

Assessment Results of Dental Students' Knowledge about Bisphosphonates and Bisphosphonate-Related Osteonecrosis of the Jaw

Greta Sereikaite¹, Vesta Guzeviciene¹, Gabriele Peceliunaite¹, Povilas Daugela¹, Gintaras Juodzbaly¹

¹Department of Maxillofacial Surgery, Faculty of Odontology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania.

Corresponding Author:

Greta Sereikaite

Department of Maxillofacial Surgery, Faculty of Odontology, Medical Academy

Lithuanian University of Health Sciences

Eivenių g. 2, LT-50028, Kaunas

Lithuania

E-mail: grsereikaite@gmail.com

ABSTRACT

Objectives: The aim of this cross-sectional study is to evaluate Lithuanian fourth- and fifth-year dental students' knowledge about bisphosphonates and bisphosphonate-related osteonecrosis of the jaw.

Material and Methods: The anonymous survey using a questionnaire was conducted from February to March 2022. The survey was sent to 173 students at Lithuanian University of Health Sciences (LSMU) and 107 of them were completed. It consisted of student data, questions about the main properties of bisphosphonates, bisphosphonate-related osteonecrosis of the jaw (BRONJ), and the necessity of additional studies for students. Chi-square test and Cramér's V coefficient were used for the analysis of variables.

Results: Most of the fifth-year students knew the main properties of bisphosphonates and what diseases they are used to treat. Twenty fifth-year students (33.9%) knew the accurate definition of BRONJ, while only 11 fourth-year students (22.9%) chose the same correct answer. Statistically significant ($P < 0.05$) data were found about the knowledge of main properties of bisphosphonates. The vast majority of fourth- and fifth-year students (39 [81.3%] and 45 [76.3%]), agreed that the University should provide more information about bisphosphonates.

Conclusions: The study revealed that fifth-year students demonstrated better knowledge about bisphosphonates compared to fourth-year students and this was due to a curriculum supplemented with information about this pathology. The overall findings of this research suggest that Universities need to expand their student curricula by providing more knowledge about bisphosphonates and its relation to bisphosphonate-related osteonecrosis of the jaw.

Keywords: bisphosphonates; dental education; dental students; knowledge; osteonecrosis; teaching.

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INTRODUCTION

Bisphosphonates are one of the most common drugs used to treat Paget's disease, osteoporosis, multiple myeloma, and tumour metastases in the bones. This group of drugs is still widely studied to expand the possibilities of its use, for example, in the treatment of neurodegenerative diseases. Bisphosphonates are prescribed due to their main property - inhibition of bone resorption [1]. Bisphosphonates are known for their strong bond formation with hydroxyapatites. When osteoclasts begin to break down the bone to which bisphosphonate molecules are attached, bisphosphonates can cause osteoclast apoptosis, thus preventing bone resorption [2]. Although these drugs are highly effective and safe, they can also cause serious side effects, such as necrosis of the jaws, which is better known as bisphosphonate-related osteonecrosis of the jaw (BRONJ) in the literature [3]. The origin of the disease is multifactorial, which occurs by inhibition of angiogenesis and disruption of bone remodelling in the jaws, continuous trauma in the oral cavity, leading to greater susceptibility to various inflammations and infections of odontogenic origin [4]. Bone remodelling disruption, which is a rather complex process, is explained by the ability of sensorial osteocytes to send a signal to osteoclasts and osteoblasts, which initiates bone resorption and remodelling [5].

BRONJ is especially dangerous in patients who take bisphosphonates for a long time, in high doses, and in those taking bisphosphonates intravenously. The risk of developing osteonecrosis is higher for patients who consume alcohol, tobacco and if chemotherapy, corticosteroids, and anti-angiogenic agents are used. Associated diseases such as diabetes and rheumatoid arthritis are considered as risk factors as well [6].

Since the blood supply of the lower jaw is provided only by one arterial branch, the inferior alveolar artery, inflammatory or necrotic inflammatory changes develop more often in the mandible, and therefore the risk of BRONJ after surgical interventions in the oral cavity is much higher (73%) compared to the maxilla (22,5%) [7].

When diagnosing the disease, the dentist needs to know the main symptoms of BRONJ i.e. painful, exposed bone in the oral cavity, signs of infection, such as oral mucosal fistula, soft tissue cellulitis, tissue swelling, purulent exudation from the fistula, lower lip and chin paraesthesia or anaesthesia [7,8].

It is important to find out whether enough attention is paid to BRONJ when teaching dentistry students in Lithuania. The study of this cross-sectional study was

to evaluate the knowledge of fourth- and fifth-year dentistry students at Lithuanian University of Health Sciences about bisphosphonates and bisphosphonate-related osteonecrosis of the jaw and make academic recommendations.

MATERIAL AND METHODS

Study design

A cross-sectional study was administrated at the Lithuanian University of Health Sciences (LSMU), Kaunas, Lithuania from February to March 2022.

Materials and subjects

The research was conducted using a questionnaire developed by the authors and sent to LSMU fourth- and fifth-year dental students. The survey was created on the questionnaire creation website (<https://apklausait.lt/>) and sent to students by LSMU Outlook via e-mail by one researcher (G.S.). Before filling out the survey, the students were informed that confidentiality was ensured, as the survey was anonymous, and the results of the study will be published only in a form of a summary (Appendix 1). Permission was received from LSMU Bioethics Centre (No. BEC-OF-91).

Paniotto's formula with 95% confidence intervals was used to find out how many students had to answer the questionnaire:

$$n = 1/(\Delta^2 + 1/N)$$

Where n is the sample size (number of students to be surveyed), Δ is the sample error size (the standard error is considered 5%, which we get with 0.95 probability), and N is the general size of the study population.

The calculation results revealed, that when the margin of error is 0.05 and the size of the study population is 173 (including fourth- and fifth-year students), the number of completed questionnaires should be 118. In this research study, 107 responses to the questionnaire were received, which is 91% of the total required sample size, therefore it can be said that the study sample is representative.

Statistical analysis

The data were analysed by means of SPSS® Statistics version 24.0 (IBM Corp.; Armonk, New York, NY, USA). Response rates for groups of nominal variables were presented in absolute numbers (n) and percentage (%). In this study, two independent

test groups were selected - fourth- and fifth-year dental students and the responses to questionnaire were compared using the following statistical tests:

- Chi-squared test (used to analyse the difference between the answers of fourth- and fifth-year students when the analysed variable had 2 variations).
- Cramér’s V coefficient (used to analyse the difference between the answers of fourth- and fifth-year students when the analysed variable had more than two variations).

Differences between the responses of fourth- and fifth-year students were considered statistically significant when the calculated significance level (P-value) was less than 0.05. The relationship between student groups and the analysed variable was weak when Cramér’s V coefficient was between 0.1 and 0.3, moderate when it was between 0.3 and 0.5, strong when it was greater than 0.5.

RESULTS

A total of 107 participants, 47 males (43.9%) and 60 females (56.1%), with a mean age of 23.5 years (ranging from 21 to 26 years) participated in the survey. The distribution of dental students by year of study was 48 (45%) fourth-year students and 59 (55%) fifth-year students who participated in the survey.

Students’ knowledge about bisphosphonates

The analysis showed no statistically significant difference (P > 0.05) of fourth- and fifth-year students’ knowledge about the administration of bisphosphonates in any of the statements (Table 1). Overall 43 (89.6%) fourth-year and 47 (79.7%) fifth-year students chose bisphosphonates for the treatment of osteoporosis patients.

Table 1. Descriptive analysis of data associated with bisphosphonates

Parameter	Students (n [%])		Criteria and P-value
	Fourth-year (n = 48)	Fifth-year (n = 59)	
In which cases bisphosphonates can be prescribed			
For patients with osteoporosis	43 (89.6%)	47 (79.7%)	$\chi^2 = 1.95, P = 0.163$
For patients with Paget’s disease	23 (47.9%)	33 (55.9%)	$\chi^2 = 0.682, P = 0.409$
For metastases in bones	23 (47.9%)	32 (54.2%)	$\chi^2 = 0.423, P = 0.515$
For gastrointestinal tract metastases	15 (31.3%)	11 (18.6%)	$\chi^2 = 2.286, P = 0.31$
Correct answers about bisphosphonates properties			
Bisphosphonates that are taken only orally	3 (6.3%)	0 (0%)	$\chi^2 = 3.794, P = 0.051^a$
Bisphosphonates that are taken only intravenously	4 (8.3%)	5 (8.5%)	$\chi^2 = 0.001, P = 0.979^a$
Bisphosphonates that are taken orally and intravenously	39 (81.3%)	49 (83.1%)	$\chi^2 = 0.059, P = 0.808$
One of the main properties of bisphosphonates is the activation of bone resorption	21 (43.8%)	15 (25.4%)	$\chi^2 = 3.982, P = 0.046$
One of the main properties of bisphosphonates is the inhibition of bone resorption	25 (52.1%)	40 (67.8%)	$\chi^2 = 2.741, P = 0.098$
Oral bisphosphonates are absorbed better than intravenous ones	9 (18.8%)	10 (16.9%)	$\chi^2 = 0.059, P = 0.808$
Absorption of intravenous bisphosphonates is better compared to oral bisphosphonates	31 (64.6%)	37 (62.7%)	$\chi^2 = 0.04, P = 0.841$
Sources of knowledge about bisphosphonates			
Scientific literature	4 (8.3%)	11 (18.6%)	Cramér’s V = 0.316, P = 0.013
Material provided by professors	9 (18.8%)	21 (35.6%)	
Additional sources	0 (0%)	2 (3.4%)	
Do not know enough about bisphosphonates	35 (72.9%)	25 (42.4%)	
Who can perform tooth extraction for patients taking bisphosphonates			
Only a general dentist	1 (2.1%)	4 (6.8%)	Cramér’s V = 0.395, P < 0.001
Only a dentist specialist	31 (64.6%)	15 (25.4%)	
Both	16 (33.3%)	40 (67.8%)	

^aFisher’s exact.
n = number.

It was found that the knowledge of dentistry students about the properties of bisphosphonates differed only in the case of the statement about the activation of bone resorption. Therefore, compared to the fifth-year students 21 (43.8%), fourth-year students 15 (25.4%) were more likely to agree with the statement that one of the main properties of bisphosphonates is the activation of bone resorption ($P = 0.046$) (Table 1).

The study found that fourth-year students' understanding of one of the main properties of bisphosphonates, inhibition of bone resorption, were lower due to lack of knowledge. Regarding other statements, the opinions of fourth- and fifth-year dental students did not differ ($P > 0.05$).

The knowledge about bisphosphonates of fourth- and fifth-year students differed statistically significantly: in the fourth-year, most of students 35 (72.9%) thought that they did not have enough knowledge about bisphosphonates compared to only 25 (42.5%) in the fifth-year. In the fourth-year, there were statistically significantly fewer students who obtained knowledge about bisphosphonates from scientific literature, lectures, and additional courses than in the fifth-year ($P = 0.013$). The relationship between the studied course and the source of information is of moderate strength (Cramér's $V = 0.316$) (Table 1).

It was found that the students' opinions about tooth extraction differ statistically significantly between fourth- and fifth-year students ($P < 0.001$). Thirty-one (64.6%) fourth-year students believed that tooth extraction could be performed by a dentist specialist only, while 40 (67.8%) fifth-year students said they believed that tooth extraction could be performed by both a general dentist and a specialist. The relationship between these students answers and the year of studies was of moderate strength (Cramér's $V = 0.395$) (Table 1).

Students' knowledge about BRONJ

A comparison of student responses using Cramér's V-test revealed that the definition did not differ statistically significantly by year of study ($P = 0.62$) (Table 2). Seventeen (35.4%) of the fourth-year students selected the answer that BRONJ is open necrotic bone that does not heal within 4 weeks in patients treated with bisphosphonates who have not received radiation therapy in the jaw area and no tumour metastases have been detected. While 20 (33.9%) fifth-year students chose correct answer: exposed, necrotic bone that does not heal within 8 weeks in patients who are on bisphosphonate

treatment when there is no history of radiation treatment to the area of the jaws, as well no tumour metastases. In contrast, only 11 (22.9%) fourth-year students chose the correct answer.

The opinions of fourth- and fifth-year dental students about BRONJ properties did not differ statistically significantly ($P > 0.05$) (Table 2). Most of the students chose the correct answers to the statements, both about the fact that osteonecrosis develops more often in the mandible (fourth-year: 36 students [75%], fifth-year: 43 students [72.9%]), and about the fact that osteonecrosis is more dangerous in those taking intravenous bisphosphonates (fourth-year: 32 [66.7%] students, fifth-year: 40 [67.8%] students).

It was found that 39 (83%) fourth-year students were more likely to send the patient to dentist specialist than fifth-year students 32 (55.2%) while the tooth extraction itself was more often tend to be done by students from the fifth-year 21 (36.2%) than from the fourth-year 4 (8.5%). The proportion of indecisive students in the fourth and fifth-years differed very little regarding tactics. The relationship between the study year and the tactics of the tooth extraction procedure was evaluated as moderate (Cramér's $V = 0.329$) (Table 2).

The knowledge about the classification of BRONJ did not differ statistically significantly between each year ($P = 0.089$), but majority of students were not familiar with the classification of the disease. More fifth-year students 17 (28.8%) were familiar with the disease classification compared to fourth-year students 7 (14.9%) (Table 2).

Twenty-one students out of 24 students were familiar with the classification of BRONJ. It turned out that the ability of students to recognize the stage of osteonecrosis of the jaws and prescribe the necessary treatment did not differ statistically significantly between each year ($P = 1.000$). Most students would not be able to recognize the stage of the disease and to prescribe the necessary treatment for it (Table 2).

The importance of additional knowledge about bisphosphonates

Students were asked to express their opinion about the need for wider education concerning bisphosphonates and BRONJ at the University. Most of fourth- and fifth-year students (39 [81.3%] and 45 [76.3%] respectively), agreed with this statement, no statistically significant difference was observed between the opinions according to the year of study (Table 2).

Table 2. Descriptive analysis of data associated with BRONJ and the opinion of dental students about the need for increased education concerning bisphosphonates at the University

Parameter	Students (n [%])		Criteria and P-value
	Fourth-year (n = 48)	Fifth-year (n = 59)	
Dental students' knowledge about BRONJ			
Exposed, necrotic bone that does not heal within 4 weeks in bisphosphonate-treated patients with no history of radiation therapy to the jaw area and no tumour metastases	17 (35.4%)	18 (30.5%)	Cramér's V = 0.129, P = 0.62
Exposed, necrotic bone that does not heal within 8 weeks in a bisphosphonate-treated patient who has never received radiation therapy to the jaw area, and no tumour metastases are detected	11 (22.9%)	20 (33.9%)	
Exposed, necrotic bone that does not heal within 4 weeks in bisphosphonate-treated patients who have received radiation therapy to the jaw area and metastases have been found	11 (22.9%)	10 (16.9%)	
Exposed, necrotic bone that does not heal within 8 weeks in bisphosphonate-treated patients who have received radiation therapy to the jaws and metastases have been found	9 (18.8%)	11 (18.6%)	
Dental students' agreement with statements about BRONJ			
Develops more often in the upper jaw	12 (25%)	14 (23.7%)	$\chi^2 = 0.023$, P = 0.879
Develops more often in the lower jaw	36 (75%)	43 (72.9%)	$\chi^2 = 0.061$, P = 0.804
More dangerous for the patients who use bisphosphonates intravenously	32 (66.7%)	40 (67.8%)	$\chi^2 = 0.015$, P = 0.901
More dangerous for patients who take bisphosphonates orally	12 (25%)	12 (20.3%)	$\chi^2 = 0.33$, P = 0.565
Choosing a tooth extraction strategy in the patient taking bisphosphonates			
Would refer the patient to a dentist-specialist	39 (83%)	32 (55.2%)	Cramér's V = 0.329, P = 0.003
Would do the tooth extraction themselves	4 (8.5%)	21 (36.2%)	
Do not know	4 (8.5%)	5 (8.6%)	
Dental students' knowledge about the classification of BRONJ			
Know	40 (85.1%)	42 (71.2%)	$\chi^2 = 2.894$, P = 0.089
Do not know	7 (14.9%)	17 (28.8%)	
The ability of dental students to recognize the stage of BRONJ and required treatment			
Would not be able to recognize the stage of the disease and would not be able to prescribe the necessary treatment	4 (80%)	13 (81.2%)	$\chi^2 = 0.004$, P = 1.000 ^a
Would be able to recognize the stage of the disease and prescribe the necessary treatment	1 (20%)	3 (18.8%)	
The opinion on increased education about bisphosphonates at the University			
Education is needed only about BRONJ	8 (16.7%)	10 (16.9%)	Cramér's V = 0.12, P = 0.674
Education is needed both about BRONJ and about bisphosphonates themselves	39 (81.3%)	45 (76.3%)	
More education is not required, enough information is received	0 (0%)	1 (1.7%)	
Do not know	1 (2.1%)	3 (5.1%)	

^aFisher's exact.

BRONJ = bisphosphonate-related osteonecrosis of the jaw; n = number.

DISCUSSION

This study aimed to evaluate the knowledge of LSMU fourth- and fifth-year dental students about bisphosphonates, their main properties and administration, the classification of BRONJ, how to recognize BRONJ and choose the appropriate treatment tactics, as well as to obtain additional

information and necessity for students of supplementary studies.

The results of present study revealed that there no statistically significant difference (P > 0.05) of fourth- and fifth-year students' knowledge about the administration of bisphosphonates. In contrast, there was different understanding about the activation of bisphosphonates for bone resorption. Consequently, compared to the fifth-year students 21 (43.8%),

fourth-year students 15 (25.4%) were more likely to agree with the statement that one of the main properties of bisphosphonates is the activation of bone resorption ($P = 0.046$). Finally, in the fourth-year, most students - 35 (72.9%) thought that they did not have enough knowledge about bisphosphonates, while in the fifth-year only 25 (42.5%) did. The reason for this may be the fact that there are statistically significantly ($P = 0.013$) fewer students who acquired knowledge about bisphosphonates from scientific literature, lectures, additional courses in the fourth-year than in the fifth-year. Furthermore, fourth-year students were convinced that only a specialist dentist can extract teeth, while fifth-year students believed that both a general dentist and a specialist can extract teeth ($P < 0.001$).

The opinions of fourth- and fifth-year dental students about BRONJ properties did not differ statistically significantly ($P > 0.05$). In addition, it was aimed to find out how many students knew the exact definition of BRONJ. Twenty (33.9%) fifth-year students knew the correct answer, compared to 11 (22.9%) fourth-year students. In a similar study by Rosella et al. [9] it was also asked dental students at "Sapienza" University of Rome, Roma, Italy, about the definition of BRONJ. The options for choosing answers were almost identical to those in the survey provided to LSU students. Sixteen (34.8%) of the 46 final year students knew the exact definition of BRONJ.

Similarly, Paredes et al. [10] assessed the knowledge in 159 (52%) of 308 dentists and dental students about bisphosphonates and BRONJ. A total of 243 (79%) of participants reported having information about bisphosphonates, 209 (68%) recognized that BRONJ could be caused by bisphosphonates, and 259 (84%) felt it was important to inquire about possible bisphosphonate use during anamnesis. In contrast, Han [11] performed questionnaire-based survey among 1000 dentists registered in an online community in Korea. Study revealed that dentists do not respond reliably to patients' drug history prior to performing dental procedures: only 650/1000 (65%) routinely documented the type of bisphosphonate used by patients and only 591/1000 (59.1%) dentists routinely requested information from doctors before performing dental surgery on patients.

LSMU dental students first get aware with bisphosphonates and BRONJ in the fourth year, studying oral pathology. Deeper knowledge

is acquired in the fifth-year of maxillofacial surgery studies, where a lecture is given on the aetiology, diagnosis, treatment, and prevention of BRONJ. Similarly, Rosella et al. [9] mentioned that a lecture on bisphosphonates and BRONJ in oral pathology is given to fourth-year students at "Sapienza" University of Rome. Almousa et al. [12] evaluating the knowledge of drug-related osteonecrosis of the jaw among practicing dentists and students in their professional years, mentioned that related education has recently been incorporated into dental curricula, although it is not consistently taught across institutions. This agrees with López-Jornet et al. [13] who assessed the knowledge of dental students about bisphosphates and BRONJ of the jaw at the School of Dentistry of the University of Murcia, Murcia, Spain, and concluded that "greater educational efforts should be made to promote knowledge of this pathology, at both undergraduate and postgraduate levels". The results of the conducted study and the data of other authors show that seeking to reduce the risk of developing BRONJ, more active education of dental students and dentists is necessary.

One of the main shortcomings of this study is the limited number of respondents. On the other hand, our study indicates the shortcomings of the curriculum and provides an opportunity to re-evaluate the students' knowledge after making teaching program corrections.

CONCLUSIONS

The study revealed that fifth-year students demonstrated better knowledge about bisphosphonates compared to fourth-year students and this was due to a curriculum supplemented with information about this pathology. The overall findings of this research suggest that Universities need to expand their student curricula by providing more knowledge about bisphosphonates and its relation to bisphosphonate-related osteonecrosis of the jaw.

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The authors report no conflict of interest related to this study.

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Appendix 1. Survey

What year of LSMU Dentistry are you in?
4 th year
5 th year
Bisphosphonates are prescribed (choose one or more answers you think are correct):
For patients with osteoporosis
For patients with Paget's disease
For metastases in bones
For gastrointestinal tract metastases
Choose the correct answers about bisphosphonates (several correct answers are available):
For oral use only
For intravenous use only
For both oral and intravenous use
One of the main properties of bisphosphonates is the activation of bone resorption
One of the main properties of bisphosphonates is the inhibition of bone resorption
Absorption of oral bisphosphonates is better compared to intravenous bisphosphonates
Absorption of intravenous bisphosphonates is better compared to oral bisphosphonates
How did you find out about bisphosphonates?
From the scientific literature
From materials provided by the lecturers
From courses
I do not think I know enough about bisphosphonates
Who do you think can perform tooth extraction for patients taking bisphosphonates?
Only a dentist
Only a dentist specialist
Both
Choose the most appropriate term for medication-induced osteonecrosis:
Exposed, necrotic bone that does not heal within 4 weeks in patients receiving bisphosphonate therapy, in the absence of radiation therapy and no metastases are diagnosed.
Exposed, necrotic bone that does not heal within 8 weeks in patients receiving bisphosphonate therapy, in the absence of radiation therapy and no metastases are diagnosed.
Exposed, necrotic bone that does not heal within 4 weeks in patients receiving bisphosphonate therapy and jaw radiation therapy and metastases are diagnosed.
Exposed, necrotic bone that does not heal within 8 weeks in patients receiving bisphosphonate therapy and jaw radiation therapy and metastases are diagnosed.
Choose one or more correct answers about bisphosphonate-induced osteonecrosis:
Bisphosphonate-induced osteonecrosis is more common in the upper jaw
Bisphosphonate-induced osteonecrosis is more common in the lower jaw
Bisphosphonate-induced osteonecrosis is more dangerous for those who take them orally
If a patient who is taking bisphosphonates needs tooth extraction, your strategy is:
I would refer the patient to a specialist
I would do tooth extraction myself
I do not know
Are you familiar with the classification of drug-induced osteonecrosis?
Yes
No
Would you be able to identify the stage of the bisphosphonate-related osteonecrosis of the jaw and assign the required treatment? (If you answered NO to the previous question, skip this question)
I have heard about the classification of the disease, but I would not be able to identify the stage of the disease and assign the treatment required.
I have heard about the classification of the disease and will be able to identify the stage of the disease and assign the required treatment
Is there a need for more university education on bisphosphonates and the osteonecrosis they cause?
Education is only required for bisphosphonate-induced osteonecrosis
Education is needed on both bisphosphonate-induced osteonecrosis and bisphosphonates
No, we get enough information
I do not know