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A survey on brazilian dentists' awareness, perception, and knowledge of bisphosphonates

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Aim: The purpose of the study was to analyze the knowledge of dentists in Belo Horizonte, Brazil, about bisphosphonates and their clinical implications. **Methods:** A cross-sectional questionnaire-based study was conducted with a convenience sample of dentists in Belo Horizonte, in a period of 8 weeks. The questionnaire was self-applied and was structured with 10 items about the dentists' demographic characteristics, professional profile, and knowledge about bisphosphonates. Associations in the data were analyzed by with the Fischer's exact test with a significance level of 5%. **Results:** Of the 214 participating dentists, 163 (76.17%) were women, and 51 (23.83%) were men, with age ranged for 21 to 73 years (mean of 30 years) and mean of 6 years of professional activity. Nearly half (106/49.53%) reported having knowledge about bisphosphonates, and undergraduate courses were the primary source of such information (73/34.11%). Osteoporosis was the most identified indication for use (75/35.04%), although no participants correctly identified all indications. Regarding the drugs' side effects, only three dentists (1.40%) could correctly identify all responses, with bone necrosis being recognized by the majority (88/41.12%). Sodium alendronate (54/25.23%) and sodium ibandronate (15/7.01%) were the most identified examples of bisphosphonates. Last, only nine dentists (4.20%) could identify all examples of the drugs, and their capacity was associated with self-reported knowledge ($p<0.05$). **Conclusions:** More information about bisphosphonates should be disseminated in Belo Horizonte, ideally via better approaches in local undergraduate and postgraduate courses. Until then, knowledge of the basic aspects of bisphosphonates will remain limited.

Keywords: Diphosphonates. Knowledge. Awareness. Drug utilization. Dentists. Brazil.

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Introduction

Bisphosphonates are chemical compounds analogous to pyrophosphoric acid that are found in the form of pyrophosphate in the human body. They act on osteoclasts and osteoblasts in the process of bone resorption and are used in treating diseases that alter bone metabolism, including osteoporosis, Paget's disease, malignant hypercalcemia, bone metastases, breast cancer, prostate cancer, osteogenesis imperfecta, and lung cancer[1–3].

With oral or intravenous application, bisphosphonates are generally well tolerated by the body systems. However, some adverse effects may be observed, including low and transient fever, fatigue, arthralgia, nausea, esophagitis, renal failure, hypocalcemia, bone pain, and osteonecrosis of the jaws[3–5]. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is considered to be the most relevant adverse event for dentistry, characterized as an area of bone exposure in the mandible and/or maxilla without remission in 8 weeks and affecting patients who use or have used systemic bisphosphonates and have not received irradiation on the head and neck region[5,6].

In the field of dentistry, BRONJ may develop after dental procedures such as extractions, implant placement, and periodontal therapy or arise either spontaneously or by prosthetic trauma[1]. A recent systematic review showed a prevalence of 2.7% of BRONJ in patients using bisphosphonates and undergoing dental treatment, with a specific prevalence of 6.9% for intravenous use[7]. Although bisphosphonates are not new in the market, with the first report of BRONJ in 2003[8], the literature shows low knowledge by most dentists, in Brazil[9] and worldwide[10-13]. To minimize the risks of developing BRONJ, preventive dental treatment should be performed before bisphosphonate therapy begins[8]. Likewise, the dentist's knowledge of bisphosphonates is important to assess the patient's risk and advise him on the need to maintain good oral hygiene to reduce the need for dental procedures[7].

In view of the low knowledge about bisphosphonates reported in the literature and the importance of the dentist in the prevention and treatment of BRONJ, associated with little data on the subject in Brazil and the absence of information about local dentists, the objective of the present study was to analyze the knowledge of dentists in Belo Horizonte - Brazil about bisphosphonates and their possible clinical implications.

Materials and methods

Study design, local, population, and sample

Following approval by the local ethics and research committee (Protocol No. 1,961,961), a cross-sectional questionnaire-based study was conducted for eight consecutive weeks.

Local, population and sample

Participated in this study dentists working in public service and private practice across Belo Horizonte, Brazil. Participants were recruited by convenience sampling through

data obtained from the Regional Council of Dentistry and signed a consent form to participate in this study. The sample was categorized according to age group and duration of professional activity.

Data collection

A questionnaire with specific questions to assess the participants' level of knowledge about bisphosphonates was developed by the researchers. A pilot study was conducted to verify the applicability of the questionnaire and make adjustments. The questionnaire had ten items, addressing participants' demographics (age and gender), professional profile (duration of professional activity and dental specialty), and knowledge about bisphosphonates (self-declared knowledge, source of information, indications, drugs' side effects, examples of drugs, and screening of use during anamnesis). Questions 1 and 3 requested information about age and time of clinical practice. Questions 2, 4, 5, and 6 presented a single option, whereas Questions 7–10 were multiple-choice.

The questionnaire was self-applied without the intervention of the researchers. When necessary, trained dentistry students answered questions regarding the completion of the questionnaire without influence or prejudice in the responses.

Statistical analysis

For the data analysis, single option questions were treated as dichotomous variables and presented as absolute and relative frequencies. Multiple-choice questions were categorized into correct answer (when all possible answers were marked) and wrong answer (when any correct answer was not identified). Also, for multiple-choice questions, the correct answers were also analyzed separately in the form of relative and absolute frequency.

The Fischer's exact test were used to analyze the associations between self-reported knowledge about bisphosphonates and specific questions about the drug class (i.e., indication, examples of drugs, and side effects). Statistical analysis was performed with Epi Info™ (version 7.2; Centers for Disease Control and Prevention, Atlanta, GA, USA). The level of significance was set at 0.05.

Results

Of the 214 participating dentists, 163 were women (76.17%), and 51 were men (23.83%) with age ranged from 21 and 73 years and mean of 30 years (Table 1). Their professional activity ranged from 0 to 43 years (mean of 6 years), and most had up to 6 years of dental education (57.01%). In terms of dental specialty, 106 dentists were specialists (49.53%), thirty-six were orthodontists (16.82%), seventeen were endodontists (7.94%), and fourteen were implantodontists (6.54%).

Regarding knowledge about bisphosphonates, 106 dentists (49.53%) reported having knowledge about the drugs (Table 1). Undergraduate courses were the primary source of knowledge about bisphosphonates for 73 dentists (34.11%), whereas 19 (8.88%) obtained such information in postgraduate courses, and 83 (38.78%) reported

"I don't know much about it." Almost all, 201 dentists (93.92%) reported questioning patients during anamnesis about the use of systemic medications.

Table 1. Gender, duration of professional activity, and knowledge about bisphosphonates by decade of life and gender, according to 214 dentists from Belo Horizonte. Brazil, 2017.

	Gender		Decade of life						Total
	Female	Male	3rd	4th	5th	6th	7th	8th	
					Gender				
Female n (%)	163 (76.71)	-	95 (44.39)	49 (22.89)	10 (4.67)	8 (3.73)	1 (0.46)	0 (0)	163 (76.71)
Male n (%)	-	51 (23.83)	16 (7.47)	18 (8.41)	6 (2.80)	4 (1.86)	6 (2.80)	1 (0.46)	51 (23.83)
					Duration of professional activity				
≤ 6 years n (%)	105 (49.41)	17 (7.94)	105 (49.05)	15 (7.00)	0 (0)	1 (0.46)	0 (0)	1 (0.46)	122 (56.97)
> 6 years n (%)	58 (27.30)	34 (15.89)	6 (2.81)	52 (24.3)	16 (7.47)	11 (5.13)	7 (3.26)	0 (0)	92 (42.97)
					Self-report knowledge about bisphosphonates				
Yes n (%)	77 (47.23)	29 (56.86)	66 (30.83)	26 (12.14)	7 (3.26)	3 (1.39)	3 (1.39)	1 0.46)	106 (49.47)
No n (%)	86 (52.76)	22 (43.13)	45 (21.03)	41 (19.16)	9 (4.21)	9 (4.21)	4 (1.87)	0 (0)	108 (50.48)
Total n (%)	163 (76.71)	51 (23.83)	111 (51.86)	67 (31.30)	16 (7.47)	12 (5.59)	7 (3.26)	1 (0.46)	214 (100)

Note: table made by the authors.

None of the participants correctly identified all the indications of the bisphosphonates, nine dentists (4.20%) correctly identified all examples of drugs, and three (1.40%) identified all correct clinical implications present in the questionnaire. Table 2 presents the number of dentists who identified each correct alternative separately in the multiple-choice questions about indications, drug examples and possible clinical dental implications in the use of bisphosphonates.

Concerning examples of bisphosphonate-based drugs, 94 (43.92%) did not answer the question. As for possible clinical implications of bisphosphonates, 68 dentists (31.77%) marked "None of the alternatives" as the correct answer.

Table 2. Correct alternatives of the multiple-choice questions and the number of dentists who ticked these alternatives, according to 214 dentists from Belo Horizonte. Brazil, 2017.

Correct answer	n	%
Question 7 – Tick the indications to use bisphosphonates		
Osteoporosis	75	35.04
Bone metastasis	34	15.88
Breast cancer	24	11.21

Continue

Continuation		
Hypercalcemia	4	1.87
Question 9 – Mark examples of bisphosphonates-based drugs		
Alendronate sodium	54	25.23
Risedronate sodium	13	3.27
Ibandronate sodium	15	7.01
Zoledronic acid	7	3.27
Question 10 – Mark the possible dental clinical implications of the use of the bisphosphonates		
Bone necrosis	88	41.12
Osteomyelitis	18	8.41
Decreased of the blood supply	13	6.07
Bone exposure	8	3.73
Presence of ulcerations	3	1.40

Note: table made by the authors.

Responses related to indications for bisphosphonates and possible adverse events of drug use were not related to self-reported knowledge, whereas the ability to correctly identify all drugs exemplified in the questionnaire was ($p<0.05$), as shown in Table 3.

Table 3. Self-reported knowledge about bisphosphonates of 214 dentists from Belo Horizonte, Brazil, 2017.

	Self-reported knowledge about bisphosphonates			p value
	Yes n (%)	No n (%)	Total n (%)	
Q7				
Correct respond	0 (0.0)	0 (0.0)	0 (0.0)	ns
Wrong or incomplete	106 (49.53)	108 (50.47)	214 (100.00)	
Q9				
Correct respond	8 (3.74)	1 (0.47)	9 (4.21)	<0.05
Wrong or incomplete	98 (45.80)	107 (49.99)	205 (95.79)	
Q10				
Correct respond	2 (0.94)	1 (0.47)	3 (1.41)	ns
Wrong or incomplete	104 (48.59)	107 (50.00)	211 (98.59)	

Note: table made by the authors. Q7 – question seven (Tick the indications to use bisphosphonates); Q9 – question nine (Mark examples of bisphosphonates-based drugs); Q10 – question 10 (Mark the possible dental clinical implications of the use of the bisphosphonates); ns - Not significant

Discussion

The present study identified low self-reported knowledge among dentists in Belo Horizonte, with slightly less than half of participants reporting knowledge about bis-

phosphonates. Similarly, another study from Brazil reported knowledge about bisphosphonates among "over half" of participants[9]. In different locations worldwide, the knowledge reported ranged from 40.1% to 71%[10-13]. Of the retrieved publications, dentists in Saudi Arabia presented the lowest level of knowledge: 40.1% considered "Reasonable to good" and only 2.4% considered "Good"[13]. This data is important given recent findings that only 12.4% of Jordan patients using bisphosphonates were aware of the risk of BRONJ due to medication[14] and that only 16.7% Israel patients knew about the need to discontinue the medication before the installation of dental implants[15]. Thus, patients using bisphosphonates are unaware of the drug's peculiarities regarding dental care. In this sense, the low knowledge of dentists could increase the risk of complications due to inadvertently performing dental procedures without specific care. In addition, it is the dentist's role to inform the patient about the dental risks relevant to the health condition.

A study conducted in Canada revealed that dentists had satisfactory knowledge about bisphosphonates regarding their indications, route of administration, and treatment of BRONJ. For Canadian dentists, the primary sources of information on the subject were scientific journals[16]. In this study, by contrast, undergraduate courses were the primary sources of knowledge about bisphosphonates. Comparative studies of the knowledge of dentists versus dental students about bisphosphonates have shown that dentists had superior knowledge, although both groups had low knowledge on the subject[9]. When only undergraduate students were evaluated, knowledge about specific issues (i.e., indications, examples of drugs, and routes of administration) was high; however, knowledge about clinical decisions to establish appropriate dental treatment plans for patients using the medication and the ability to recognize and treat the stages of osteonecrosis were extremely low[17]. This shows that the information acquired during graduation is not enough to cover all specific knowledge in the area, requiring updates and other sources of knowledge, such as scientific journals or postgraduate courses. Additionally, the low knowledge of dentists in the present study can be attributed, in part, to the insufficiency in the undergraduate curriculum, given that most of them present the undergraduate degree as the main source of information.

Analysis of the curriculum of the undergraduate course in Dentistry at the university with greater local importance and national and international recognition did not find any specific mention of bisphosphonates[18]. Considering that this curriculum serves as the basis for several other local courses, the absence of this specific topic may represent a possible omission of this information during graduation, representing a possible justification for the low knowledge.

Corroborating the hypothesis raised, a Brazilian study shows the dentists with specialties focused on oral medicine, pathology, and palliative care had greater knowledge about risk factors, treatment planning for patients using bisphosphonates, preventive measures, and the treatment of osteonecrosis[19]. In this study, orthodontics and implantodontics were among the three most frequent specialties, and because they are areas that deal directly with bone metabolism, greater knowledge about bisphosphonates was expected. However, that expectation could not be confirmed because the data were not sufficient to verify statistical significance.

The sample results of this study show that, although participants reported knowledge about bisphosphonates, there is a conflict between low knowledge about indications, examples of medications, and adverse events, which suggests that such knowledge has not been consolidated. Similar findings have also been evidenced by other studies in Brazil and various locations around the world[9-11,20], indicating that almost 20 years after the first report of BRONJ[8], bisphosphonates are still a topic that many dentists have not mastered and that they may not be prepared for provide clinical care of patients using the drug.

A study conducted with patients in use of bisphosphonate for osteoporosis and osteopenia undergoing dental treatment revealed that almost halt dentists were unaware of the patients' health condition and that majority did not question patients about the type of medication used or the duration of treatment for osteoporosis[15]. Although this study showed that almost all participants questioned their patients about the use of systemic medications, the limited knowledge evidenced and the failure to pinpoint the indications, types, and adverse effects of bisphosphonates may prompt the underestimation of the drug and increase patients' exposure to the risk of osteonecrosis. A study conducted in South Korea showed similar results, with one also almost all of dentists questioned about the use of systemic medications but only a little more than half wanting to know about the type and duration of the medication[21]. Although dentists question their patients about the use of systemic medications, many ignore the information collected or do not understand its clinical significance. Thus, the simple fact of questioning patients about medications in use does not guarantee that the dentist really knows the subject and applies this finding in his/her practice.

Knowledge about adverse events from medications in use is important both to establish a correct treatment plan and to predict possible surgical complications. Although BRONJ is considered to be an uncommon adverse event[5] with low incidence (i.e., 1.04–69.0 per 100,000 patients/year for oral bisphosphonates and 0.0–12.22 per 100,000 patients/year for intravenous bisphosphonates)[6], it represents a significant finding for dental practice. A few of participants in this study could correctly identify all of the adverse events resulting from the use of bisphosphonates on the questionnaire and almost half could identify osteonecrosis was clinical implication. Although most participants identified BRONJ as an adverse event, the relative frequency was quite low, which suggests the risk of performing procedures without proper care or based on any protocols.

Sodium alendronate was the most recognized drug by the participants in this study, possibly because it is the most commonly used oral bisphosphonate[22]. However, a systematic review has classified it as the third drug most related to adverse reactions of dental interest[1]. In the same review, zoledronate was identified as the most frequent in adverse situations and was the fourth most identified by participants in this study[1]. In other study, sodium alendronate was also the most-cited type of bisphosphonate, followed by zoledronate[11]. Although the number of participants in this study able to correctly indicate all types of bisphosphonates on the questionnaire was small, the capacity significantly related to self-reported knowledge ($p<0.05$). In turn, knowledge about indications and adverse reactions were not associated

with self-reported knowledge (p>0.05). This may indicate that the knowledge presented by dentists is limited to the identification of the types of bisphosphonates and the existence of this pharmacological class. More specific topics whose clinical implications are more significant are neglected, increasing the risk of complications and a negative impact on patients' quality of life.

Although this study has limitations in terms of sample size, the results are important to start the discussion on the need to improve the knowledge of bisphosphonates by dentists. Thus, the data can be treated as a pilot study, serving as a basis for future studies with a representative sample of the dentist population in Belo Horizonte.

The results of this study reveal that the dentists interviewed have poor knowledge about bisphosphonates. Although they reported knowing the type of drug, they could not correctly identify the examples of the drug, indications for use, or adverse reactions, thereby making their clinical practice and planning susceptible to errors and complications associated with the use of the drug. Information on bisphosphonates therefore needs to be better disseminated among dentists in Belo Horizonte, and undergraduate courses, as a primary source of information, and postgraduate courses need better approaches to teaching the subject.

Other studies focused on the curriculum of local undergraduate and postgraduate courses may help to identify the causes associated with the low knowledge found. Furthermore, studies associating the level of knowledge about bisphosphonates with the occurrence of adverse reactions in the dental clinic due to the use of the drug may provide information on the impact of low knowledge on clinical practice. As a suggestion, didactic videos addressing primary information on bisphosphonates and deficiencies identified in this study, should also be broadcast on digital platforms with free access and shared with dentists.

Conflict of interest

The authors have no conflict of interest

Statement of compliance with ethical standards of research

This study was approval by the local ethics and research committee (Protocol No. 1,961,961). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in the study.

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Data statement

Author elects to not share data.

Author contribution

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APPENDICES

QUESTIONNAIRE nº

1. Age: _____

2. Sex:

( ) Female

( ) Male

3. Time of professional practice (in years): _____

4. Specialist:

( ) Yes

( ) No

What's the speciality? _____

5. Do you always question the patient, during the anamnesis, about the use of systemic drugs?

( ) Yes

( ) No

6. Do you Know the bisphosphonate based drugs?

( ) Yes

( ) No

7. Tick the indications to use bisphosphonates? *multiple-choice

( ) Breast cancer

( ) Bone metastasis

( ) Rheumatological diseases

( ) Hypercalcemia

( ) Osteoporosis

( ) I don't know about it

8. By what means did you gain knowledge about bisphosphonates? *multiple-choice

( ) During the graduation

( ) During the specialization

( ) During the postgraduation

( ) Reading articles and books

( ) Search sites

( ) I don't know much about it

9. Mark examples of bisphosphonates-based drugs: *multiple-choice

( ) Alendronate Sodium

( ) Risedronate Sodium

( ) Ibandronate Sodium

( ) Zoledronic Acid

( ) Prednisone

( ) Clavulanic Acid

10. Mark the possible dental clinical implications of the use of the bisphosphonates: *multiple-choice

( ) Decreased of the blood supply

( ) Bone necrosis

( ) Osteomyelitis

( ) Presence of the ulcerations

( ) Bone exposure

( ) None of the alternatives