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Prevalence and Risk Factors of Osteonecrosis of the Jaw in Patients with Bisphosphonate Exposure in Casablanca, Morocco: An Observational Study

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Abstract

Objective: To study the prevalence of bisphosphonate-related osteonecrosis of the jaw (BRONJ) and to determine the risk factors associated with the occurrence of this pathology. **Method**: An observational retrospective study was conducted in the Department of Oncology, Rheumatology, and Maxillofacial Surgery of Ibn Rochd University Hospital, Casablanca. The study utilized complete medical records from 2014 to 2022 and included consultations of patients receiving bisphosphonates (BPs) in July and September 2022. Statistical analysis was performed using SPSS version 16.0. **Results**: Our study population comprised 104 patients, of whom 91% were women and 49% were over 65 years old. Seventy-two percent of patients had a general pathology. Among them, 64 patients were treated with zoledronate, 43 with alendronate, and the remainder with risedronate, ibandronate, and pamidronate. The most common indications for treatment were bone metastasis following breast cancer (29.8%) and osteoporotic fractures (19.2%). Sixty-seven patients received intravenous (IV) treatment; only 10.5% exhibited good oral health. Fifty percent of patients underwent dental treatment, primarily tooth extractions. Osteonecrosis of the jaw (ONJ) was diagnosed in 1.9% of patients, predominantly in stages 1 and 2. **Conclusion**: Second and third-generation bisphosphonates are more strongly associated with the development of ONJ. Risk factors include monthly IV administration, poor oral health, comorbidities such as diabetes, medications like corticosteroids, invasive dental procedures, and not only oncological conditions but also rare indications such as bone algodystrophy. Nevertheless, our observed prevalence of 1.9% aligns with international rates ranging from 0.8% to 12%. However, most of the

studies that have been carried out have been retrospective studies with insufficient numbers of patients. Further prospective epidemiological studies based on standardized protocols with rigorous and appropriate follow-up over several years are essential to determine the exact prevalence of ONJ.

Keywords

Bisphosphonate-Related Osteonecrosis of the Jaw, Bisphosphonates, Osteonecrosis of the Jaw, Prevalence

1. Introduction

Bisphosphonates (BPs) are the most commonly used antiresorptive drug to treat conditions involving excessive bone resorption. They have a half-life of up to 12 years [1].

Based on their structure, BPs can be divided into two distinct groups: non-amine BPs, known as the first generation (etidronate, clodronate, tiludronate), which do not contain nitrogen, and amino BPs, which represent the second (pamidronate and alendronate) and third generation (risedronate, ibandronate, and zoledronate) [2].

Bisphosphonates have a strong affinity for hydroxyapatite crystals, allowing them to act by slowing down bone remodeling [3].

They are administered orally or intravenously, depending on the indication. They are used orally for the treatment of osteoporosis, as prevention after hip replacement surgery, and intravenously for the treatment of bone metastases from cancer (breast, prostate, lung, etc.), malignant hypercalcemia, multiple myeloma, and Paget's disease [4].

Despite their benefits, BPs have multiple transient adverse effects that usually regress within 48 hours following administration, such as gastrointestinal, neurological, and ocular manifestations. However, since 2003, the American Association of Oral and Maxillofacial Surgeons (AAOMS) has reported a more severe side effect in patients receiving intravenous bisphosphonates for oncology, namely osteonecrosis of the jaw (ONJ) [5] [6] [7].

ONJ can significantly impact patients, reducing their quality of life. It is a painful condition that can be challenging to treat. According to AAOMS, ONJ is defined by four characteristics:

- A mucosal lesion in the maxillofacial region exposing necrotic bone persisting for more than 8 weeks.
- Previous or current treatment with bisphosphonates.
- No history of radiotherapy to the head and neck region.
- Absence of metastatic involvement in the ONJ area as confirmed by systematic histopathological examination [8].

Several theories have been proposed to explain the etiopathogenesis of ONJ; however, its origin remains unclear, posing obstacles to understanding its pre-

vention and therapeutic management [9] [10] [11] [12].

Assessing the prevalence of osteonecrosis is challenging and seems to vary depending on various risk factors, such as the prescribed molecule, dosage, treatment duration, and oral health factors related to oral hygiene, dental infections, or invasive dental procedures.

Indeed, patients with ONJ often present with multiple risk factors contributing to increased incidence.

Given the significant and growing number of BP-treated patients in the Moroccan population, we aim to investigate the prevalence of ONJ and understand associated risk factors specific to this population, as there is limited or no existing data describing this.

We conducted an observational retrospective study within the Oncology, Rheumatology, and Maxillofacial Surgery departments at Ibn Rochd University Hospital in Casablanca. The study covered complete medical records from 2014 to 2022 and patient consultations involving BPs treatment in July and August 2022.

Our study aims to investigate the prevalence of BP-induced ONJ in a Moroccan population and identify associated risk factors contributing to its development.

2. Materials and Methods

Study design: We conducted a retrospective observational study by analyzing patients' medical records over 2 months, from July 11 to September 8, 2022.

Target population: The target population consists of patients followed between 2014 and 2022 in the oncology, rheumatology, and maxillofacial surgery departments of the Ibn Rochd University Hospital in Casablanca, Morocco.

A random sampling was conducted using a two-phase sampling method. In the first phase, patients were categorized as follows:

- Patients treated with bisphosphonates (included).
- Patients not treated with bisphosphonates (excluded).

In the second phase, a simple random sampling of the subunits including patients treated with BPs was conducted, based on the distribution of patients across departments. A total of 104 patients were selected.

Inclusion criteria:

Patients on bisphosphonates (BPs) or with a history of BPs treatment, with complete medical records or present during the consultation.

Exclusion criteria:

Patients treated with head and neck radiotherapy and those with incomplete medical records or absent during the consultation.

Patients were informed of the study objectives, and their oral consent was obtained. Throughout the study, anonymity and data confidentiality were ensured.

Data was collected using a study form consisting of 42 questions, through

direct patient interviews during consultations or by accessing complete records in digital archives (oncology, rheumatology) and paper archives (maxillofacial surgery).

The study form questions were divided into 4 sections as follows:

- The first section focuses on sociodemographic data, general health status, lifestyle habits, and reason for patient consultation.
- The second section covers the medical history indicating the use of bisphosphonates (BP), their route of administration, dosage, and duration of exposure.
- The third section pertains to dental history and the relationship between the treating physician and the dentist.
- The fourth section relates to ONJ (osteonecrosis of the jaw), its diagnosis, and potential management.

Statistical analysis was performed using SPSS version 16.0 software. It included a descriptive part of the studied population. All variables are described based on their absolute (n) and relative frequency (%).

Before carrying out this study, it was presented and validated by the Thesis Committee of the faculty, which is the ethics committee of our institution. All participants were informed that the questionnaire was anonymous, and consent was obtained after explaining the purpose and content of the study.

3. Results:

Our study population comprised 104 patients, distributed as follows: 60% from the rheumatology department, 39% from the oncology department, and 1% from the maxillofacial surgery department of Ibn Rochd University Hospital in Casablanca. Of these patients, 91% were female, and 49% were over 65 years old. Seventy-four percent hailed from urban areas, 16.3% were classified as obese, and 98% did not report toxic habits (Table 1).

Regarding bisphosphonate treatment, 64 patients were treated with Zoledronic acid, 43 with Alendronate, and the remainder with Risedronate, Ibandronate, and Pamidronate. Sixty-seven patients received this treatment intravenously, while 48 received it orally. The average duration of bisphosphonate exposure was 12 months for IV administration and 28 months for oral administration. The number of IV infusions ranged from 0 to 12 (Table 2).

78% of patients had moderate oral health conditions, while only 10.5% showed good oral health. 66.3% were advised on the necessity of dental care before bisphosphonate treatment, but only 50% received dental care, mainly tooth extractions. ONJ was diagnosed in 1.9% of patients (Table 3).

ONJ developed in two women aged 34 and 55 years, who were treated intravenously with 2nd and 3rd generation BPs following breast cancer metastasis in one case and bone algodystrophy in the other. Both patients were on prolonged corticosteroid therapy with BP exposure exceeding 25 months. Clinically, both patients presented with poor oral health and were diagnosed at ONJ stages 1 and

2 following premolar-molar tooth extraction (Table 4).

Table 1. Baseline population characteristics.

Population Characteristics		Frequency (n)	Percentage (%)
Sex	Female	95	91,3
	Male	9	8,7
Interval age(years)	< 20	0	0
	20-40	7	6,7
	40-65	46	44,2
	> 65	51	49
Residency	Urban	77	74
	Rural	27	26
Obesity	Yes	17	16,3
	No	87	83,7
Toxic habits	Tobacco	2	1,9
	No toxic habits	102	98,1
Family history	Tumor pathology	8	7,7
	Without history	96	92,3
Received treatment for underlying pathologies	Chemotherapy	47	
	Hormonotherapy	37	
	non-head and neck radiotherapy	31	
	Corticotherapy	20	
	Oral hypoglycemic	11	
	Immunotherapy	6	
	Antihypertensive	5	
	Beta-blockers	5	
	Antiepileptics	4	
	Anticoagulant	3	
	Antidepressants	2	
	Diuretics	2	
Total		104	100

Table 2. BP treatment characteristics.

		Frequency (n)	Percentage (%)
Molecule administered	Zoledronic acid	64	
	Alendronate	43	
	Risedronate	5	
	Ibandronate	2	
	Pamidronate acid	1	

Continued

Route of administration	**IV**	**67**	
	Per os	48	
number of BP infusions administered intravenously	0	37	35,6
	1	30	28,8
	2	9	8,7
	3	8	7,7
	4	8	7,7
	5	4	3,8
	6	3	2,9
	7	2	1,9
	8	2	1,9
	12	1	0,9
TOTAL		104	100

Table 3. Oral health status and dental care.

		Frequency (n)	**Percentage (%)**
Hygiene frequency	Regular brushing	16	21,1
	Irregular brushing	60	78,9
Oral health status	Good	8	10,5
	Medium	56	78,9
	Bad	12	10,6
A check-up with a dentist before BP treatment	Yes	69	66,3
	No	35	33,7
Dental care carried out before BP treatment	Dental extractions	30	
	Conservative care	19	
	Prosthetic treatment	4	
	Periodontal care	23	
Occurrence of ONJ	YES	2	1,9
	NO	102	98,1
Location of the ONJ	MAxilla	2	100
	Mandible	0	0
Initiating factors	Extraction	2	
	Trauma	0	
	Infection	0	
	Spontaneous	0	
TOTAL		104	100

Table 4. Profile of patients with ONJ.

Profile of patients with ONJ	Case 1	Case 2
Sex	Women	Women
Age	34 years	55 Years
General pathology	No general pathology	type II diabetes high blood pressure
Administered molecule	Pamidronate	Zoledronate
Indication treatment BP	Bone algodystrophy	Bone metastases secondary to breast cancer
Route of administration	IV	IV
Time exposure	36 months	26 months
Dentist-Doctor communication	Yes	Yes
ONJ stage	2	1
Sector location	Maxillary Premolar-molar	Maxillary Premolar
Initiating factors	Tooth extraction	Tooth extraction
ONJ treatment	Elimination of bone sequestration without tooth extractions	Superficial debridement
Recurrence	No	No

4. Discussion

4.1. Prevalence of ONJ and Risk Factors

In 2003, Marx *et al.* [13] identified a novel form of osteonecrosis of the jaw (ONJ) resistant to conventional therapies, specifically linked to bisphosphonates (BPs), establishing a potential association. Patients with bisphosphonate-related osteonecrosis of the jaw (BRONJ) exhibit multiple risk factors, including specific characteristics of BPs (molecule administered, route of administration, dose, duration of exposure), concurrent drug therapies (such as corticosteroids and chemotherapy), and local factors (such as dental infections, invasive dental procedures, and oral health conditions) [14] [15] [16]. Our study aims to investigate the prevalence of BRONJ in a Moroccan population and identify patient profiles associated with developing this condition.

The American Association of Oral and Maxillofacial Surgery (AAOMS) in the United States reported a prevalence of BRONJ ranging from 0.8% to 12% [17]. K. Kim *et al.* [18] reported a prevalence of 0.18% in South Korea. Studies by Bamias *et al.* [19] in Greece and Durie *et al.* in England [20] indicated an incidence of BRONJ ranging from 1% to 11% in patients with malignant osteopathy treated with intravenous amino BPs. In Brazil, A. Soares *et al.* [21] reported a prevalence of 3% among women with metastatic breast cancer undergoing BPs treatment. In Australia, Kokki *et al.* [22] indicated a prevalence of 1.15%. Consistent with these global findings, our study found a prevalence of BRONJ at

1.9%. However, the interpretation of any prevalence must consider the risk factors associated with the development of ONJ.

Investigating these factors thoroughly offers valuable insights for stratifying patient risks, customizing preventive approaches, and optimizing clinical decisions in BPs therapy.

4.2. Administered Molecule

The two BRONJ cases in our study involved one patient on Zoledronate and another on Pamidronate. In a similar study by K. Zervas *et al.*, [23] most BRONJ cases were diagnosed in patients treated with Zoledronate alone, or after treatment with Pamidronate. Only one patient treated with Pamidronate developed BRONJ.

According to the literature, Pamidronate and Zoledronate are categorized as second and third-generation bisphosphonates (containing nitrogen). Second-generation BPs are 100 to 500 times more potent than non-nitrogenous BPs. Third-generation BPs, which also feature amine group methylation, are 10 to 20 times more potent than second-generation BPs. In addition to their anti-resorptive effects through direct action on osteoclasts and anti-angiogenic effects, they accumulate in bones and have a prolonged impact due to their non-metabolized nature, explaining their higher association with bone necrosis [20]. No reported cases of BRONJ are associated with non-nitrogenous BPs such as Alendronate, Residronate, and Ibandronate, which are commonly used today due to their rapid metabolism [5].

4.3. Route of Administration

Since oral bisphosphonates introduction approximately 20 years ago, fewer than 50 cases of osteoporotic patients developing BRONJ have been reported, highlighting the low potential for adverse effects of oral amino bisphosphonates [24]. S. Najm *et al.* [25] report a low risk of osteonecrosis of the jaws linked to the oral administration of BPs, particularly in osteoporosis (1 case per 20,000 patients).

Khan *et al.* [26] and Dupic *et al.* [27] reported that the risk of BRONJ increases with monthly IV injections. In our study, both cases of BRONJ involved the intravenous administration of BPs, aligning with literature suggesting that intravenous BPs are more frequently associated with BRONJ development compared to oral administration.

4.4. Dose and Duration of Exposure

In our study, the number of infusions received by patients varied between one and 12. Bonacina *et al.*, reported that patients received between 6 and 74 infusions of zoledronate, with a higher number of infusions correlating with an increased risk of developing BRONJ [19].

In our study, the average duration of exposure to intravenous bisphosphonates was 12 months, while exposure to oral bisphosphonates averaged 28

months. According to Hoff *et al.*, [28] the risk of BRONJ increases significantly with the duration of exposure to BPs; in patients treated with intravenous BPs, this risk appears early, with a significant increase after 18 to 24 months of treatment with zoledronate and 60 months with Pamidronate.

Furthermore, BPs have a bone half-life of around 10 years, leading to their accumulation in the skeleton with prolonged use. The risk of BRONJ occurrence is therefore proportional to the cumulative dose and increases with the duration of exposure. The American Dental Association (ADA) and the AAOMS confirm this dose- and duration-dependent increase in risk [19].

4.5. Drug Therapies

In our study, 47 out of 104 patients received cytotoxic chemotherapy, with only one developing ONJ. This suggests a relatively low incidence of ONJ in this subgroup. Concurrently, ONJ cases associated with Avastin® (chemotherapy) and bisphosphonates were reported by the European Medicines Agency (EMA) in 2010 and the French Health Products Safety Agency (AFSSAPS). Cytotoxic chemotherapy emerged as a significant contributor to ONJ incidence [29].

Furthermore, the two ONJ cases observed in our study were in patients undergoing long-term corticosteroid therapy. Several studies, including those by Badros *et al.*, [30] Dimopoulos *et al.*, [31], and Hoff *et al.*, [28] have highlighted the increased ONJ risk associated with corticosteroid therapy.

These findings underscore the critical need for vigilant monitoring and consideration of alternative treatment strategies in patients receiving long-term corticosteroid therapy to mitigate the risk of ONJ.

4.6. Local Risk Factors

In our study, few participants maintained regular tooth-brushing habits, while most brushed irregularly or absently, but most patients were informed by their treating physician about the necessity of dental cavity management before BPs treatment, and half of the population received dental care, what can explain the low rate of ONJ occurrence. Magremanne *et al.* [32] state that inadequate oral hygiene constitutes a risk factor for ONJ.

According to the American Association of Oral and Maxillofacial Surgeons (AAOMS), local risk factors for ONJ include various dentoalveolar surgeries such as tooth extractions, dental implants, periapical surgeries, and periodontal procedures involving bone injury. The risk of developing ONJ escalates approximately sevenfold (from 5.3 to 21) following such procedures, with an average onset period of 6.6 months post-surgery [8].

Dental extractions precipitated both cases of BRONJ in our study. Multiple studies indicate that invasive dental procedures contribute significantly to ONJ cases, constituting 50% to 80% of reported instances. Bamias *et al.* [19] reinforce this observation, reporting that 88% of ONJ patients had undergone dental extractions within 12 months before their ONJ diagnosis. SB. Woo *et al.*, [33],

support these findings in a systematic review, emphasizing that 60% of jaw osteonecrosis cases occur following dental extractions or related surgeries.

In conclusion, our study underscores the critical role of oral hygiene practices and the potential risks associated with invasive dental procedures in ONJ development, emphasizing the importance of proactive preventive measures in clinical management.

5. Conclusion

Second and third-generation bisphosphonates are more frequently associated with the development of osteonecrosis of the jaw (ONJ). This risk escalates with monthly intravenous injections, poor oral health, medications such as corticosteroids, invasive dental procedures, and not only in oncologic conditions but also in rare cases such as bone algodystrophy. Our observed prevalence of 1.9% aligns with international studies. However, most studies in this regard are retrospective with insufficient sample sizes. Further prospective epidemiological studies based on standardized protocols with rigorous follow-up over several years are essential to determine the exact prevalence of this adverse effect, to understand its etiopathogenesis, to better target management, and in particular, to adjust more effectively therapeutic doses for different pathologies.

Limitations of This Study

Our study has several limitations. Firstly, the daily number of patients receiving bisphosphonates was restricted in the Oncology department due to the unavailability of the bisphosphonate (Zometa) used. Secondly, a significant majority of medical records were incomplete. Additionally, the number of cases reviewed in our study is not extensive enough to represent the overall situation, thereby imposing certain quantitative limitations.

Conflicts of Interest

There is no conflict of interest.

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