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Prevalence of osteonecrosis of the jaw and oral characteristics of oncologic patients treated with bisphosphonates at the General Hospital of Mexico

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Abstract (J Korean Assoc Oral Maxillofac Surg 2016;42:365-369)

Objectives: To determine the prevalence and oral characteristics of cancer patients treated with bisphosphonates in the oncology and maxillofacial prosthesis departments of the General Hospital of Mexico between 2011 and 2013.

Materials and Methods: This cross-sectional study included patients who received prior treatment with bisphosphonates; an intraoral examination was performed by 2 standardized examiners.

Results: The prevalence of bisphosphonate-related necrosis in 75 patients was 2.6%; the most common malignancy was breast cancer (84.0%), followed by prostate cancer (16.0%). Exostosis was present in 9.3% of patients and the mean Decayed, Missing, Filled Teeth index was 4.64; 44.0% of the study group had a Community Periodontal Index value between 2 and 2.9 (mean, 0.60).

Conclusion: A detailed intraoral assessment must be performed before initiating treatment with bisphosphonates to identify risk factors for osteonecrosis.

Key words: Prevalence, Osteonecrosis, Bisphosphonates

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I. Introduction

Osteonecrosis of the jaw (ONJ) is a disease initially described more than 100 years ago as 'phossy jaw' and appeared in workers of specific industries, including phosphate mines. In the United States and Great Britain, bone exposure was attributed to nonhealing of oral cavity lesions and was related to the time workers had spent in the mines[1].

There is no universal definition of ONJ due to bisphosphonates, but a panel of experts from the American Society for Bone and Mineral Research (ASBMR) recently proposed that it is an "area of exposed bone which persists for more than 8 weeks in the absence of prior radiation and/or metastasis in the maxilla and/or jaw"[2].

A person may become susceptible to jaw osteonecrosis when the rate of alveolar bone replacement is 10 times greater than the long bones due to high uptake and significant accumulation of bisphosphonates in the jaw[3].

Mastication force on the apical region and root bifurcation area exerts pressure on the lamina dura, which radiates throughout the periodontal ligament. The process of remodeling counteracts these forces, but if the patient has absorbed and accumulated a sufficient amount of bisphosphonates, the lamina dura cannot facilitate bone remodeling and becomes hypermineralized[4].

In a large database, more than 2,400 cases of ONJ were reported from 2003 to 2009; the majority were treated with intravenous bisphosphonates[5], and incidence worldwide has been estimated to range from 1% to 10% according to the ASBMR in 2007[2]. In 2015, Kim et al.[6] reported that the incidence of ONJ in patients treated with intravenous bisphosphonates was 0-90 per 100,000 patient-year, and the

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incidence in patients with malignant neoplasm who took zoledronic acid was 0.019-1.9 per 10,000 patients. There are no data on the prevalence of ONJ in Mexico.

In the present study, we determined the prevalence and oral characteristics of cancer patients treated with bisphosphonates in the oncology and maxillofacial prosthesis departments of the General Hospital of Mexico between 2011 and 2013. We hypothesized that patients with bisphosphonate treatment would not require invasive dental treatment.

II. Materials and Methods

We reviewed the clinical records of patients from the medical oncology and maxillofacial prosthesis departments of the General Hospital 'Dr. Eduardo Liceaga', in Mexico City. Patients treated with bisphosphonates during their scheduled appointments from January 2011 to December 2013 were recruited for this study. Only the patients who signed an informed consent form were included in the study. This study was approved by the Institutional Review Board of General Hospital of México (IRB no. 4870).

All participants received intraoral scans performed by 2 examiners and cases with ONJ were identified. The intraoral examinations were based on the Decayed, Missing, Filled Teeth (DMFT) index and Community Periodontal Index (CPI). Mucous membranes and other parts of the oral cavity were also examined to identify exostosis, which is considered a risk factor for ONJ.

All data, including clinical records, type of bisphosphonate used, number of cycles applied, route of administration, neoplastic disease, concomitant use of corticosteroids and frequency of diabetes or hypertension, were evaluated. Descriptive statistics and χ^2 test were used to identify associations. A *P*-value less than 0.05 was considered statistically significant. The database and statistical analysis was performed using IBM SPSS Statistics 20 (IBM Co., Armonk, NY, USA).

III. Results

Overall, 84.0% of the study population were females and the average age was 55.91 years with a σ value of 13.79. The subjects were subdivided into four groups based on age: 34 years and under, 35 to 49 years, 50 to 74 years, and 75 years and older; 40 patients (53.3%) were in the 50 to 74 years group.

The most common neoplasia treated by bisphosphonates was breast cancer (84.0%) followed by prostate cancer (16.0%). In 100% of cases, the bisphosphonate was zoledronic acid at doses of 3 mg in 3 patients (4.0%) and 4 mg in 72 patients (96.0%). Additionally, 32.0% of the population was taking corticosteroids.

Of 75 patients, 2.6% had ONJ. One 41-year-old male was diagnosed with prostate cancer and one 42-year-old female with breast cancer. Both subjects received a monthly dose of 4 mg zoledronic acid for 11 and 26 cycles, respectively; neither patient had diabetes or hypertension.

Regarding chronic diseases, hypertension was diagnosed in 32% of the study population vs. 13.3% with type 2 diabetes. The minimum number of cycles was 1 in 6 patients (8.0%) and the maximum was 30 cycles in 1 patient (1.3%), resulting in an average of 9.35 cycles.(Table 1)

Exostosis was observed in 9.3% of subjects. The mean DMFT index was 4.64 and 44.0% of the study population had a CPI between 2 and 2.9 (mean 0.60 overall). Statistical analysis showed a correlation between age and the number of cycles (χ^2=30.187; *P*=0.001).

In patients with ONJ, the lesions were located bilaterally in the jaw (Fig. 1) with an area of exposed bone 0.5 to 1 cm in length. The soft tissue did not show any signs or symptoms

Table 1. Clinical features of the study population

Variable	No. of cases (%)
Sex	
Female	63 (84.0)
Male	12 (16.0)
Diagnosis	
Breast cancer	63 (84.0)
Prostate cancer	12 (16.0)
Bisphosphonate zoledronic acid	75 (100)
Dose (mg)	
3	3 (4.0)
4	72 (96.0)
Cycle	
1 (minimum)	6 (8.0)
30 (maximum)	1 (1.3)
9.35 cycles in average	
Drug	
Corticosteroids	24 (32.0)
Chronic disease	
Hypertension	24 (32.0)
Type 2 diabetes	10 (13.3)
Oral characteristics	
Exostosis	7 (9.3)
CPI index	
0-1	6 (8.0)
1.1-1.9	29 (38.7)
2-2.9	32 (42.7)
≥3	8 (10.7)

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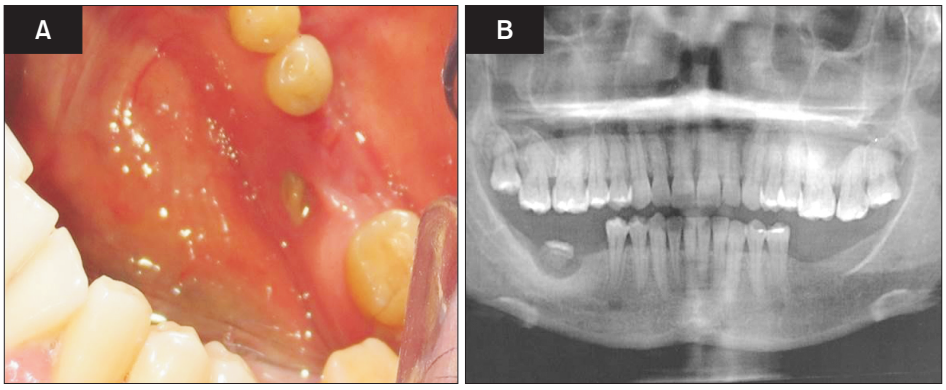

Fig. 1. A. Patient treated with zoledronic acid with left lingual bone exposure table and no signs of soft tissue infection. B. Orthopantomography patient. Radiolucent scleral area is observed in the presence of bone sequestration in the right jaw.
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of infection and the patients had not previously used dental prostheses. The male patient presented with spontaneous exposure, but the lesion in the female subject appeared after the first and second lower right molars were extracted. Both lesions were treated conservatively using surgical cement dressings with neomycin and chlorhexidine rinses. In both patients, necrotic bone fragments were removed and a rigorous oral hygiene was recommended, resulting in the remission of the lesion after 1 month of treatment.

IV. Discussion

The clinical characteristics of bisphosphonate-related bone exposure have been described by the American Association of Oral and Maxillofacial Surgeons (AAOMS) since 2007, who classified bone exposure into 3 stages: exposure without signs of infection, exposure with obvious signs of infection, and exposure with a pathological fracture caused by bone exposure[7]. Both of our cases were in the first stage, thus, conservative treatment was administered.

The incidence of ONJ varies significantly because the development of the injury depends on the time exposed to bisphosphonates, the route of administration, and local risk factors, such as periodontal disease and a history of dental extraction. We reported a 2.6% prevalence of ONJ in the study population. The treatment included prevention of tooth decay, periodontal treatment, tooth extraction, removal of dental calculus, and education of patients in oral hygiene techniques.

In 2013, Solomon et al.[8] reported a 0.02% incidence of ONJ in patients with osteoporosis; however, the prevalence varies in other reports. Casal et al.[9] reported a 0.81% incidence when bisphosphonate is applied intravenously, Varun et al.[10] reported a 2.8% incidence in breast cancer patients and Lee et al.[11] reported an estimated incidence in Korea of at least 0.04% or 1 per 2,300 patients taking bisphosphonates. In 2014, the AAOMS estimated the risk of developing ONJ in patients treated with zoledronic acid was between 50 and 100 times higher than in patients treated with placebo[12].

Although zoledronic acid is the most commonly used drug to prevent bone damage, denosumab has become important due to its advantages compared to bisphosphonate. Mainly, denosumab is not fixed to the bone; however, the risk of developing ONJ in these patients is the same as those treated with zoledronic acid[12]. In our study, 100% of cases were treated with zoledronic acid since it is the drug mainly reported in the literature.

In 2015, Kos[13] reported the incidence and the risk factors associated with the development of ONJ. Advanced age is a risk factor since aging impairs healing and regeneration processes and increases dental problems such as tooth decay and periodontal disease. In our study, the average patient age was 55.91 years. We found a correlation between age and the number of cycles of bisphosphonates. Older patients were exposed to bisphosphonates for longer periods. The approximate age at the disease onset was 40 years whereas the average age of the cohort was 55 years.

Breast cancer is predominant among females. In Mexico, this neoplasm has had the highest prevalence since 2011, accounting for 11.34% of all cancer cases[14]. A study by Robles-Castillo et al.[15] in 2011 reported the mean age of breast cancer patients was 53.64 years, which is similar to our study population (55.91 years).

Bonacina et al.[16] reported that less than 50% of patients had breast cancer, followed by prostate (18.8%), lung and liver cancer. Similar to our study group, patients received zoledronic acid at a dose of 4 mg with an average therapy duration of 8 months.

The main risk factor for ONJ is the exposure time to bisphosphonate. In 2007, Marx[3] found that bisphosphonates accumulate in bone and when administered intravenously,

often accumulate faster due to the higher dose. Thus, dental treatments where bone is exposed are limited after the third application.

The population in this study underwent 9.35 treatment cycles on average; thus, clinicians should ensure that treatments do not compromise bone integrity, underscoring the importance of performing a comprehensive assessment before initiating treatment and taking into account the effects on bone for the 10-year period after the last application[17].

The risk factors for developing ONJ can be systemic or local. Diabetes is a systemic factor because it is associated with bone microvascular ischemia, endothelial cell dysfunction and decreased bone remodeling. Overall, 32% of patients in our cancer center had diabetes mellitus type 2, thus, we encouraged the use of preventive protocols in this subgroup[18].

In 2009, Ruggiero et al.[19] concluded that patients with exostosis have a thin mucosa and are susceptible to lacerations due to food or poor-fitting dentures, which can cause direct damage to the bone. Fuentes et al.[20] reported an exostosis prevalence of 5.6% while in our study, the prevalence was 13.3%. Exostosis should be considered when implementing medical-dental care protocols to educate patients regarding the irritating effects of buccal exostosis due to hard foods and prosthetic attachments.

Periodontal disease is a local risk factor that has become increasingly important due to its relationship with ONJ. The AAOMS has reported that individuals with periodontal disease have a 7-fold greater risk of developing ONJ[7]. The CPI measures the need of periodontal treatment, ranging from 0 (no need) to 4 or higher (needs periodontal surgery). Overall, 44.0% of the study population had CPI values ranging from 2 to 2.9 and only 8.0% of the population did not require scaling and root planing treatment, thus, improving oral hygiene is necessary.

Although tooth decay lesions are not directly associated with the development of ONJ, patients must be educated regarding oral health and made aware of the consequences when caries progresses and becomes a trigger for ONJ.

The mean DMFT in the General Hospital of Mexico was 4.64, indicating the population has 4.64 teeth with some past or present caries, similar to what was reported by de la Fuente-Hernández et al.[21] (index of 5) in different populations.

In 2011, Bonacina et al.[16] analyzed 282 patients and concluded that preventive therapies are essential to halt the development of ONJ. As discussed, including control patients that do not undergo treatment with bisphosphonates, significantly decreases the incidence of ONJ. The care provided by professional health specialists in dentistry is crucial to prevent this disease.

V. Conclusion

According to our study results, females with an average age of 55.91 years were more exposed to bisphosphonate (zoledronic acid), and 53% (CPI=2 to 3 or more) required dental treatment that involved bone manipulation. Thus, we propose the following recommendations:

1. Identify the population at risk in a timely manner. Based on our study results, this population was females over 50 years of age treated with bisphosphonates and who had a periodontal disease. The goal is to control the local risk factors for the development of ONJ.

2. Dental and medical staff should be aware of the importance of performing an adequate intraoral assessment to identify local risk factors before initiating treatment with bisphosphonates. A follow-up throughout the treatment period is important to maintain the health of the oral cavity and prevent the occurrence of ONJ.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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