



## RESEARCH ON RISK FACTORS FOR DEVELOPMENT OF BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAWS AMONG BULGARIAN PATIENTS OVER 18 YEARS OF AGE

Boryana Ilieva<sup>1</sup>, Yanko G. Yankov<sup>2,3</sup>, Tsvetelina Borisova-Papancheva<sup>4</sup>, Georgi Papanchev<sup>5</sup>, Vasil Sveshtarov<sup>1</sup>

1) Department of Dental, Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Medical University of Sofia, Bulgaria.

2) Clinic of Maxillofacial Surgery, University Hospital "St. Marina", Varna, Bulgaria.

3) Department of General and Operative Surgery, Faculty of Medicine, Medical University Varna, Bulgaria.

4) Department of Conservative Dental Treatment and Oral Pathology, Faculty of Dental Medicine, Medical University of Varna, Bulgaria.

5) Department of Oral Surgery, Faculty of Dental Medicine, Medical University of Varna, Bulgaria.

### ABSTRACT

**Introduction:** The widespread use of bisphosphonates (BF) led to the discovery of a probable link with the subsequent development of osteonecrosis of the jaw. The aim of the present study is to investigate and analyze the risk factors for the development of bisphosphonate-related osteonecrosis of the jaw (BRONJ) in the Bulgarian population and to compare with those described so far in the world literature.

**Material and methodology:** This is a retrospective study in which we included 44 patients with BRONJ treated and followed up by the authors' collective for 13 years (2009-2023). In all of them, demographic characteristics, primary disease, initiating cause of the necrosis, type of bisphosphonates, duration of BF therapy, mode of administration of BF, localization of the necrosis were observed and analysed.

**Results:** There was no statistically significant difference between the two sexes. BRONJ mainly affects patients in the age group of 61-70 years. A significantly higher proportion of the patients had a primary diagnosis of malignancy. The BF administered was mainly Zoledronic acid. BF was administered intravenously. In most of the patients dentoalveolar surgical intervention was carried out. The lower jaw, mainly the distal region, was affected.

**Discussion:** BRONJ is a multifactorial disease, and knowing the factors influencing the onset of the disease, as well as those influencing the outcome of its treatment, is of utmost importance when choosing a preventive and treatment strategy for the patients receiving BF.

**Conclusions:** The present article confirms that the demographic characteristics, etiology, and organ involvement of the Bulgarian population with BRONJ match the data in the world literature on the condition.

**Keywords:** bisphosphonates, osteonecrosis of the jaws, maxillofacial surgery, osteoporosis, malignant disease, tooth extraction, bisphosphonate intake, dentoalveolar surgical intervention,

### INTRODUCTION

Bisphosphonates are a group of drugs that are widely used in the treatment of diseases associated with osteoclast-mediated bone loss [1]. Although rare, avascular osteonecrosis of the jaw has been recognized as a complication of bisphosphonate use. In 2003, Marx first described "painful bone-exposure" of the upper and lower jaws in patients taking pamidronate (Aredia; Novartis Pharmaceuticals, East Hanover, NJ) and zoledronate (Zometa; Novartis Pharmaceuticals) [2]. Since then, the question of bisphosphonate-associated osteonecrosis of the jaw bones (BRONJ) has been raised, and a number of authors have published their observed cases [2, 3].

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a current or previous treatment with anti-resorptive or antiangiogenic agents resulting in exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial area, which persists for more than 8 weeks, in the absence of evidence of radiation therapy to the jawbones or obvious metastatic disease of the jawbones [3]. It is a multifactorial disease, and the risk factors for the development of the disease are divided into risk factors related to bisphosphonate therapy, local risk factors, demographic and systemic factors, genetic factors and preventive factors [1, 3].

The aim of this study is to examine the risk factors for the development of BRONJ in the Bulgarian population, including demographic and clinical characteristics of the patients - age, sex, main disease, presence of previous surgical intervention and characteristics of the BF (type of BF, duration of administration, dosage form), localization of lesions and to compare them to the ones described in the world literature up to date.

**MATERIALS AND METHODS**

This is a retrospective study that included all 44 cases of patients with bisphosphonate-related osteonecrosis of the jaws that the author’s team treated from 2009 to 2023 and who met the set follow-up inclusion criteria. Among them, 21 (47.7%) were treated at the Clinic of Maxillofacial Surgery at the University General Hospital St. Anna, Sofia, Bulgaria, for active treatment, and 23 (52.3%) were treated in outpatient settings by maxillofacial and oral surgeons. Of these, 20 (45.5%) were women and 24 (54.5%) were men. With regard to the main disease, due to which it is necessary to take BF, 40 (90.9%) of the patients have malignancy, and 4 patients (9.1%) have idiopathic osteoporosis. Intravenous administration of BF was registered in 40 (90.9%) of the patients, and oral administration in 4 patients (9.1%).

The values of the following parameters were determined in all of the examined patients: regarding the patients, demographic information collected includes data on patients’ age at diagnosis and gender. For our convenience, we divided the examined patients into six age groups as follows: I group (30-40 years); II group (41-50 years); III group (51-60 years); IV group (61-70 years); Group V (71-80 years); VI group (81-90 years); gender - women and men; according to the primary disease - malignancy or osteoporosis; according to the initiating cause of the necrosis - previous surgical intervention for performed dentoalveolar surgical intervention (extraction of a tooth or placement of a dental implant) or mechanical trauma from a removable prosthesis; according to the localization of the process - involvement of the maxilla, of the mandible or both jaws. We divided the maxilla and mandible into two regions: anterior (encompassing the area of canines, lateral and central incisors, and the area of first and second premolars) and posterior (first, second, and third molars).

Regarding the bisphosphonates taken, we observed the type of bisphosphonate/bisphosphonates: Zoledronic acid, Alendronic acid, Ibandronic acid, Pamidronic acid; Zoledronic acid (alone or in combination with another drug from the BF group) and all other BF; duration of BF therapy (in months); mode of administration of BF (oral or intravenous).

The inclusion criteria are patients that were included in the study should have been on current or previous treatment with bisphosphonates, at an age over 18 years, with a presence of advanced jaw bone necrosis meeting the following criteria: exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that persists for more than eight weeks, a lack of data on performed radiation treatment of the head and neck and available complete medical documentation of all patients.

The exclusion criteria are patients with the presence of lesions resulting from a neoplastic process in the jaw bones, the presence of lesions resulting from a metastatic process in the jaw bones, performed radiation treatment of the jaw bones were excluded from the study, age under 18 years and lack of complete medical documentation.

For each patient included in the study, an analysis of

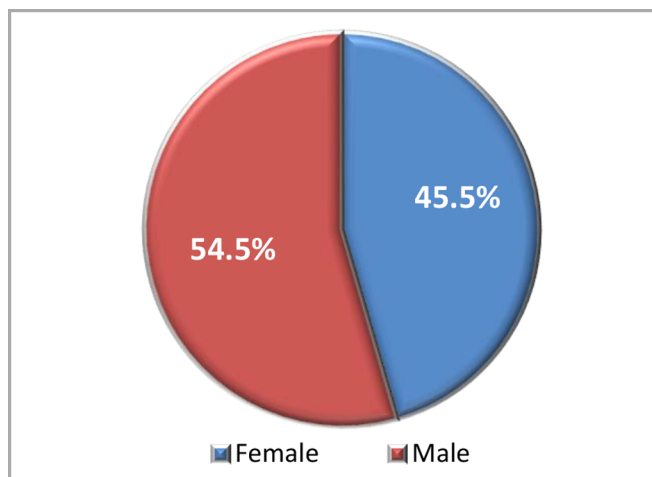
their hospital documentation, including gender, age, underlying disease, type, route of administration, and duration of bisphosphonate intake, localization of the BRONJ, and performed dentoalveolar surgical intervention, was made.

The specialized statistical package SPSS (Statistical Package for the Social Sciences) version 20.0 was used to process the survey data statistical methods: descriptive analysis, Mann-Whitney test, Fisher’s exact test. The threshold level of significance adopted is  $\alpha=0.05$ . Statistical significance was assumed when the p value was less than  $\alpha$  ( $p<0.05$ ). Microsoft Excel 2007 was used for graphic analysis to visually present the results. Quantitative variables are presented by summarizing statistical characteristics - arithmetic mean (Mean value) and standard deviation (SD). Categorical variables are presented by absolute frequencies (n) and relative frequencies (%).

**RESULTS**

Regarding the distribution of patients by gender, we found that 20 (45.5%) of the patients were women and 24 (54.5%) were men, and the difference between the sexes was not statistically significant ( $p>0.05$ ). The male: female gender distribution is 1.1:0.9 (Figure 1).

**Fig. 1.** Distribution of the studied patients by gender



According to the age of the patients, they were divided into six age groups presented in Table 1.

**Table 1.** Frequency distribution of the studied patients in age groups

Age group (years)	Number of patients	Percentage (%)
30-40	2	4.545
41-50	2	4.545
51-60	6	13.636
61-70	19	43.182
71-80	14	31.818
81-90	1	2.273

In Table 1, it can be seen that BRONJ occurs most often in the age between 60-70 years. There were 19 (43.2%) patients in this age group. The age group between 70 and 80 patients is also highly represented (31.8%). The percentage distribution in the 50-60 age group is lower (13.6%). We observe only two cases (4.6%) of BRONJ in the 30-40 and 40-50 age groups. Only one patient (2.3%) of the examined was aged 80-90 years. In the studied material, we did not find a case under the age of 30 years and over 91 years.

Regarding the age factor of patients with BRONJ, we found a minimum age of 36 years, a maximum age of 88 years, an average age of 62 years, and a standard deviation of 10.42 (Table 2).

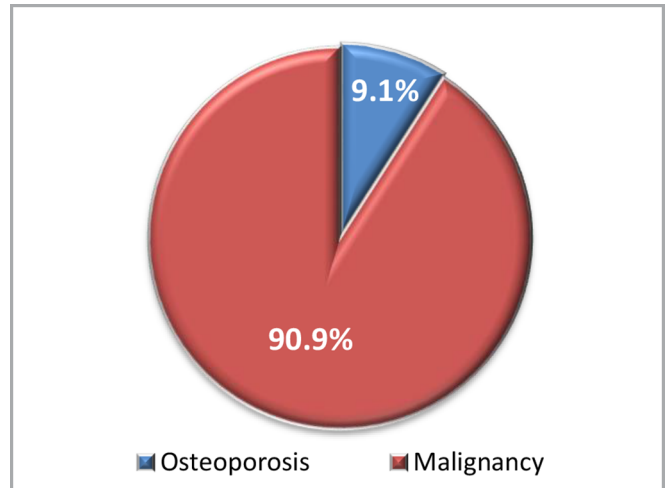
**Table 2.** Frequency distribution of the studied patients according to the variable age

	Mean age	Minimum age	Maximum age	Standard deviation
Age (years)	65.273	36	88	10.422

Regarding the main diagnosis of the patients, the present study shows that a significantly higher proportion - 40 (90.9%) of the patients had a primary diagnosis of malignancy. In four patients (9.1%), the intake of BF was indicated by an underlying disease of osteoporosis (Figure 2).

When examining the patients according to the type of administered BF, it was found that the administered BF with the highest frequency was Zoledronic acid - in 32 of the patients (72.7%). The second place is taken by

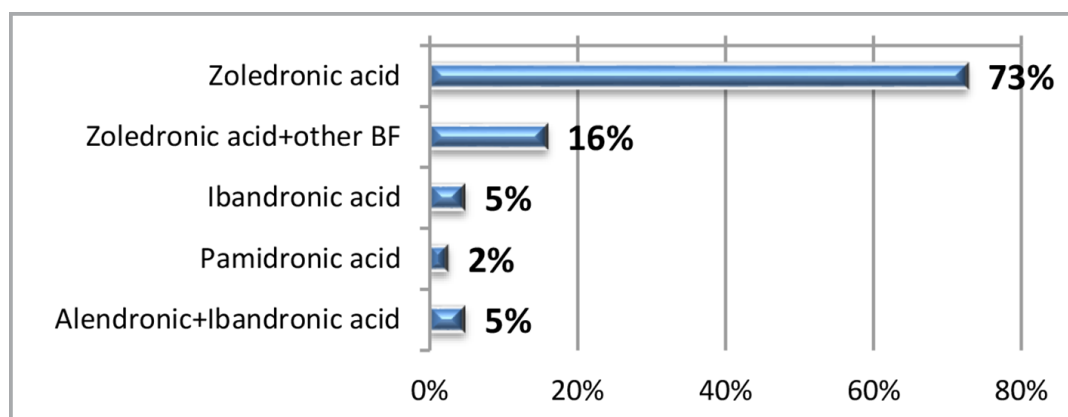
**Fig. 2.** Distribution of the studied patients according to their main diagnosis



Zoledronic and Pamidronic acid in five patients (11.4%). Alendronic acid and Ibandronic acid in two (4.5%) and Ibandronic acid in two (4.5%) of the studied patients followed in the same percentage. In the last place in distribution are Pamidronic acid in one patient (2.3%), Zoledronic and Alendronic acid in one (2.3%) and Zoledronic, Ibandronic and Pamidronic acid also in one patient (2.3%).

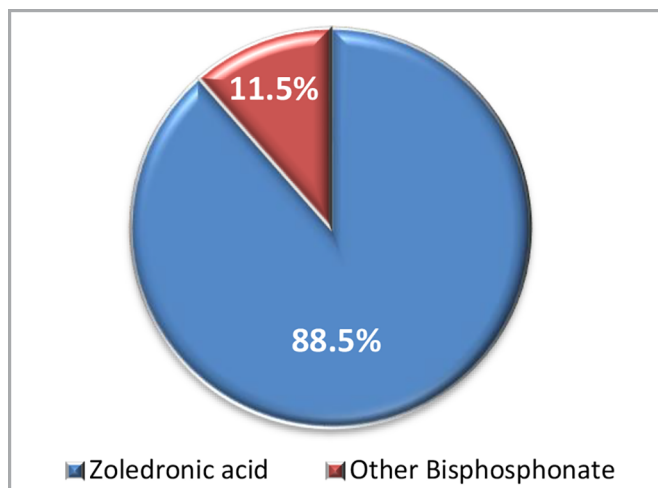
It was also established that in the largest percentage of cases, Zoledronic acid was taken - in 32 (72.7%), followed by Zoledronic acid and another BF - in 16% (seven of the patients). In a significantly smaller percentage of cases with an equal number of patients, Ibandronic acid (4.5%, two patients) and Alendronic acid and Ibandronic acid (4.5%, two patients) and Pamidronic acid in one patient (2.3%) (Figure 3).

**Fig. 3.** Distribution of the studied patients according to the type of the received BF



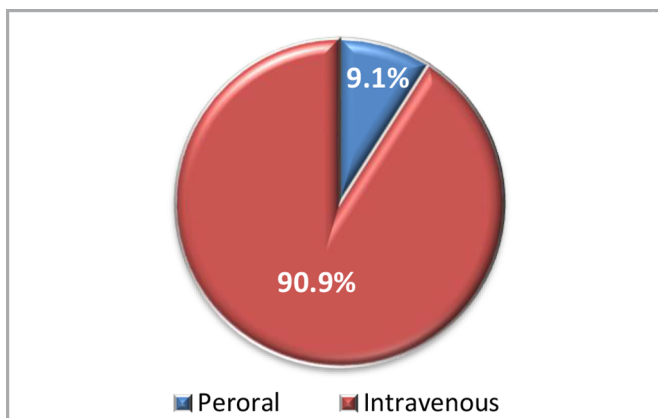
It was also found that in a significantly larger percentage - 88.5% of the cases, the BF administered was Zoledronic acid (alone or in combination with another drug from the BF group), compared to 11.5% in total for all other BF (Figure 4).

**Fig. 4.** Distribution of the studied patients according to the type of the introduced BF



According to the method of introduction of BF into the body, we found the following distribution: in a significantly greater percentage of cases, BF was administered intravenously in 40 patients (90.1%), compared to four of the patients (9.1%), in which BF was administered orally (Figure 5).

**Fig. 5.** Distribution of the studied patients according to the method of administration of BF



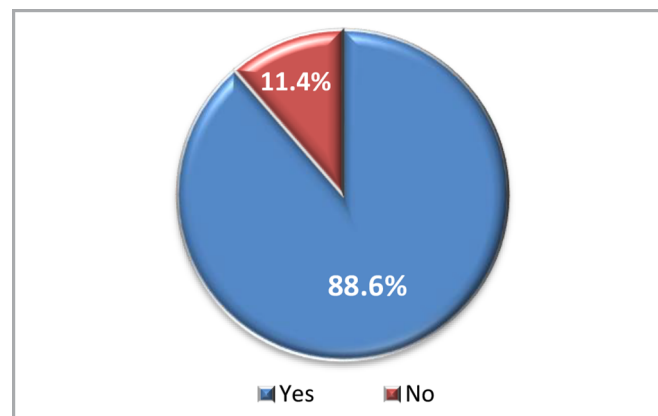
Our study showed a maximum value of the duration of the BF intake of 108 months, a minimum value of eight months, an average value of 41.75 months, with a standard deviation of 27.1 months. The distribution graphically is shown in Table 3.

**Table 3.** Distribution of cases according to the duration of BF intake in the studied patients

	Average value	Minimum value	Maximum value	Standard deviation
Duration of BF intake (months)	41.75	8	108	27.08

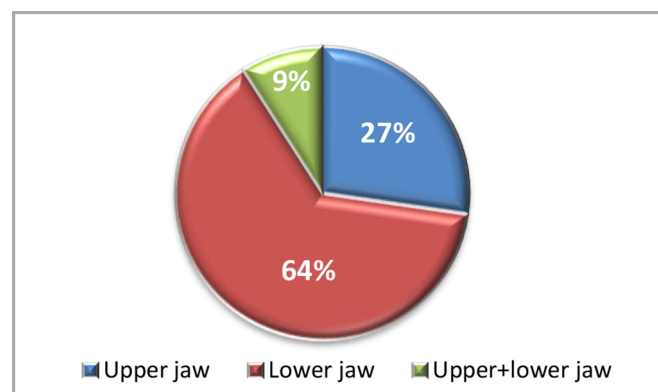
In relevance to the presence of previous surgical intervention or mechanical trauma, the examination of the clinical material shows that in a significantly higher percentage of cases before the appearance of BRONJ, a dentoalveolar surgical intervention (tooth extraction or placement of a dental implant) was carried out - 88.6% (39 patients), compared to 11.4% (five patients) with mechanical trauma from a removable dental prosthesis (Figure 6).

**Fig. 6.** Distribution of the studied patients according to the presence of previous surgical intervention or mechanical trauma



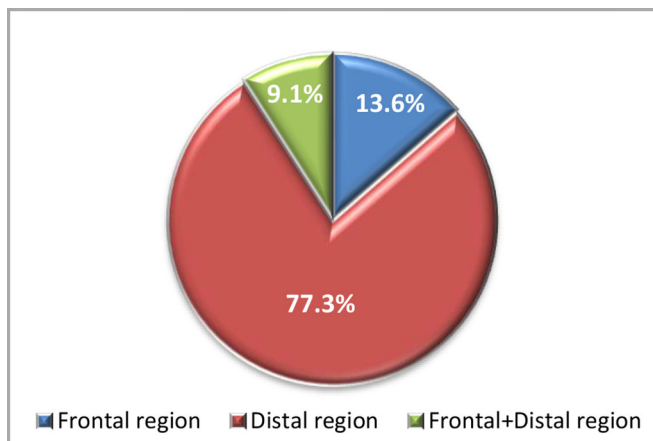
The research carried out regarding the localization of BRONJ shows that in the largest percentage - in 63.6% (28 patients) the lower jaw is affected, followed by 27.3% (12 patients) with involvement of the upper jaw, and only in 9.1% (four patients) the disease affects both the upper and lower jaw (Figure 7).

**Fig. 7.** Distribution of the studied patients according to the localization of BRONJ depending on which of the jaw bones is affected



The most common localization in the studied group was the distal region of the jaw - in 34 patients (77.3%). Next was the frontal region in six of them (13.6%), and the lowest rate was observed in four of the patients (9.1%), in which both the frontal and distal regions of the jaw bones were affected (Figure 8).

**Fig. 8.** Distribution of the studied patients according to the localization of BRONJ depending on which part of the jaw bones is affected



## DISCUSSION

According to the age and gender of the studied contingent, our results coincide with the data from the literature on the absence of a statistically significant difference between the sexes as a demographic factor that is relevant to the development of BRONJ. According to Badros A et al., gender is not statistically significantly associated with BRONJ [4]. Some authors, however, report a preferential involvement of female patients -73-87% of all studied patients with BRONJ. We found no such dependence in our study [5]. According to the AAOMS, the higher rate of this complication in women is more likely a reflection of the underlying disease necessitating BF intake (i.e., osteoporosis, breast carcinoma) [6].

From the analysis of the distribution of cases by age groups, it can be seen that BRONJ is a disease of adults. The frequency of the disease increases with age. A peak is established in the 61-70-year-old group and remains high for the 71-80-year-old patients as well. The average age of the studied contingent in our study is 62 years and varies between 36 and 88 years.

A number of studies have linked the advanced age of patients with BRONJ, which is also confirmed with our study [1, 7]. This may be due to the slowing down of restorative and healing processes in elderly people. Also, in older patients, the complications of caries and periodontal diseases increase, so the need to perform dentoalveolar surgical treatments and the percentage of patients using removable dentures increases. Dentoalveolar surgery and trauma from removable dentures are considered risk factors for the development of BRONJ [6, 8]. In addition, advanced age may be associated with a longer period of BF intake due to a longer course of the underlying disease. That is why we cannot consider advanced age as a predictive factor for the development of BRONJ on its own. More extensive research is needed to establish the role of age as a factor in the development of BRONJ [8]. According to

Badros et al., the risk of developing BRONJ increases with each additional year of follow-up and the patient's advancing age [4]. We observe a significant decrease in the frequency of BRONJ in 81-90-year-old patients. This is most likely due to genetic or lifestyle factors and associated comorbidity. In this group, we found only one patient (2.27%) - an 88-year-old man in the third stage of oncological disease. In the group that we studied, the cases with young people (younger than 40 years) occupy 4.55% (two patients - a woman aged 36 and a man aged 38). We did not find development of BRONJ in the age of less than 30 years. In this age group, BFs are used to treat diseases such as Osteogenesis imperfecta. Our results are consistent with those published so far in the literature. Despite the long-term use of BF, no cases of BRONJ have been identified in children and young patients (up to 24 years) [5, 7, 9]. Data analysis showed that the difference in underlying disease was statistically significant (K-S  $d=0.53180$ ,  $p<0.01$ ). Therefore, the main diagnosis of the patient's malignant disease is a risk factor for the development of BRONJ, compared to the main disease of osteoporosis. Our results are close to those published in the literature to date.

According to several authors, the frequency of BRONJ is significantly higher in patients who undergo BF therapy due to the underlying disease of multiple myeloma, prostate carcinoma, and breast carcinoma [9]. Patients treated for benign bone diseases such as osteoporosis, osteogenesis imperfecta show a relatively low incidence of BRONJ. This may be due to the lack of oncological treatment and the fact that a relatively low cumulative dose of BF is sufficient to achieve a therapeutic effect [6,8]. In the osteoporotic patient population, the incidence of ONJ is estimated to be 0.001% to 0.01%, slightly higher than the incidence in the general population [10]. The percentage distribution in our study concerning the type of the used BF is close to the results published in the literature.

According to Boonyapakorn T, et al., the type of BF taken may play a role in the occurrence of BRONJ [11]. As the action potential of BF increases, so does the risk of developing BRONJ. Zoledronate, Pamidronate (intravenously) and Alendronate (peroral) were administered in the largest number of reported cases of patients with BRONJ [3, 12]. Other studies have shown that patients who have ever received zoledronate had a 4.5- to 28-fold increase in the relative risk of developing BRONJ [6, 9]. Otto et al. reported the following percentage distribution, depending on the BF used: with the greatest frequency - Zoledronat (47.6%), Zoledronat combined with another BF (24.6%), i.v. administered Pamidronate (15.1%), i.v. Ibandronate (7.1%), 5.6%-combination of intravenous BFs, 3.2%- oral BFs- Risedronate and Alendronate [12]. According to a study by Sook-Bin Woo, 94% of patients who developed BRONJ were treated with Pamidronate and Zoledronic acid [13]. In our country, this percentage reaches 92.9%.

When comparing BFs administered intravenously, the one with the strongest potential of action, zoledronate, is more often associated with the occurrence of BRONJ, compared to the one with a lower potential, pamidronate [11, 13].

Studying the method of administration of BF, we found out that intravenous intake of BF dominates significantly over oral intake and is a risk factor for the development of BRONJ ( $p < 0.01$ ). Our results are close to those described in the literature. Otto et al. found that 96.8% of their studied patients with BRONJ had a clinical history of intravenous BF, with only 3.2% taking BF orally [12]. A number of authors reported a frequency of intravenous BF in patients with BRONJ close to that found in our study - a frequency higher than 90% [11, 12, 13]. This is most likely due to the fact that the bioavailability of intravenous BF derivatives in the body is approximately 100 times higher than that of oral BFs [13].

According to other authors, the two risk factors of greatest importance for the development of BRONJ are the intravenous intake of BF and dentoalveolar procedures [3, 13]. A number of authors found that the intake of BF for a long period of time is associated with an increased risk of developing BRONJ. In his study, Kos found a mean duration of BF intake of 34 months, which is lower compared to our results (41.75 months) [6]. A study by Otto S. et al. showed that the average duration of the period from the initiation of BF therapy to the diagnosis of BRONJ was 38.9 months, values close to our study [12].

According to Marx et al., the most critical factor for the development of BRONJ in patients taking oral BF is the duration of the BF intake. He defines a duration of admission over three years as critical for the development of BRONJ [14]. We found a higher value for the minimum duration of BF intake that leads to the development of BRONJ compared to Vahntsevanos et al., who stated that the development of BRONJ is very unlikely if BF intake is shorter than six months [15]. Other authors found a greater value of the minimum duration of BF intake at which BRONJ develops - 12-13 months, compared to our results (eight months) [10, 11].

Dentoalveolar surgical intervention is a risk factor for the development of BRONJ. 88.6% of patients underwent dentoalveolar surgical intervention (tooth extraction or placement of a dental implant), and 11.4% of patients had mechanical trauma from a removable prosthesis. Our results are similar to those of Hess L, et al., who found that 88.9% of patients taking oral BFs reported a dental procedure preceding the appearance of BRONJ [16]. Other authors found a lower percentage (data vary between 50-77%) of development of BRONJ after dentoalveolar surgical intervention. Boonyapakorn et al. found the spontaneous occurrence of BRONJ in 23% of the studied patients on intravenous BF therapy, and in the remaining 77%, there had been a development of BRONJ after tooth extrac-

tion [11]. According to Kos, this percentage reaches 78% [6]. Sven Otto et al. reported that the frequency of dental procedures preceding the development of BRONJ was 63.6% (including tooth extractions or extractions combined with endodontic or periodontal procedures or decubitus injuries) [12]. Another study involving patients taking oral BFs showed that 50% of cases of BRONJ occur spontaneously, the remaining 50% - as a result of a dental procedure - 40% after tooth extraction, 6.7% - after placement of a dental implant and 3.3% - after taking a palatal connective tissue graft [5, 7].

According to the AAOMS, dentoalveolar surgery is a major risk factor for the development of MAONJ, citing studies in which dental extractions were performed in 52-61% of patients with MAONJ. In the absence of sufficient data, the committee considered that the risk of ONJ after placement of dental implants and endodontic or periodontal procedures that require bone exposure and manipulation is comparable to the risk associated with tooth extraction [3]. According to another study, there is a plausible relationship between dental extractions and the development of BRONJ in cancer patients [4, 13].

In view of the presented facts, the question arises as to whether the intake of BF itself is a sufficient condition for the development of BRONJ. Although necrosis can occur spontaneously, in a greater percentage of cases, it is associated with trauma from dentoalveolar surgery (88.6% in our study) or mechanical trauma from a removable prosthesis (11.4% in the present study). A number of authors raise the question of the role of infection in the pathogenesis of BRONJ, but most likely, it does not lead to the development of the disease if there is no exposed bone [1, 5]. The exposure of the alveolar bone during dentoalveolar surgery creates an open door for microorganisms, bacterial invasion and the development of infection. This may explain the correlation we found between BRONJ and dental surgical interventions.

According to the localization of BRONJ, our results are similar to those of studies published in the literature, with the highest percentage of involvement of the mandible, followed by the maxilla, and the least common involvement of both jaws [4]. Ruggiero et al. studied 63 patients with BRONJ and found that 63% were affected by the lower jaw and 37% by the upper jaw [3]. In another study, he reported that the ratio of the incidence of mandibular involvement to the incidence of maxillary involvement was 2:1 [14]. Marx RE, et al. studied 119 patients and reported the following distribution: 68.1% mandible, 27.7% maxilla, 4.2% in both jaws [2]. Sook-Bin Woo et al. summarized 368 published cases of BRONJ in which the upper jaw was affected in 65%, the lower jaw in 26%, and both jaws in 9% [13]. Boonyapakorn et al. reported that the lower jaw was affected in 59% of cases, the upper jaw in 27%, and both jaws in 14% [11]. Otto et al. found the

following frequency distribution regarding the localization of BRONJ - in 70.6%, the mandible was affected, in 18.3% - the maxilla and in 11.1% - both jaws [12]. In a study by Lesclous et al., 54% of cases of ONJ occur in the mandible, 43% in the maxilla and 3% in both jaws [17]. In the cited literature, the frequency of involvement of the lower jaw is from 59-70.6%, for the upper jaw, the frequency ranges from 18.3-38%, and involvement of both jaws is observed in 4.2-14%, results close to our research.

Bone turnover in alveolar bones is enhanced, leading to a greater probability of incorporating BF into their structure compared to other skeletal bones [3]. This, as well as the presence of teeth in these bones, which may be a gateway for infection, may explain the exclusive involvement of the upper and lower jaws by BRONJ. In addition, the oral mucosa is thin and susceptible to injuries caused by, for example, dentures. Consistent with studies reported in the literature, we found that BRONJ most commonly affects the mandible. This is because the mandible, like other bones such as the femur, is surrounded by cortical bone, but the teeth located within this bone provide a pathway for microorganisms to penetrate from the periodontal space into the bone marrow. A possible explanation for the preferential involvement of the mandible is that the maxilla has an abundant blood supply that is greater than in the mandible. The results of another study using the bone scintigraphy method showed that the bone metabolism of the intact mandible was affected by long-term administration of BF [18].

Data from the literature overlap with our results concerning which part of the jaw bones is affected - frontal, distal or both. Regarding the site affected by the necrosis, Otto et al. found that predilection sites for the development of BRONJ are the molar and premolar areas of both jaws [12]. According to a study by Thumbigere-Math et

al., the distal parts of the mandible are indicated as the most frequently affected area by BRONJ [19]. Marx et al. found that the most frequently affected region was the distal part of the mandible, in the area of the molars (65.5%), followed by the distal part of the maxilla (22.7%) [14]. The increased accumulation of BF in the jaw bones, as well as the greater mechanical forces to which these bones are subjected, may explain why the distal regions of the maxilla and mandible (which are exposed to the greatest loading forces) are more frequently affected [13]. The structure and blood supply of the jawbones in these areas (dense, compact bone, less cancellous bone, fewer blood vessels) may also be relevant to the more frequent involvement of the distal areas by BRONJ.

## CONCLUSIONS

The results from our study regarding the risk factors for the development of BRONJ in the Bulgarian population are close to the ones published in the literature up-to-date. The factor that does not affect the BRONJ is the sex of the patient. BRONJ is a disease of elderly people with a mean value of 62 years. We can confirm that the risk factors that are connected with the development of BRONJ are malignancy as a main disease, zoledronate as a type of BF, intravenous intake of the BF and the prolonged period of administration of the drug (an average value of 41.75 months in our study). Dentoalveolar surgical intervention is also a major factor in the development of BRONJ. In terms of localization, the distal areas of the mandible are at increased risk of BRONJ occurrence. BRONJ is a multifactorial disease, and knowing the factors influencing the onset of the disease, as well as those influencing the outcome of its treatment, is of utmost importance when choosing a preventive and treatment strategy for the patients receiving BF.

---

## REFERENCES:

1. Scala R, Maqoud F, Antonacci M, Dibenedetto JR, Perrone MG, Scilimati A, et al. Bisphosphonates Targeting Ion Channels and Musculoskeletal Effects. *Front Pharmacol*. 2022 Mar 15;13: 837534. [[PubMed](#)]
2. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg*. 2003 Sep;61(9):1115-7. [[PubMed](#)]
3. Thomas JG, Ouanounou A. Medication-related osteonecrosis of the jaw: a narrative review of risk factors, diagnosis, and management. *Front Oral Maxillofac Med*. 2023 Dec 30;5:31. [[Crossref](#)]
4. Badros AZ, Meddeb M, Weikel D, Philip S, Milliron T, Lapidus R, et al. Prospective Observational Study of Bisphosphonate-Related Osteonecrosis of the Jaw in Multiple Myeloma: Microbiota Profiling and Cytokine Expression. *Front Oncol*. 2021 Jun 24; 11:704722. [[PubMed](#)]
5. Maciel AP, Quispe RA, Martins LJO, Caldas RJ, Santos PSDS. Clinical profile of individuals with bisphosphonate-related osteonecrosis of the jaw: an integrative review. *Sao Paulo Med J*. 2020 Jul-Aug;138(4): 326-35. [[Crossref](#)]
6. Kos M. Association of dental and periodontal status with bisphosphonate-related osteonecrosis of the jaws. A retrospective case controlled study. *Arch Med Sci*. 2014 Feb 24; 10(1):117-23. [[PubMed](#)]
7. Boston B, Ipe D, Capitanescu B, Gresita A, Hamlet S, Love R, et al. Medication-related osteonecrosis of the jaw: A disease of significant importance for older patients. *J Am Geriatr Soc*. 2023 Aug;71(8):2640-52. [[Crossref](#)]
8. Kos M, Luczak K, Godzinski J, Klempous J. Treatment of monostotic fibrous dysplasia with pamidronate. *J Craniomaxillofac Surg*. 2004 Feb; 32(1):10-5.
9. Hoff AO, Toth B, Hu M,

- Hortobagyi GN, Gagel RF. Epidemiology and risk factors for osteonecrosis of the jaw in cancer patients. *Ann N Y Acad Sci.* 2011 Feb;1218:47-54. [[PubMed](#)]
10. Everts-Graber J, Lehmann D, Burkard JP, Schaller B, Gahl B, Häuselmann H, et al. Risk of Osteonecrosis of the Jaw Under Denosumab Compared to Bisphosphonates in Patients With Osteoporosis. *J Bone Miner Res.* 2022 Feb;37(2): 340-8. [[PubMed](#)]
11. Boonyapakorn T, Schirmer I, Reichart PA, Sturm I, Massenkeil G. Bisphosphonate-induced osteonecrosis of the jaws: prospective study of 80 patients with multiple myeloma and other malignancies. *Oral Oncol.* 2008 Sep;44(9):857-69. [[PubMed](#)]
12. Otto S, Schreyer C, Hafner S, Mast G, Ehrenfeld M, Stürzenbaum S, Pautke C. Bisphosphonate-related osteonecrosis of the jaws - characteristics, risk factors, clinical features, localization and impact on oncological treatment. *J Craniomaxillofac Surg.* 2012 Jun;40(4):303-9. [[PubMed](#)]
13. Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med.* 2006 May 16;144(10):753-61. [[PubMed](#)]
14. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg.* 2005 Nov;63(11): 1567-75. [[PubMed](#)]
15. Vahtsevanos K, Kyrgidis A, Verrou E, Katodritou E, Triaridis S, Andreadis CG, et al. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. *J Clin Oncol.* 2009 Nov 10;27(32):5356-62. [[PubMed](#)]
16. Hess LM, Jeter JM, Benham-Hutchins M, Alberts DS. Factors associated with osteonecrosis of the jaw among bisphosphonate users. *Am J Med.* 2008 Jun;121(6):475-83. [[PubMed](#)]
17. Lesclous P, Grabar S, Abi Najm S, Carrel JP, Lombardi T, Saffar JL, et al. Relevance of surgical management of patients affected by bisphosphonate-associated osteonecrosis of the jaws. A prospective clinical and radiological study. *Clin Oral Investig.* 2014 Mar;18(2):391-9. [[Crossref](#)]
18. Nakai F, Ohbayashi Y, Nakai Y, Iwasaki A, Miyake M. Bone metabolism of the jaw in response to bisphosphonate: a quantitative analysis of bone scintigraphy images. *Odontology.* 2020 Oct;108(4):653-60. [[PubMed](#)]
19. Dioguardi M, Di Cosola M, Copelli C, Cantore S, Quarta C, Nitsch G, et al. Oral bisphosphonate-induced osteonecrosis complications in patients undergoing tooth extraction: a systematic review and literature updates. *Eur Rev Med Pharmacol Sci.* 2023 Jul; 27(13):6359-73. [[PubMed](#)]

*Please cite this article as:* Ilieva B, Yankov YG, Borisova-Papancheva T, Papanchev G, Sveshtarov V. Research on Risk Factors for Development of Bisphosphonate-Related Osteonecrosis of the Jaws Among Bulgarian Patients Over 18 Years of Age. *J of IMAB.* 2025 Jan-Mar;31(1):6061-6068. [[Crossref](#) - <https://doi.org/10.5272/jimab.2025311.6061>]

Received: 28/08/2024; Published online: 10/03/2025



#### Address for correspondence:

Boryana Ilieva,  
 Department of Dental, Oral and Maxillofacial Surgery, Faculty of Dental  
 Medicine, Medical University of Sofia;  
 1, St Georgi Sofiyski Blvd., 1431 Sofia, Bulgaria.  
 E-mail: [dr.ilieva@abv.bg](mailto:dr.ilieva@abv.bg),