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# BISFOSFONATIMA IZAZVANA OSTEONEKROZA VILICA POZNATA PATOLOŠKA POJAVA ILI NE?

## BISPHOSPHONATE RELATED OSTEONECROSIS OF THE JAW – KNOWN PATHOLOGICAL ENTITY OR NOT?

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### Sažetak

**Uvod:** Pojava novih terapijskih mogućnosti za onkološke, autoimune i reumatološke pacijente, dovela je do značajnog poboljšanja kvaliteta njihovog života. Ipak, kako su ovi pacijenti na dugoročnoj terapiji lekovima koji pokazuju neželjena dejstva, uporedo sa prevencijom pogoršanja osnovne bolesti, javlja se novi patološki problem u vilicama, takozvana bisfosfonatna osteonekroza viličnih kostiju (BRONJ).

**Cilj** ove epidemiološke studije bio je da se utvrdi koliki je procenat stomatologa u Severnoj Makedoniji upoznat sa pojavom, problemima i komplikacijama koje prate pacijente koji koriste terapiju koja može izazvati bisfosfonatne lezije vilica, kao i mogućnost prepoznavanja bisfosfonatne osteonekroze vilica.

**Materijal i metode:** Istraživanje je sprovedeno u Republici Severnoj Makedoniji, u ukupno 100 stomatoloških ordinacija u periodu od jula do avgusta 2024.godine. Anketa je sardžala 10 pitanja o informisanosti i načinu informisanosti lekara, kao i sposobnostima prepoznavanja osteonekroze vilica i lečenja bisfosfonatima izazvane osteonekroze vilica.

**Rezultati:** Od ukupno 100 podeljenih anketa, 35 stomatologa je vratilo popunjene upitnike, odnosno, 35% stomatologa je želelo da učestvuje u anketiranju. Od tog broja 68,5% nije do sada čulo za pojavu bisfosfonatne osteonekroze vilica. Od 31,5% koji su imali saznanja o ovoj patološkoj pojavi, 60% saznalo od kolega, 25% na kontinuiranoj medicinskoj edukaciji, 15% iz literature. 88,5% stomatologa ne zna da li i koji lekovi mogu da dovedu do BRONJ, dok 68,5% ne postavlja anamnestička pitanja vezano za stanja u kojim se ovi lekovi koriste. Osamdeset procenata stomatologa ne poznaje bilo kakve preventivne niti terapijske mere za BRONJ.

**Zaključak:** Mali procenat stomatologa Severne Makedonije ima znanje o BRONJ-u. Informisanost o pojavi, preventivi i lečenju trebalo bi da se poveća, kroz programe kontinuirane medicinske edukacije, kao i kroz ostale vidove dobijanja stručnih saznanja.

**Cljučne reči:** osteonekroza, BRONJ, edukacija

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### Abstract

**Introduction:** The appearance of new therapeutic options for oncological, and rheumatological patients has led to a significant improvement in their quality of life. These patients are on long-term therapy with drugs that show unwanted effects, along with the prevention of worsening of the underlying disease, a new pathological problem in the jaws appears, the so-called bisphosphonate related osteonecrosis of the jaw bones (BRONJ).

**The aim** of this epidemiological study was to determine the percentage of dentists in North Macedonia who are aware of the occurrence, problems and complications that accompany patients BRONJ as well as the ability to recognize it.

**Material and methods:** The research was conducted in the Republic of North Macedonia, in a total of 100 dental practices. The survey included 10 questions about the information and the way doctors were informed, as well as the ability to recognize osteonecrosis of the jaws and treatment of osteonecrosis of the jaws caused by bisphosphonates.

**Results:** Out of a total of 100 distributed surveys, 35 dentists returned completed questionnaires, i.e., 35% of dentists wanted to participate in the survey. Of the total of 35 processed questionnaires, 68.5% have not heard of the occurrence of bisphosphonate osteonecrosis of the jaws. Of the 31.5% who had knowledge of this pathological phenomenon, 60% learned from colleagues, 25% during continuing medical education, 15% from the literature. 88.5% do not know whether and which drugs can lead to BRONJ, while 68.5% do not ask anamnestic questions about the conditions in which these drugs are used. Eighty percent of dentists do not know any preventive or therapeutic measures for BRONJ.

**Conclusion:** A small percentage of dentists in North Macedonia have knowledge about BRONJ. Awareness of occurrence, prevention and treatment should be increased, through programs of continuous medical education, as well as through other ways of obtaining professional knowledge.

**Key words:** osteonecrosis, BRONJ, education

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## Introduction

For the first time, osteonecrosis of the jaws as a consequence of therapy was definitively associated with radiotherapy, with the initial paper on radioosteonecrosis published in 1922.<sup>1</sup> Nearly a century later, in 2003<sup>2</sup>, studies began to emerge regarding the negative effects of bisphosphonate therapy. This phenomenon has since been termed Bisphosphonate-Related Osteonecrosis of the Jaws -BRONJ<sup>3</sup>.

Bisphosphonates are potent antiresorptive agents. The primary objective of antiresorptive therapy is to prevent pathological fractures in bones weakened by primary and secondary bone diseases, most commonly osteoporosis and oncological conditions. First documented in the literature in 2003<sup>2</sup>, Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) was characterized as avascular, aseptic necrosis of the jaw resulting from pharmacological agents that disrupt normal bone metabolism. Interestingly, a similar condition, historically known as "Phosphorus jaw," was observed in the nineteenth century among match factory workers<sup>4</sup>.

Bisphosphonates were first synthesized in 1865 in Germany for use in the agricultural industry<sup>5</sup>. Their role in bone resorption became widely recognized in the 1960s. More than fifty years have passed since the biological effects of bisphosphonates in that period termed as diphosphonates—were first described in *Science and Nature* in 1969<sup>6</sup>. Bisphosphonates possess two key characteristics: a strong affinity for bone minerals and the ability to inhibit osteoclast activity. Extensive evaluation of nitrogen-containing bisphosphonates during the 1980s and 1990s led to a pivotal discovery: the antiresorptive effects of these advanced analogues primarily result from their potent inhibition of the enzyme farnesyl diphosphate synthase<sup>7</sup>.

Bisphosphonates (BPs) are classified into two main groups based on their chemical composition and mechanism of action. Nitrogen-free bisphosphonates (low potency), such as etidronate and clodronate, disrupt ATP-dependent intracellular pathways, leading to osteoclast apoptosis. In contrast, nitrogen-containing bisphosphonates (high potency), including pamidronate, alendronate, ibandronate, and zoledronate, exert their effects by inhibiting key enzymes in the mevalonate biosynthetic pathway. The elucidation of the enzyme's crystal structure has demonstrated that nitrogen-containing bisphosphonates bind to its active site via their critical nitrogen atom, effectively inhibiting key enzymes in the mevalonate biosynthetic pathway. This inhibition disrupts osteoclast function and

survival, leading to a substantial reduction in bone resorption. As a result, nitrogen-containing bisphosphonates have become highly effective therapeutic agents in the management of osteoporosis, metastatic bone disease, and other conditions associated with excessive bone turnover<sup>3</sup>.

Bisphosphonates form a strong bond with osteoclasts, initially inhibiting their apoptosis. However, once apoptosis occurs, these agents remain embedded in the bone matrix, integrating into the surrounding bone and exerting cumulative effects that can persist for 5 to 12 years<sup>8</sup>. The retention of bisphosphonates in the skeleton is closely linked to bone turnover, as their release is dependent on the rate of bone remodeling.

Pathological remodeling arises when there is an imbalance between bone resorption and formation, or when both processes occur excessively. Notably, jawbones have a significantly higher metabolic turnover compared to long tubular bones, rendering them particularly vulnerable to the effects of bisphosphonates. Consequently, the majority of bisphosphonate-related osteonecrosis of the jaw (BRONJ) cases occur following tooth extraction or minor surgical interventions, poorly adapted prosthesis that causes pressure on the soft and bone tissue, poor dental fillings that can create periodontal pockets.

All these facts highlight the extremely potent effects of bisphosphonates, surpassing even the impact of radiation therapy on bone metabolism. Due to their strong affinity for bone and prolonged retention in the skeletal system, bisphosphonates play a crucial role in the management of various pathological conditions affecting bone health. Bisphosphonates are widely used in the treatment of osteoporosis, osteomalacia, osteogenesis imperfecta, and Paget's disease, as well as endocrine disorders that influence bone metabolism. Additionally, they are employed in oncology for both primary bone malignancies (e.g., multiple myeloma, sarcoma, and thyroid cancer) and metastatic bone disease arising from cancers such as prostate, breast, and lung cancer. The reported prevalence of BRONJ varies significantly, ranging from 3% to 20%, depending on factors such as dosage, duration of therapy, and patient-specific risk factors<sup>9</sup>.

Certain criteria must be met to classify a condition as Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ)<sup>10</sup>. According to established definitions, the diagnosis requires the following conditions to be fulfilled: History of bisphosphonate use (either oral or intravenous administration); Presence of non-healing intraoral or extraoral fistula or exposed necrotic bone in the maxillofacial region persisting for more than 8

weeks; No history of radiation therapy in the head and neck region; Absence of metastatic tumors or other malignancies affecting the jaw.

These criteria help distinguish BRONJ from other osteonecrotic conditions, such as radiation-induced osteonecrosis or tumor-related bone destruction.

The appearance of BRONJ can be staged in four stages from 0 to 3.<sup>10</sup> dependant of bone exposure, symptoms and infection.

Stage 0 represents an asymptomatic phase during which there is no clinically visible bone exposure; In approximately 50% of patients, bone exposure subsequently occurs within 1–7 months, most commonly around 4–5 months<sup>9,10</sup>. Stage 1 is characterized by the presence of an area of exposed necrotic bone or a fistula. Generally, patients in this phase remain asymptomatic and do not exhibit any signs of inflammation or infection. Stage 2 is characterized by clearly exposed necrotic bone, accompanied by an intraoral fistula, pain, and impaired oral function. This stage is invariably associated with inflammatory signs and infection in the surrounding soft tissues. Stage 3 is advanced stage, the necrotic area extends beyond the alveolar ridge to involve the base of the mandible; alternatively, it may extend into the maxillary sinus or affect the zygomatic process of the maxilla. Typically, extraoral fistulas, as well as oroantral or oronasal communications, are observed. Additionally, spontaneous detachment of small fragments of necrotic bone may occur, as well as pathological bone fractures<sup>10</sup>.

Factors influencing on appearance of BRONJ are :the dose, type and length of therapy; oral health enlightenment – awareness of the importance of oral hygiene; geographical area - Scandinavian countries have more patients with osteoporosis due to lack of sunny days<sup>11</sup>; socioeconomic status - regulation of the health system in the country and knowledge of medical doctors and dental doctors about the possibility of appearance of BRONJ.

**The aim** of this study was to assess the awareness of dentists in the Republic of North Macedonia regarding the potential development of osteonecrosis of the jaw as a consequence of bisphosphonate therapy.

### ***Materials and Methods***

The study was conducted from 1 July to 1 August 2024 in 100 private dental practices in the Republic of North Macedonia. The assessment of knowledge regarding BRONJ was carried out using a questionnaire comprising 10 questions addressing the

occurrence of osteonecrosis of the jaw in relation to bisphosphonate therapy.

#### **Questionnaire Content:**

1. How many complications related to difficult wound healing after tooth extraction do you experience per month/year?

2. During anamnesis, do you routinely inquire if patients are currently undergoing or have previously received treatment for malignant diseases?

3. What is the recommended minimum period before initiating radiation therapy during which it is safe to perform tooth extraction?

4. Are you aware of any oncological therapies, aside from radiation and chemotherapy, that negatively affect the healing of extraction wounds?

5. During anamnesis, do you routinely ask patients if they suffer from osteoporosis or other bone system disorders?

6. During anamnesis, do you routinely ask patients about the specific therapies they use to treat osteoporosis or other bone system disorders?

7. Are you knowledgeable about the drugs used in treating osteoporosis and bone malignancies?

8. Have you heard of bisphosphonate therapy?

9. Have you ever encountered the association between bisphosphonate therapy and lesions in the jawbones?

10. How did you first receive information regarding the relationship between jaw changes and the use of bisphosphonate therapy?

After the completion and return of the questionnaires, the data were processed and the results were presented in percentages.

### ***The Results***

Out of a total of 100 private dental practices where the questionnaire was administered, as many as 65 were not motivated to complete it, i.e. 35% questionnaires were assessed. The primary reason for dentist's demotivation cited was a lack of knowledge regarding the answers to most of the questions.

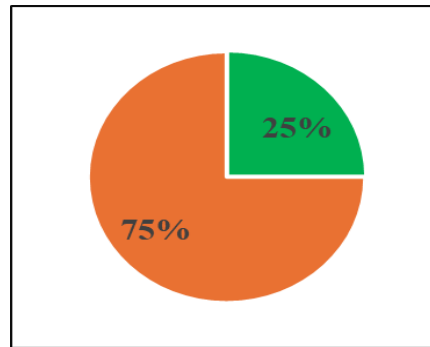
Among the remaining 35 completed questionnaires, findings indicated that approximately 25% of tooth extractions resulted in complications related to the healing process, meaning that every fourth extraction exhibited prolonged or difficult healing (Figure 1). During patient anamnesis, 65% of dentists

reported inquiring about medication use, whereas 35% did not (Figure 2). Regarding the time considered safe for extraction wound healing, only 14% correctly identified a period of three or more weeks (Figure 3).

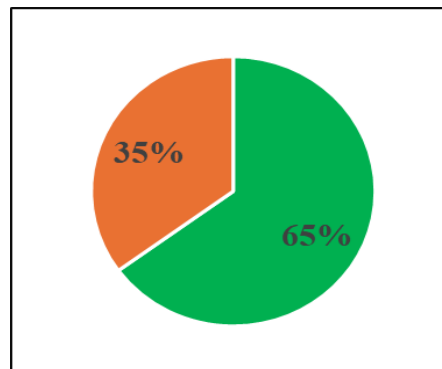
Concerning oncological therapies, 72% of dentists were unaware of any treatment other than radiation therapy that could affect jawbone healing (Figure 4). Additionally, 63% of dentists did not ask patients about their bone health regarding osteoporosis during anamnesis (Figure 5), while 68.5% failed to inquire whether patients were taking medications for bone diseases (Figure 6). Alarming, 89% of dentists could not identify which medications

might impact bone metabolism (Figure 7). Furthermore, 68.5% had never heard of bisphosphonate therapy (Figure 8).

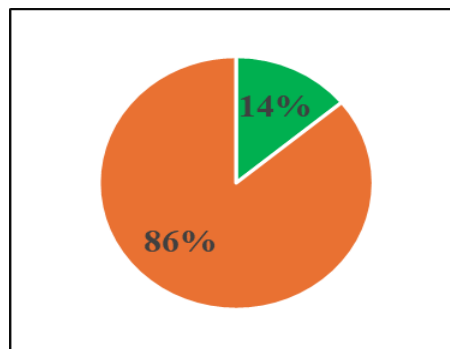
Approximately 80% of dentists were unable to recognize or manage bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Figure 9). Moreover, 58% had never heard of osteonecrosis of the jaw at all. Among the small proportion of informed dentists (35%), 60% reported learning about BRONJ from colleagues, 15% through the academic literature, and 25% via continuing medical education (Figure 10). (Green color=yes, Orange-No)



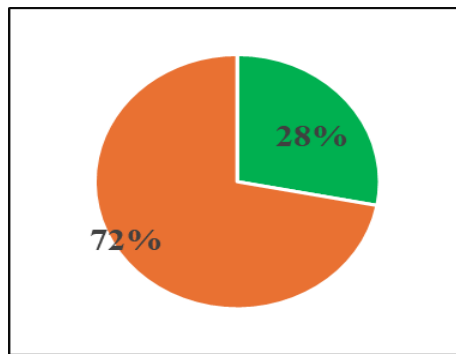
**Figure 1.** The presence of complications after tooth extraction



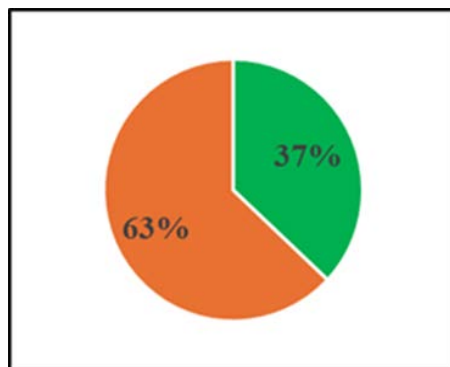
**Figure 2.** The percent of dentists who take data on oncology and bone diseases



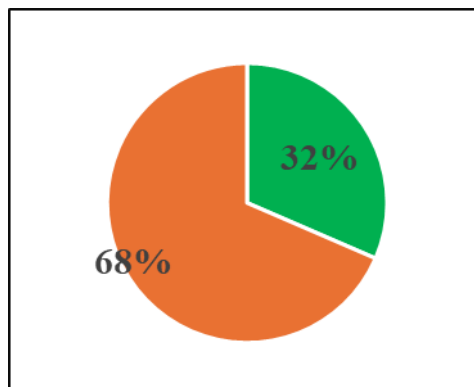
**Figure 3.** The knowledge of dentists about timely tooth extraction before radiation therapy



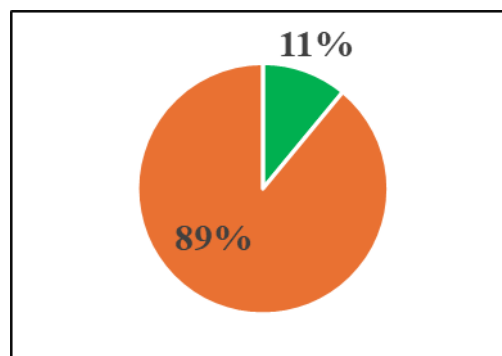
**Figure 4.** The knowledge of dentists about any therapy (excluding radiation) that disturbs post extraction wound healing



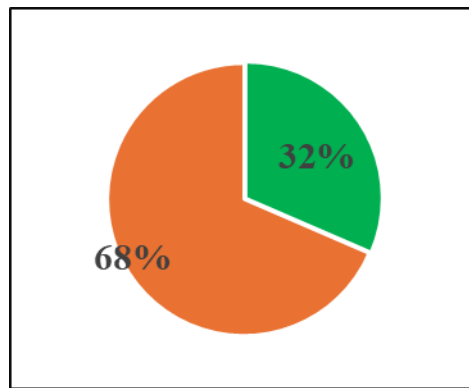
**Figure 5.** The percentage of dentists taking detailed data about bone diseases



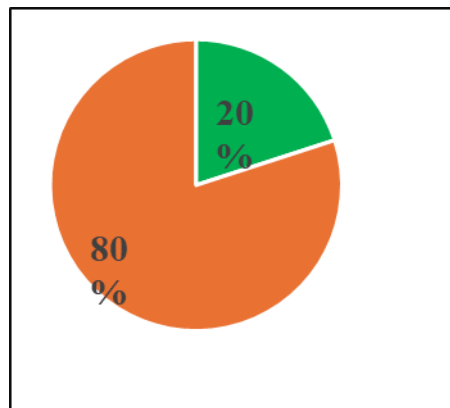
**Figure 6.** The percentage of dentists taking data about consuming medication for osteoporosis and bone diseases



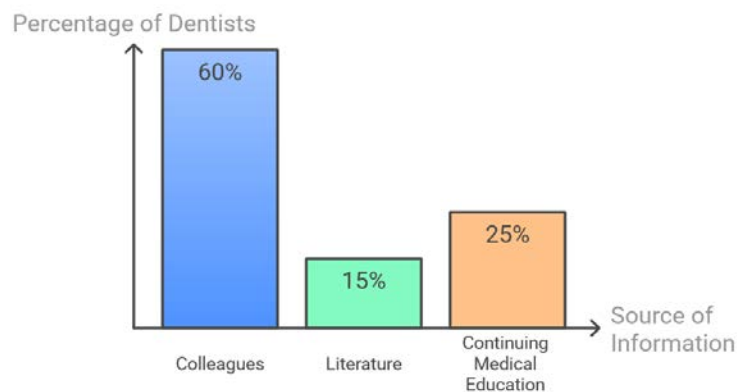
**Figure 7.** Knowledge about medications for osteoporosis and malignancy treatment



**Figure 8.** The percentage of dentists never heard about bisphosphonate therapy



**Figure 9.** The percentage of dentists able to recognize BRONJ



**Figure 10.** Sources of awareness about BRONJ among dentists

## Discussion

Antiresorptive agents, specifically bisphosphonates, exhibit a high affinity for osteoclasts, influencing their differentiation and promoting apoptosis. By integrating into the bone matrix, bisphosphonates exert a prolonged cumulative effect on bone remodeling and healing. The suppression of osteoclastic activity, which is responsible for bone resorption, consequently leads to a reduction in osteoblastic function, thereby impairing bone formation. Additionally, bisphosphonates

induce alterations in the microstructure of bone tissue, leading to vascular disturbances that compromise bone circulation and nutrient supply<sup>12</sup>.

The emergence of novel therapeutic options for oncological and rheumatological patients has significantly enhanced their quality of life. Bisphosphonate therapy plays a crucial role in regulating bone conditions and resorption associated with primary or metastatic tumors, as well as advanced osteoporosis<sup>13</sup>.

In women, the most common indications for bisphosphonate use, which may lead to

bisphosphonate-related osteonecrosis of the jaw (BRONJ), include osteoporosis and bone metastases from breast cancer (73% of cases metastasize to the bones) and uterine cancer (29%)<sup>14</sup>. Notably, 78% of postmenopausal women aged  $\geq 50$  years present with osteopenia and/or osteoporosis, with one in three experiencing osteoporotic fractures. In Macedonia, the female population is approximately 1,000,000 (average age  $\geq 40$ ). In men, bisphosphonate therapy is primarily indicated for bone metastases from malignant tumors, most commonly prostate cancer (68%), lung cancer (36%), and kidney cancer (22%)<sup>14,15</sup>. Additionally, around 20% of men over 50 years of age have osteoporosis. The male population of Macedonia is estimated at approximately 870,000 (average age  $\geq 42$ ).

The fact that 80% of dentists are not aware of the possibility of osteonecrosis of the jaw as a result of medication use, and that 69% of dentist had never heard about bisphosphonate therapy. In total of 100 examined dentists, only 35 were motivated to participate in the study. Also discouraging fact was that 35% of dentists do not take a complete medical history that includes systemic and oncological diseases, or appropriate information about their therapy. Osteoporosis can cause problems itself, even if it was not treated with bisphosphonates.

The pathophysiology of BRONJ remains incompletely understood. It is widely considered multifactorial, involving a complex interplay of mechanisms. Key contributing factors include impaired physiological bone remodeling, persistent inflammation and infection, inhibition of angiogenesis, and dysfunction of both innate and acquired immunity. These factors collectively compromise bone homeostasis and wound healing, predisposing affected individuals to osteonecrosis<sup>16</sup>.

Interventions that contribute to the development of BRONJ include procedures that directly involve jawbone tissue, such as tooth extractions, implant placement, periodontal pocket curettage, and periapical surgeries. Additionally, interventions that result in mucosal damage, compromising the integrity of the oral soft tissues, may also increase the risk of BRONJ. To avoid BRONJ it is essential to conduct a comprehensive medical and dental history assessment, along with a thorough clinical examination and the necessary radiographic imaging.

General Medical History should obtain detailed insight into systemic diseases and ongoing pharmacological treatments, data

about oncology treatment. Dentists should be aware that radiation therapy in the chest region can cause partial irradiation of the mandible and salivary glands. Xerostomia is a predisposing factor for the occurrence of BRONJ. Cytotoxic drugs induce xerostomia by directly damaging the salivary glands, whereas anticholinergic agents inhibit salivary secretion by disrupting neural stimulation. Additionally, diuretics contribute to dehydration and increased excretion of bodily fluids, further exacerbating dry mouth<sup>17</sup>.

Dental history and examination should obtain an assessment of any changes in sensitivity, vitality, postponed wound healing, the appearance of fistula formation (onset, etiology), periodontal probing, percussion sensitivity, evaluation of the presence of periodontitis, soft tissue inflammation and infections. Cytokines, including tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin-1 beta (IL-1 $\beta$ ), may contribute to the development of osteonecrosis of the jaw by exacerbating inflammation and enhancing bone resorption<sup>18</sup>.

Bisphosphonates are anticipated to have applications beyond their conventional role as antiresorptive agents. Emerging research suggests their potential use as vectors for targeted drug delivery into the skeletal system, capitalizing on their high affinity for bone mineral<sup>19</sup>.

The indications for the use of bisphosphonate therapy are expanding, while awareness of the risks associated with this type of therapy in some regions remains very low<sup>20</sup>.

## Conclusion

Dentists are responsible for raising awareness about bisphosphonate-related osteonecrosis of the jaw, as well as other medical doctors. Nurses can also play role in facilitating communication between physicians and dentists, ensuring coordinated patient care. This responsibility implies educating of medical staff through continuous professional education, including seminars, ongoing training, and other educational opportunities.

## Conflicts of Interest

The authors declare that they have no conflict of interest.

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