship between use of AM and ONJ.

Table 5. Results of Fisher's exact test for associations between clinical behaviors and answers to other questions.

Q2. Do you think it is important to know whether the patient takes or took AM during the anamnesis?	Not performed**		Extraction - use of oral BP for more than 3 years		p-value
	Performed	Discontinuing BP, performing the procedure and resuming BP	Performed	Discontinuing BP, performing the procedure and resuming BP	
No	6	1	6	1	<0.01
Yes	44	26	7	26	
Q12. Where did you learn about AM and ONJ? Neverlearned	Notperformed**		Extraction - use of oral BP for less than 3 years		p-value
No	28	25	13	25	
Yes	18	3	5	3	0.03
Q12. Where did you learn about AM and ONJ? Post-graduate dental courses	Notperformed**		Extraction - use of oral BP for more than 3 years		p-value
No	45	23	14	23	
Yes	1	3	4	3	0.01
Q12. Where did you learn about AM and ONJ? Under-graduate dental courses	Notperformed**		Extraction - use of oral BP for more than 3 years		p-value
No	29	7	9	7	
Yes	21	20	4	20	<0.01
Q12. Where did you learn about AM and ONJ? Neverlearned	Notperformed**		Extraction - use of oral BP for more than 3 years		p-value
No	31	26	6	26	
Yes	19	1	7	1	<0.01
Q12. Where did you learn about AM and ONJ? Under-graduate dental courses	Notperformed**		Dental implant – use of IV BP for less than 3 years		p-value
No	41	3	3	3	
Yes	31	14	3	14	0.01
Q12. Where did you learn about AM and ONJ? Neverlearned	Notperformed**		Dental implant – use of IV BP for less than 3 years		p-value
No	46	17	3	17	
Yes	26	0	3	0	<0.01
Q12. Where did you learn about AM and ONJ? Under-graduate dental courses	Notperformed**		Dental implant – use of IV BP for more than 3 years		p-value
No	45	1	2	1	
Yes	37	9	2	9	0.02

BP: Bisphosphonate; * Intravenously; ** Referral.

Table 6. Results of logistic regression analysis between dependent and explicative variables.

Co-variable (Explicative variable)	Dependentvariable - Q3b.				
	SE*	Standard error	z-test	p-value	F value**
Intercept***	-0.6931	0.3273	-2.118	0.0342	
Q12. Post-graduate course	2,0794	0.8557	2.430	0.0151	0.80
Co-variable (Explicative variable)	Dependentvariable - Q4b.				
	SE*	Standard error	z-test	p-value	F value**
Intercept***	3.4447	1.9564	1.761	0.0783	
Age****	-0.2025	0.0797	- 2.542	0.0110	0.91
Q6a. Systemic risk factors	1.4311	0.7057	2.028	0.0426	
Q12. Post-graduate course	2.5368	1.2819	1.979	0.0478	
Co-variable (Explicative variable)	Dependentvariable - Q5b.				
	SE*	Standard error	z-test	p-value	F value**
Intercept***	3.3916	1.7160	1.976	0.0481	
Age****	- 0.1529	0.0608w	- 2.517	0.0118	0.91
Dentistry school	1.78	0.8797	2.024	0.0430	
Q12. Scientific articles	3.1688	1.3773	2.299	0.0215	
Co-variable (Explicative variable)	Dependentvariable - Q6b.				
	SE*	Standard error	z-test	p-value	F value**
Intercept***	- 2.079	1.061	- 1.961	0.0499	0.66
Q4a. Indications for use of AM	2.773	1.110	2.498	0.0125	

Note: *Punctual estimation; **Estimated predictive value, propensity score or odds ratio; ***Model level; ****Age group of the oral surgeons close to the median.

However, these results should be cautiously analyzed because the survey instrument contains questions assessing the knowledge on the theme, which might condition the participants to give biased answers [21,22]. Therefore, a broader questionnaire was used to identify indications for use, brand names (active ingredient) of the anti-resorptive medications, risk factors (i.e. systemic and local) for development of ONJ and possible behaviors in hypothetical clinical cases.

Although dentists believed it is important to know whether the patient undergoes or underwent treatment with AM, 49% of them reported that they recognized none of these medications, 46% recognized them partially and only 5% recognized AM fully. The proportions of dentists with partial or full knowledge could identify up to two indications (57%) and at least three brand names (43%). This result is contradictory because approximately half of the dentists did not recognize anti-resorptive medications by their brand names and believed that it is important to obtain this information during anamnesis. According to Lima et al., the lack of knowledge on these drugs might directly influence the dentists as he or she

would incompletely evaluate the patient during anamnesis, thus making prevention, diagnosis and treatment of ONJ difficult [3].

Most of the dentists (63%) reported that they can identify indications for the use of AM, that is, 36% of them identifying up to one indication and 36% at least two indications, with this question consisting of five pathological conditions. These results showed that 41 dentists recognized that AM can be indicated for treatment of osteoporosis, but only 23 were able to identify other condition. This scenario demonstrated that oral surgeons have a limited knowledge on therapeutic indications for AM, as some intravenous drugs (e.g. alendronate and pamidronate) can be used in treatments for patients with imperfect osteogenesis [23] and multiple myeloma [24]. In addition, clodronate and denosumab can be used in neoplastic patients who can potentially develop bone metastasis [11,25]. According to Ruggiero et al, the risk of development of ONJ may be related to the therapeutic indication, which, in turn, is associated with administration route and potency of the AM [12]. Therefore, dentists who did not recognize pathological conditions with therapeutic

indications of AM could not know either, at least presumably, the variations in its activity and the different route administrations, thus making the incidences of ONJ diversified [26].

As shown in table 2, 53% of the dentists reported they knew about ONJ, but only 34 had correctly identified ONJ in the oral cavity as a side effect of AM. In a similar study, Yoo et al. found that in a sample of 254 dentists, 56% of them knew about BP-related ONJ [14]. For Migliorati et al., it is important that dentists know to recognize ONJ as a side effect of treatments with AM because there is evidence that patients are not properly told about side effects and risk factors (i.e. systemic and local) [22]. This can be explained by the fact that oral surgeons prescribing AM do not have knowledge on ONJ and resist giving information to patients, which perhaps might impair the treatment adhesion.

Regarding the risk factors, 50% and 65% of the dentists, respectively, reported that they can recognize systemic and local risk factors associated with AM. As for systemic risk factors, 22 oral surgeons could identify up to four risk factors and 29 identified at least five. As for local risk factor, 44 oral surgeons identified up to four risk factors and 25 at least five (Table 2). Dentists should be capable of recognizing both systemic and local factors because conditions such as diabetes and the use of immune-suppressors and corticosteroids lead to a difficult control of the inflammation, thus delaying the healing of oral tissues as a result of either dental procedures or unfavorable oral health conditions [26]. However, the majority of the dentists knew to identify more easily local risk factors than systemic ones. These facts require more attention from the oral surgeons as they should instruct patients who take AM about the risk inherent to its use and the predisposing local and systemic factors [3]. Oral surgeons should track and eliminate oral cavity factor risks prior to the beginning of the treatment with AM, thus minimizing the predisposition to ONJ occurrence [25]. If dental procedures are to be performed in osteoporosis patients undergoing treatment with AM, guidelines on the inherent risks of ONJ and oral healthcare should be given. Also, an informed consent form should be signed by the patient if a more invasive treatment is necessary [26].

The hypothetical clinical cases presented different characteristics regarding surgical procedure, medication usage time and administration route of AM, which would allow for evaluation of clinical behaviors depending on

the complexity involved. With regard to the clinical case of a patient undergoing tooth extraction and oral use of AM for less than three years, 51% of the dentists reported they would choose not to perform the procedure and instead refer the patient, 30% reported they would perform the procedure provided that AM was discontinued before and after the surgery, and only 19% reported they would simply perform the surgical procedure. The answer patterns of the dentists were slightly different when the same patient used AM for more than three years (i.e. 14% would perform surgical procedure, 30% would perform surgical procedure only if AM was discontinued, 56% would not perform any surgical procedure and refer the patient. In a similar study, Rosella et al. found conflicting results regarding the recognition of AM and insufficient knowledge to provide a safe dental treatment [5]. Although 94% of the participants reported that it is important to recognize patients under treatment, only 39% knew how to treat patients taking oral AM for less than four years and 44% did not know how to treat those taking oral AM for more than four years. According to guidelines of the AAOMS position paper [12], a simple tooth extraction could be performed without the need to discontinue the treatment of AM within the time periods used in this hypothetical case, but dentists should be concerned when treating patients who take AM for more than four years as the possibility of occurrence of ONJ increases (0.21%). However, the occurrence of BP-related ONJ in osteoporosis patients under treatment for more than four years remains low, as reported by Brindon and Adams [27].

The second clinical case presented greater complexity as the patient was taking intravenous AM and would undergo oral surgery for dental implant placement. This case was more complex because intravenous AM has a higher activity and, in association with a long-term treatment, increases the occurrence of ONJ. In this sense, the results indicated that more than 76% of the dentists did not perform any dental procedure, referring the patient instead, regardless of whether intravenous AM was used for a period greater than three years or not. According to Ruggiero et al., dental procedures involving manipulation of bone tissues in the maxilla or mandible should be avoided in oncological patients undergoing treatment with intravenous AM, with oral surgeons having to seek for alternatives to dental treatment [12]. However, Ata-Ali et al. performed a meta-analysis to evaluate whether therapies with AM could reduce the success rate of dental

implants, with the results showing that such treatments did not affect the installed dental implants [28]. Yoneda et al. [29] have recently demonstrated that there is no evidence that dental implant procedures are a risk factor in patients treated with intravenous AM, but the authors emphasized that these procedures should not be performed in oncological patients undergoing treatment with AM and that oral surgeons should instead choose alternative dental treatments. One can observe that the majority of the oral surgeons would refer such patients because there is no well-established conduct protocol yet, mainly in more complex clinical situations.

Regardless of the complexity of the hypothetical clinical cases, most of the dentists reported that they would refer patients taking AM rather than performing dental procedures – a behavior which was perceptibly adopted as the complexity of the clinical case increased. Although the participants were not asked to cite the reasons for not treating such patients, this scenario may be corroborated by Alhussein et al. [15], who found that oral surgeons would assume a high risk of procedural complications if they had to treat patients taking AM because they were not acquainted with anti-resorptive medications and the possibility of occurrence of ONJ.

In the hypothetical clinical cases, no C-terminal telopeptide test was used to predict the development of BP-related ONJ because a systematic review revealed that among 1,442 patients receiving alendronate and undergoing tooth extraction, 2% developed BP-related ONJ. The results showed evidence that the C-terminal telopeptide test seems to have no predictive value for determining the risk of ONJ in patients taking AM [30].

In this study, dentists were asked to cite the means or resources they used to acquire knowledge on AM and ONJ. The results were contradictory as 74% of the dentists reported to acquire dental knowledge by reading scientific articles, but only 21% reported that they learned about AM and ONJ by means of scientific articles. Most of the dentists reported that they learned about the issue during undergraduate courses (49%), possibly in the classroom, with this knowledge being restricted and poorly established by the oral surgeons. According to Dihma et al, it is possible that there is a learning gap in the basic disciplines of oral lesion diagnosis and oral pathology during under-graduate courses, resulting in inadequate exposure to these specialties, which would have a direct

reflection on the students' opportunity to treat patients requiring special care dentistry and specific protocols [31].

According to the results on the resources used by dentists, one can highlight that they would hardly have a previous access to the guidelines from AAOMS position papers and Japanese Allied Committee on ONJ [7,12,29]. As well as Alhussein et al, we also suggest that a greater knowledge on ONJ would make dentists more comfortable treating patients properly [15]. Therefore, the results on clinical behavior and the imprecision on the resources of knowledge on this issue showed that dentists tend to feel uncomfortable treating patients who took or takes AM. Regardless of whether dentists learned or not about AM and ONJ during their undergraduate or post-graduate courses, or even never, there was a statistically significant association with their answer patterns as they reported they would refer patients under AM therapy rather than performing dental procedures, which confirms this trend. Similarly, there was also an association between the answer patterns of dentists and their clinical behavior, since they believed it is important to recognize the use of AM during anamnesis.

The results of the logistic regression analysis estimated that dentists who learned about AM and ONJ in the post-graduate courses were more likely (80%) to recognize at least three brand names of AM. Younger oral surgeons reporting that they knew that systemic risk factors related to the use of AM could favor the development of ONJ also learned about AM and ONJ in their post-graduate courses, with 91% of them tending to correctly recognize two or more indications for the use of these drugs. In certain way, these results might be explained by the fact that under-graduate courses do not expose students adequately to more complex cases requiring a multidisciplinary approach, perhaps due to the lack of faculty sufficiently trained in oral pathology and diagnosis, which would increase their clinical experience during the post-graduate period [31]. In fact, younger oral surgeons (age group close to the median) who completed undergraduate courses at public institutions and learned about AM and ONJ by reading scientific articles were more likely (91%) to correctly recognize ONJ in the oral cavity as a side effect. However, the interpretation of these results should be cautiously performed because the estimation of proportion does not cover the whole sample of oral surgeons, meaning that only those participants with variables conditioned by analysis were considered. These

results demonstrated a certain characterization of the clinical behavior among dentists, which also suggests that there is a limited knowledge on AM and ONJ.

CONCLUSION

One can conclude that most of the dentists can recognize anti-resorptive medications, systemic and oral risk factors and the importance of knowing whether the patients were or are under medication, but they only reported that AM could be used for treatment of up to two bone pathological conditions. However, the dentists felt uncomfortable treating patients under AM or affected by ONJ. The clinical behavior of the majority of the dentists in the hypothetical clinical cases was limited to referrals of patients.

The results showed evidence that educational efforts should be carried out to promote knowledge during under-graduate and post-graduate courses, thus stimulating dentists to seek up-dated resources in order to consolidate their understanding of the management of ONJ patients under treatment with AM.

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Collaborators

DAA MARLIÈRE, had full access to all study data and assumes responsibility for the integrity of said data as well as the accuracy of the data analysis. Study concept and design: DAA MARLIÈRE, HDM CHAVES NETTO. Acquisition of data: TE COSTA. Statistical analysis: DAA MARLIÈRE. Analysis and interpretation of data: DAA MARLIÈRE, TE COSTA, L ASPRINO, HDM CHAVES NETTO. Drafting of the manuscript: DAA MARLIÈRE, TE COSTA. Critical revision of the manuscript in terms of significant editorial content: SM BARBOSA, L ASPRINO, RB JUNQUEIRA. Study supervision: HDM CHAVES NETTO.

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