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Subclinical Oral Bisphosphonate-related Osteonecrosis of the Jaw: Systematic Review of the Literature and an Additional Case

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SPV and FB designed the study, performed the statistical analysis, wrote the protocol and the first draft of the manuscript. Authors ALPL and FB managed the analyses of the study. Authors SPV and ALPL managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Bisphosphonate-related *osteonecrosis* of the jaw (*BRONJ*), which has few studies despite the increase in the number of cases published in the literature in the last decade, is a rare complication related to the use of oral bisphosphonates. The objectives of this study are to perform a systematic review of the literature on cases of osteonecrosis of jaw associated with the use of oral bisphosphonates in the treatment of osteoporosis and to identify the main clinical characteristics and risk factors related to the cases described in the literature. In addition, a case of subclinical osteonecrosis of jaw associated with the use of oral bisphosphonate for a short period of time was reported.
Methods: A systematic review was conducted to identify cases of BRONJ among individuals using oral bisphosphonate. The survey included articles published in English from the period January 1950 to October 2016 in the PubMed and Cochraine databases.
Results: 49 published articles were selected, totalling 284 patients diagnosed with BRONJ. The

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mean age of the patients was 72.68 years and 96% were female. Alendronate was the most prescribed bisphosphonate, being used by 88.08% of the patients and osteoporosis/osteopenia was the indication of the treatment in 95% of the cases. The median duration of therapy until diagnosis of osteonecrosis of jaw was 5.23 years; 12.38% were on corticosteroids use at diagnosis and 82% of the patients performed some dental procedure preceding the onset of lesions. The mandible was the site most affected (74.64% of the cases) and 57,81% of the cases were in stage 2 at diagnosis. The most frequent associated conditions were: hypertension, corticosteroid use rheumatoid arthritis and diabetes mellitus, and 28% of cases occurred during the first 3 years of therapy.

Conclusion: Bisphosphonate-related osteonecrosis of the jaw is a rare disease which is associated with dental procedures and systemic conditions, and may occur at any time during therapy.

Keywords: Bisphosphonates; osteonecrosis associated with the use of bisphosphonates; osteoporosis.

1. INTRODUCTION

Bisphosphonates (BPs) are considered to be one of the top-class drugs in the treatment of osteoporosis and have been prescribed by up to 73% in osteoporosis consultations [1]. Based on the evidence available to date, bisphosphonates are considered safe drugs, however, reports of some rare complications have arisen in the literature, among them is the osteonecrosis of the jaw [1].

In 2003, Bisphosphonate-related osteonecrosis of the Jaw (BRONJ) was first described initially in cancer patients under the use of injectable bisphosphonates for the treatment of bone metastases, with subsequent cases involving patients using oral bisphosphonate for treatment of osteoporosis [2,3].

The term BRONJ is associated with the use of bisphosphonates, however, there are reports of other medications that may cause osteonecrosis of the jaw, such as denosumab and raloxifene, thus, the importance of broadening the concept for medication-related osteonecrosis of the jaw (MRONJ) [4].

The frequency of BRONJ ranges from 0.94% to 10% depending on the type of bisphosphonate used. [2,5] In patients taking weekly alendronate, the frequency of BRONJ ranges from 0.01% to 0.04%, increasing from 0.09% to 0.34% in those on alendronate submitted to dental extraction, with an incidence of 0.7 cases for 100,000 patients exposed by year [6,7].

Among patients with osteoporosis exposed to placebo the risk of BRONJ or MRONJ, ranges from 0% to 0.02%, predicting a total of 0-2 cases for every 10,000 individuals. Regarding zolendronic acid, the risk is 0.02% (2 cases for 10,000 individuals) while denosumab is associated with a risk of 0.04% to 0.2% (4-20 cases for 10,000 individuals) [4].

Among oral bisphosphonate users, in a study by Malden and Lopes, there was an incidence of 0.004% (0.4 cases for 10,000 patients) of MRONJ in patients exposed to alendronate. The work consisted of 11 reported cases in a population of 900,000 in the south of Scotland [8].

According to the American Association of Oral and Maxillofacial Surgeons (AAOMS), BRONJ is diagnosed by the presence of exposed necrotic bone, associated or not with symptoms such as pain, edema and erythema, lasting for more than 8 weeks in patients under current or previous treatment with bisphosphonates, without previous history of radiotherapy of the mandible [9]. These lesions may occur spontaneously or after local trauma or dental procedure and may involve only the mandible (65% of cases) or the maxilla (26% of cases) and in 9% of cases, it may involve the jaw and maxila simultaneously [10].

BRONJ patients may present with signs and symptoms ranging from pain, edema, erythema and/or local ulceration, which may precede, proceed or occur simultaneously to the exposure to necrotic bone, and may also lead to complications such as infection (osteomyelitis), fracture and oral fistula. For this reason, Ruggiero *et al.* proposed a model of clinical staging that was reviewed by AAOMS in 2014 (Table 1) [9,11].

Table 1. Staging of the Medication-related osteonecrosis of the jaw (MRONJ), based on the recommendations of the American Association of Oral & Maxillofacial Surgeons (AAOMS, 2014)

Stage	Clinicalfindings
Stage 0	No clinical evidence of necrotic bone, but non-specific clinica lfindings, radiographic changes and symptoms.
Stage 1	Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection.
Stage 2	Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in there gion of the exposed boné with or without purulent drainage.
Stage 3	Exposed and necrotic bone or a fistula that probesto bone in patients with pain, infection, and oneor more of the following: exposed and necrotic boné extending beyond there gionof alveolar bone,(i.e., inferior border and ramus in the mandible, maxilar sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor.

Known risk factors are as follows: History of dentoalveolar trauma, dental procedures, periodontal inflammation/abscess, chronic use of corticosteroids, duration of exposure to bisphosphonate and type of bisphosphonate used, being the most potent injectable and most related to BRONJ, such as pamidronate and zoledronate [12].

Risk factors for the development of jaw osteonecrosis associated to the bisphosphonate therapy includes the time of exposure and intravenous administration. The chronic use of the glucocorticoids and smoking are also risk factors . Regarding the place of involvement, patients submitted to dental extraction, trauma, infection or dental procedures present a greater chance of developing BRONJ [4,11].

In this study, a case of BRONJ diagnosed early and associated with the use of weekly alendronate for a short period of time for the treatment of osteoporosis was described. In addition, a literature review of the published cases of BRONJ, associated with the use of oral bisphosphonates in the treatment of osteometabolic diseases, was carried out in order to identify the main clinical characteristics and risk factors related to the cases described.

2. MATERIALS AND METHODS

A systematic review was conducted to identify BRONJ cases among individuals using oral bisphosphonate. The research included articles published in English from January 1950 to October 2016 from both PubMed and Cochraine databases. The following terms such as *MeSH*: *"Osteonecrosis"* and *"Bisphosphonates"* were used, and articles called "Case reports", "Meta-analysis" and "Multicenter Study" were included. All included cases had an established diagnosis of BRONJ in their description and individuals were over 18 years of age.

Articles that met the following criteria were excluded: articles published in a language other than English; cases involving individuals younger than 18 years; description of cases involving patients using bisphosphonate for treatment of metastatic bone disease; cases involving the use of injectable bisphosphonate; Case reports with insufficient data regarding the use of oral bisphosphonate making it impossible to analyze (duration of use, type of bisphosphonate); Case reports involving other conditions or use of other drugs that could interfere with data analysis; and articles without BRONJ case descriptions.

The main variables were population characteristics (age, gender, comorbidities, concomitant medications, history of smoking, history of dental procedures or dentoalveolar trauma), characteristics of bisphosphonate treatment (dose, type and duration of bisphosphonate used) and clinical characteristics (stage at diagnosis and bone affected).

3. CASE REPORT

A 62-year-old female patient with a history of treatment for osteoporosis with alendronate, 70 mg per week, for 2 years. After an endodontic procedure, with the replacement of the dental prosthesis, she developed continuous and progressive local pain.

After dental evaluation no lesion was evident in the oral cavity, but the same intense pain persisted even when using analgesics. For this reason, we performed a Panoramic Computer Tomography (CT), which showed a severe modification of trabecular and bone density in the mandible, especially in the anterior region and region of premolar teeth on the left and right side, which is the pathognomonic radiological profile of mandible osteonecrosis associated with the use of bisphosphonates (Fig. 1).

At that time, serum C-Telopeptide (CTX) was 96pg/mL (normal 90-450) and serum osteocalcin was 9.0µ/mL (normal 11-40). Oral alendronate was replaced by oral strontium ranelate 2g/day plus vitamin D3 (2000 UI/day).

During subsequent re-evaluations, the patient was asymptomatic and had no evidence of lesions in the oral cavity. After starting strontium ranelate, serum CTX increased to 177 pg/mL (84% increase) and 199 pg/mL (107% increase) and Osteocalcin 8.0 ng/mL and 15.0 ng/mL (66.6% increase), at 3 and 8 months, respectively. Eight months after the onset of Strontium Ranelate, the patient remained asymptomatic, and a new CT evaluation showed a complete healing of the lesion (Fig. 2).

4. RESULTS

The initial survey identified 699 publications that included the terms "Bisphosphonates" and "Osteonecrosis", 43 of which met the inclusion criteria and were selected for analysis. A total of 651 articles were excluded, of which the majority comprised of case reports involving cancer patients, use of injectable bisphosphonate, animal studies and articles with insufficient data for data analysis. Eleven articles were excluded because they were inaccessible. After the detailed analysis of the 41 articles initially selected, another 7 articles were found that met the inclusion criteria, and therefore, were included in the study. Fig. 3 illustrates the article selection process.

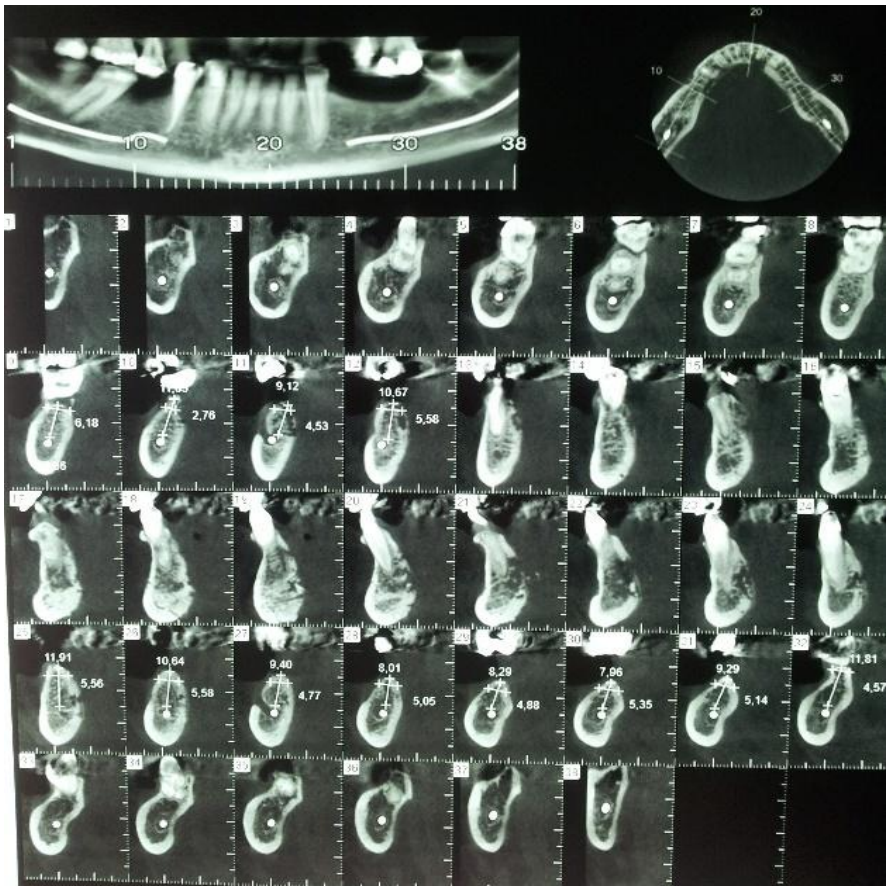

Fig. 1. Initial panoramic tomography showing pathognomonic lesions of BRONJ

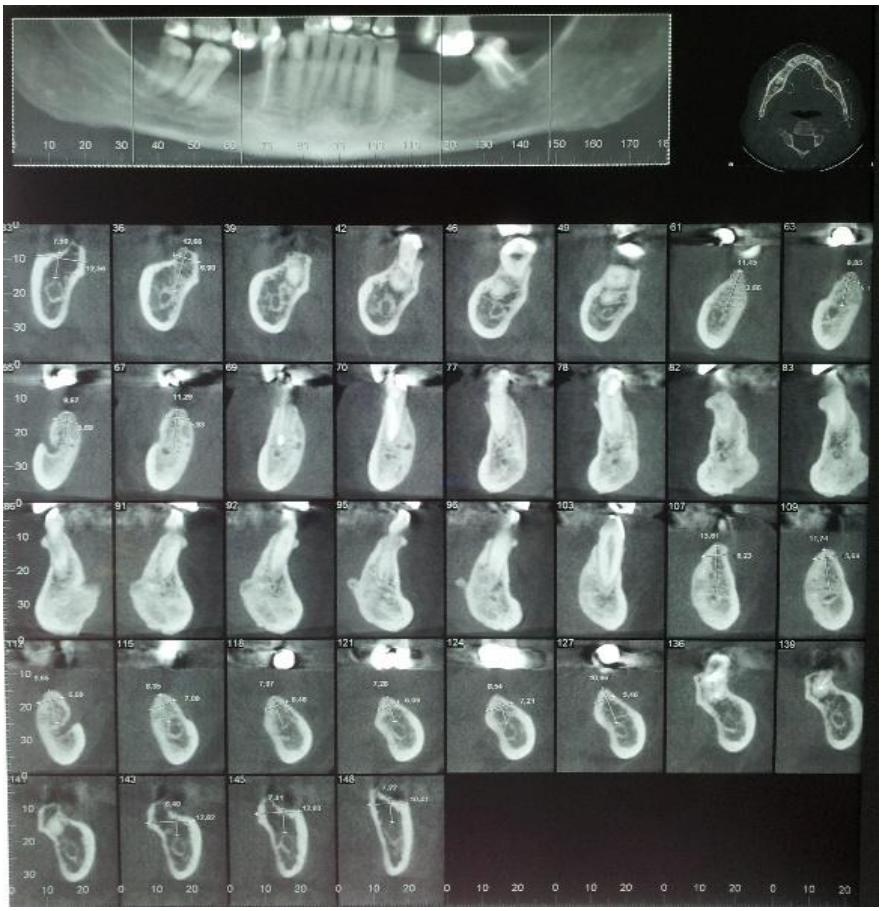

Fig 2. Panoramic tomography 7 months after the onset of Strontium Ranelate, with complete remission of the lesions

Forty eight published articles were selected from 2006 to 2016, totalling 284 patients diagnosed with BRONJ. Forty-one articles consisted of case reports or series of cases [13-61] and the other cross-sectional prospective or retrospective studies. Some of the studies (cases series) involved patients using oral and injectable bisphosphonate, and only the cases involving oral bisphosphonates were selected. Table 2 summarizes the main characteristics of the selected publications.

4.1 Population Characteristics

4.1.1 Age and gender

Forty-seven publications described the age and gender of 164 and 269 patients, respectively. Only one article did not contain information about age [59] and one did not contain gender information [43]. Age ranged from 52 to 92 years, with a mean of 72.68 years. Forty percent of patients were in the 70-80 age group and 34.8% in the 60-70 age group (Table 3). Regarding gender, BRONJ was more common in women (96.65%) than in men (3.34%) - Table 3.

4.1.2Comorbidities and use of corticosteroids

Comorbidities were described in 188 patients of the selected studies, being hypertension, rheumatoid arthritis, diabetes mellitus and dyslipidemia, the most frequent ones, present in 24.77%, 08.25%, 08.55% and 04.13%, respectively. Eighty nine patients had no comorbidities, representing 26.25% of the cases described. Four patients had a history of cancer, but all were using bisphosphonate for the treatment of bone disorders other than metastatic disease, had no history of radiation in the head and neck and were not in cancer therapy at diagnosis of BRONJ. Table 4 summarizes the main comorbidities described. Forty-two patients (12.38%) were using corticosteroids at the diagnosis of BRONJ, most of them for the control of rheumatic diseases such as rheumatoid

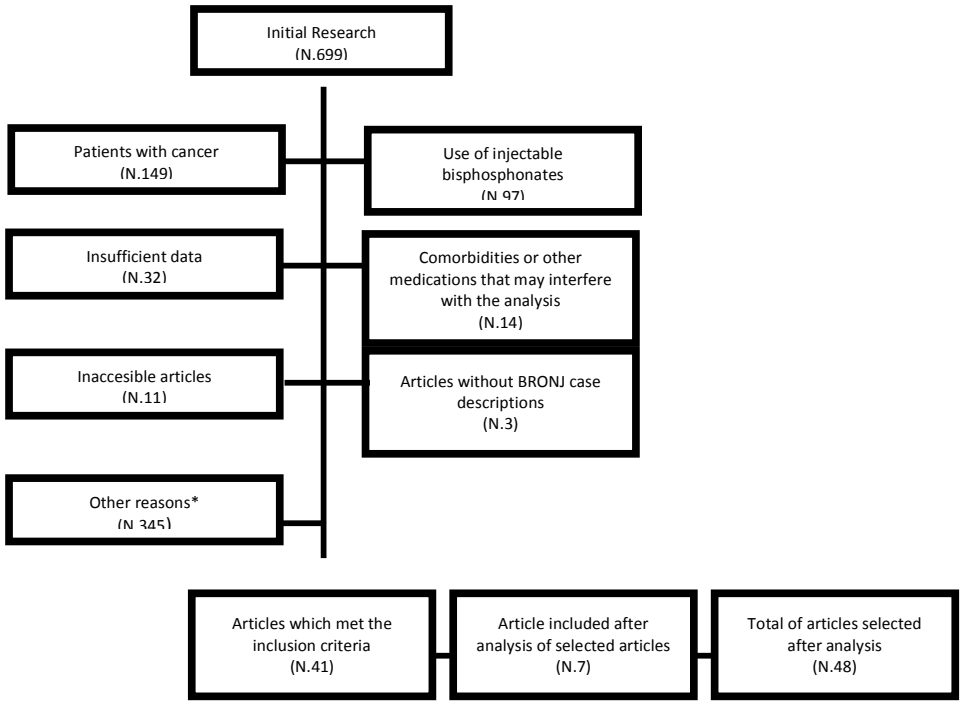

Fig. 3. Flowchart illustrating the literature searching process

**Other reasons why articles were excluded are: Review articles without BRONJ cases, cases involving osteonecrosis of sites other than the mandible and osteonecrosis for other causes, reports of cases in children, work involving animal studies, articles published in languages other than English, and articles that did not meet the inclusion criteria and did not fit into other related topics*

arthritis, polymyalgia rheumatica and systemic lupus erythematosus, and for the control of respiratory diseases such as bronchial asthma and chronic obstructive pulmonary disease (COPD).

4.1.3 Smoking

The history of smoking was described in only 62 cases, with 13 smoking patients diagnosed with BRONJ, representing 20.97% of the cases described, and 49 patients with no history of smoking at diagnosis, two of whom were former smokers, representing 79.03% of the cases.

4.2 Characteristics of the Treatment with Bisphosphonates

4.2.1 Type and dose of the oral bisphosphonate used

Alendronate was the most used, with a total of 244 patients taking this medication (88.08%). In addition, cases with risedronate (6.14%), ibandronate (3.61%) and drug combination (Table 5). The dose of the bisphosphonate used was described in 144 articles and varied according to the prescribed drug, (Table 5).

4.2.2 Duration of bisphosphonate therapy

The duration of bisphosphonate therapy until the development of BRONJ ranged from 2 months to more than 15 years, with 60.91% of patients presenting BRONJ with treatment duration of less than 5 years, (Table 6). The mean duration of therapy from the first administration of bisphosphonate to the clinical diagnosis of BRONJ was 5.23 years. The mean duration of therapy separately for each prescribed bisphosphonate until diagnosis of BRONJ was 4.8 years for alendronate, 3 years for risedronate and 2 years for ibandronate.

4.2.3 Indication of the therapy with bisphosphonate

BPs were used for the treatment of osteoporosis in the great majority of patients (228 cases, 80.28%). The remaining patients were using them to prevent osteoporosis in patients with osteopenia (21 cases - 12.42%) or rheumatoid arthritis (7 cases - 4.14%). Twenty-eight cases did not describe the indication of bisphosphonate therapy.

Table 2. Main characteristics of the publications included in the study

	Year	No of cases	Age (years)	Gender	Risk factors	Bone disease	Bps	Duration Bps	Precipitator factor	Stage bronj	Site
Kim et al.[13]	2016	1	73	F	No description	Osteoporosis	Alend	4 years	Dental implant	2	Jaw
Ayora et al.[14]	2015	1	82	F	No description	Osteoporosis	Risend	15 years	Dental extraction + Implant	3	Jaw
Manson et al.[15]	2014	1	68	F	Use of steroids	Osteoporosis	Iband	9 years	Dental extraction	2	Jaw
Thumbigere-Math et al.[16]	2013	1	58	F	-	Osteopenia	Alend	8 years	Dental extraction	1	Max
Siniscalchi et al.[17]	2013	1	70	F	No description	Osteoporosis	Risend	3 years	-	3	Jaw
Ohbayashi et al.[18]	2013	1	78	F	Diabetes Mellitus	Osteoporosis	Alend	5.5 years	Dental extraction	3	Jaw
Chiu et al.[19]	2013	1	63	F	Diabetes Mellitus	Osteopenia	Alend	7 years	Dental implant	3	Max
Yoshiga et al.[20]	2013	2	87 81	F F	No description	No descriptionNo description	Alend Alend	4 years 5 years	No description No description	3 3	Max Jaw
Molcho et al.[21]	2013	3	Average: 72.3 (63 a 88)	F: 2 M: 1	No description	Osteoporosis: 3	Alend: 3	average: 3 years	No description	SD: 3	Jaw: 3
Ghazali et al.[22]	2012	1	82	F	-	Osteoporosis	Alend	7 years	Dental extraction	3	Jaw
Zadick et al.[23]	2012	1	73	F	Use of steroids, smoking	Osteoporosis	Alend	4.5 years	Dental implant	2	Max
Zadik et al.[24]	2012	1	68	F	smoking	Osteoporosis	Alend	4 years	Dental implant	2	Jaw
Kilic et al.[25]	2012	1	78	M	No description	Osteoporosis	Alend	4 years	Dental extraction	2	Jaw

	Year	No of cases	Age (years)	Gender	Risk factors	Bone disease	Bps	Duration Bps	Precipitator factor	Stage bronj	Site
Kwon et al.[26]	2012	6	Average: 77.5 (68 a 88)	F: 4 M: 2	Diabetes Mellitus: 3 Use of steroids: 1 None: 2	No description	Alend: 4 Risend: 1 Alen, Risen eIband: 1	average: 4.67 (3 a 8 years)	No description	SD: 6	Jaw: 5 Max: 1
Diniz-Freitas et al.[27]	2012	20	Average: 71.2 (53 a 82)	F: 19 M: 1	Use of steroids: 7 Diabetes mellitus: 5 smoking: 1 None: 8	Osteoporosis:17 rheumatoid arthritis.: 3	Alend: 16 Iband: 4	average: 5.5 (0.5 a 10.9 years)	Dental extraction: 11 Implant: 2 Infection: 1 No description: 6	Stage 0: 2 Stage 1: 2 Stage 2: 14 Stage 3: 2	Jaw: 15 Max: 4 Palate: 1
Lee et al.[28]	2011	1	78	F	-	Osteoporosis	Alend	5 years	Dental extraction	2	Jaw
Kuijpers et al.[29]	2011	1	74	F	Use of steroids	No description	Alend	4 years	-	3	Jaw
Kang et al.[30]	2011	1	67	F	No description	Osteoporosis	Alend	3 years	Dental extraction	3	Jaw
Conte-Neto et al.[31]	2011	2	58 68	F F	- Use of steroids, smoking	Art.rheumatoid Art. rheumatoid	Alend Alend	4 years 6 years	Denture -	0 0	Jaw Jaw
Narváez et al.[32]	2011	2	79 75	F F	Use of steroids No description	Osteoporosis Osteoporosis	Iband Alend	2.7 years 1year	- Dental extraction	SD SD	Jaw SD
Moretti et al.[33]	2011	4	Average: 71,5 (64 a 81)	F: 4 M: 0	No description	No description	Alend: 4	average: 9.25 (1 a 14 years)	No description	SD: 4	Max: 4
Bedogni et al.[34]	2010	1	63	F	No description	Osteoporosis	Alend	9 years	Dental implant + Denture	2	Jaw

	Year	No of cases	Age (years)	Gender	Risk factors	Bone disease	Bps	Duration Bps	Precipitator factor	Stage bronj	Site
Takaishi et al.[35]	2010	1	75	F	Use of steroids	Osteoporosis	Alend	6 years	-	0	Jaw
Narongroeknawin et al.[36]	2010	1	63	M	-	Osteoporosis	Alend	5 years	Dental implant	SD	Max
Tsai et al.[37]	2010	1	72	F	No description	No description	Alend	4 years	Dental implant	3	Jaw
Cheung et al.[38]	2010	1	88	F	Use of steroids	Osteoporosis	Alend	10 years	Dental extraction	2	Jaw
Tong et al.[39]	2010	2	70	F	No	Osteoporosis	Risend	4 years	Dental	SD	Jaw
			78	F	description	Osteoporosis	Alend	3 years	extraction	SD	Jaw
					No description				Dental extraction		
Yamaguchi et al.[40]	2010	2	76	F	-	Osteoporosis	Risend	4.8 years	Dental	0	Jaw
			83	F	No description	Osteoporosis	Risend	5.5 years	extraction Dental extraction	0	Jaw
Park et al.[41]	2010	5	Average: 72.6 (68 a 81)	F: 5 M: 0	Use of steroids: 3	Osteoporosis: 4 Osteopenia: 1	Alend: 5	average: 7 years (5 a 10 years)	extraction: 2 Implant: 1 Denture: 1 None: 1	SD: 5	Jaw: 4 Max: 1
Shin et al.[42]	2010	1	67 years	F	No description	Osteoporosis	Alend	1 year	Dental implant	2	Max
Chiu et al.[43]	2010	12	Average: 69.7 (57 a 82)	SD	Use of steroids: 12	No description	Alend: 12	average: 3 years (2 a 4 years)	extraction: 7 Denture: 2 Surgical procedure: 1 None: 2	Stage 1: 3 Stage 2: 5 Stage 3: 4	Jaw: 8 Max: 4
Manfredi et al.[44]	2010	18	Average: 69.3 (52 a 89)	F: 18 M: 0	Diabetes mellitus: 3 smoking: 3 None: 12	Osteoporosis:18	Alend: 12 Iband: 1 Ale+ Rise: 2 Ale + Iban: 3	average: 4.8 (1 a 15 years)	Extraction: 8 Denture: 4 Implant: 2 Surgical procedure: 1 More	Stage 1: 1 Stage2: 15 Stage 3: 2	Jaw: 11 Max: 7

	Year	No of cases	Age (years)	Gender	Risk factors	Bone disease	Bps	Duration Bps	Precipitator factor	Stage bronj	Site
									thanone procedure: 2 None: 1		
Junquera et al.[45]	2009	1	73	M	Use of steroids	No description	Alend	3.8 years	Dental extraction	2	Jaw
Kwon et al.[46]	2009	1	71	F	Use of steroids	Osteoporosis	Alend	3 years	-	2	Max + Jaw
Kwon et al.[47]	2009	18	Average: 74.6 (61 a 86)	F: 16 M: 2	Use of steroids: 1 No description: 17	Osteoporosis:18	Alend: 17 Risend: 1	average: 3.9 (2 a 10 years)	Extraction: 13 Denture: 1 Surgical procedure: 1 None: 3	Stage 1: 8 Stage 2: 7 Stage 3: 3	Jaw: 10 Max: 5 Jaw + Max: 3
Favia et al.[48]	2009	19	Average: 70.3 (60 a 83)	F: 19 M: 0	Use of steroids: 2 Diabetes mellitus: 1 None: 16	Osteoporosis:19	Alend: 15 Risend: 2 Iband: 2	average: 1.6 (11 monthsto 3 years)	Extraction: 14 Implant: 2 Infection: 2 None: 1	Stage 1: 2 Stage 2: 17	Jaw: 12 Max: 6 Jaw + Max: 1
Wongchuensoontorn et al.[49]	2009	1	83	F	-	Osteoporosis	Alend	10 years	-	3	Jaw
Takagi et al.[50]	2009	1	71	F	No description	Osteoporosis	Risend	5 months	Denture	1	Jaw
Wong et al.[51]	2008	1	79	F	Diabetes mellitus	Osteoporosis	Alend	> 10 years	-	2	Jaw
Kumar et al.[52]	2008	9	Média: 73.2 (63 a 80)	F: 8 M: 0	Diabetes Mellitus: 2 Use of steroids: 1 No description: 6	Osteoporosis: 9	Alend: 9	average: 4.56 (1 a 10 years)	Denture: 5 Extraction: 4	Stage 2: 1 Stage 3: 1 SD: 7	Jaw: 7 Max: 2
Grana et al.[53]	2008	1	64	F	Use of steroids	Osteoporosis	Alend	2 years	Dental extraction	3	Jaw
Levin et al.[54]	2007	1	66	F	No	No description	Alend	8 years	Dental	2	Max

	Year	No of cases	Age (years)	Gender	Risk factors	Bone disease	Bps	Duration Bps	Precipitator factor	Stage bronj	Site
					description				prosthesis		
Lee et al.[55]	2007	1	84	F	-	Osteoporosis	Alend	9 years	Dental implant	3	Max
Yarom et al.[56]	2007	11	Average: 69.7 (55 a 79)	F: 11 M: 0	smoking: 4 Diabetes Mellitus: 1 Use of steroids: 1 None: 6	Osteoporosis: 9 rheumatoid arthritis: 2	Alend: 11	average: 4.1 (1.5 a 7 years)	Extraction: 6 Implant: 3 Denture: 2	Stage 2: 8 Stage 3: 3	Jaw: 8 Max: 3
Brooks et al.[57]	2007	2	70	F	Use of steroids,	Osteopenia	Risend	1.3 years	Dental extraction	1 3	Jaw Max
			62	F	smoking smoking	Osteopenia	Risend	2 years	Dental extraction		
Wang et al.[58]	2007	1	65 years	F	Ex- smoking	Osteoporosis	Alend	>10 years	Dental implant	1	Jaw
Marx et al.[59]	2007	30	SD	F: 30 M: 0	Use of steroids: 4 None: 16	Osteoporosis:14 Osteopenia: 16	Alend: 27 Risend: 3	average: 5.6 (3.3 a 10.2)	Extraction: 12 Implant: 2 Surgical procedure: 1 None: 15	Stage 1:12 Stage 2:14 Stage 3:4	Jaw: 29 Max: 1
Nase et al.[60]	2006	1	78	F	-	Osteoporosis	Alend	5 years	Surgical procedure	1	Jaw
Di Fede et al.[61]	2013	87	72(53-92)	F: 87 M: 0	No description	Osteoporosis	Alend: 77 Risend: 02 Iband: 01 Clodron: 07	Average: 38 months (2 a 200 months)	Extraction: 57 Implant: 0 Denture: 2 Infection: 02 None: 26	Stage 0: 15 Stage 1: 12 Stage 2: 53 Stage 3: 07	Jaw: 61 Max: 23 Jaw+max:3

Table 3. Distribution of patients for age and gender

Age	Gender
< 50 years: 0 50 a <60 years: 11 (6.7%) 60 a < 70 years: 57 (34.8%) 70 a < 80 years: 66 (40.2%) ≥ 80 years: 30 (18.3%)	Female:260 (96.65%) Male: 9 (3.34%)
Total: 164 cases with description of age	Total: 269 cases with description of gender

Table 4. Main comorbidites associated with BRONJ

Comorbidity	No of cases (%)
Arterial Hypertension	84 (24.77%)
Users of Corticosteroids	42 (12.38%)
Rheumatoid Arthritis	28 (08.25%)
Diabetes mellitus	29 (08.55%)
Dyslipidaemia	14 (04.13%)
Hypothyroidism	9 (02.65%)
Osteoarthritis	7 (02.06%)
Lung Conditions (Asthma / DPOC)	7 (02.06%)
Gastroeintestinal Disorders	7 (02.06%)
Heart Disease	14 (04.12%)
Cancer	4 (01.18%)
Polymyalgia rheumatica	2 (00.59%)
Systemic Lupus Erythematosus	2 (00.59%)
HCV-related liver diseases	1 (00.29%)
Without comorbidity	89 (26.25%)

4.3 Clinical Features of BRONJ

4.3.1 BRONJ stage

BRONJ staging followed the recommendations of the American Association of Oral & Maxillofacial Surgeons 2014 (Table 1) [9]. When the staging was not quoted in the text of the article, it was done according to the description of the clinical condition, examination of the oral cavity and/or complementary examinations (panoramic radiography or tomography) present in the case reports. In 30 articles, it was not possible to define the BRONJ stage due to insufficient description of the characteristics required for this. One hundred forty-eight patients (57.81%) were in stage 2 at diagnosis, 45 patients (17.57%) were in stage 1, 41 patients (16.01%) were in stage 3 and 22 patients (8.59%) were in stage 0.

4.3.2 Site affected

The jaw was the site most frequently affected by BRONJ, being involved alone in 73.33% of the cases (143 patients). The maxilla involved in 24.10% of the cases (65 patients) were isolated and there were five cases involving the jaw and maxilla simultaneously (2.56%).

4.4 Risk Factors for BRONJ

4.4.1 Dentoalveolar trauma and dental procedures

Of the 284 cases analyzed, there were descriptions about the presence of dental procedures or dentoalveolar trauma in 205 of them. These triggering factors were present in 80.39% of BRONJ cases and included dental extraction and implant, denture use, infection and surgical procedures (Table 7). BRONJ occurred spontaneously in 50 patients, without reports of procedures or trauma preceding its development. Of these 50 patients, 11 were on corticosteroids.

4.4.2 Use of corticosteroids

As previously described, 42 patients were using corticosteroids on diagnosis of BRONJ and the mean duration of bisphosphonate therapy until this diagnosis was 4.3 years. Among these patients, 11 had been using bisphosphonate for less than 3 years (26.20%) and 17 had been using bisphosphonate for 3 to more than 5 years (40.47%). Of the 14 remaining patients, 11 were on bisphosphonate for 5 to 10 years (26.20%) and 3 were on bisphosphonates more than 10 years (7.14%).

4.4.3 Duration of bisphosphonate use

Of the 284 cases described, only 39 did not present risk factors for the development of BRONJ (trauma or dental procedure and use of corticosteroids). When analyzing this group of patients, 45% were on BPs for a period of less than 5 years, 45% for a period of 5 to 10 years and 10% for a period greater than or equal to 10 years.

5. DISCUSSION

As a result of this research, 284 cases of mandible osteonecrosis related to the use of oral BPs were found, this being the first systematic review that included in its analysis only oral BPs for the treatment of osteoporosis/osteopenia. In

this study, the clinical characteristics of patients and treatment with BPs, risk factors and BRONJ characteristics were analyzed, as well as a description of a clinical case involving a patient using alendronate for treatment of osteoporosis for less than 3 years.

Sixty-nine percent of the patients had some comorbidity, the most frequent being hypertension, diabetes mellitus, dyslipidemia and rheumatoid arthritis. This figure is slightly higher than that described in an Italian study involving 87 cases of BRONJ, in which 48.3% of patients presented some associated condition, hypertension being the most common ones [61]. More recent studies have shown that the presence of relevant comorbidities, such as diabetes mellitus, rheumatoid arthritis and other systemic inflammatory diseases, as well as glucocorticoid therapy, has been related to the prognosis of BRONJ, leading to a lower probability of healing and a longer average time to heal (20 months) when compared to patients without comorbidities (7.5 months) [62].

Among the indications for BPs use, 87.67% of the patients included in the study had osteoporosis or osteopenia and alendronate was used by most of these patients (88.08%). This was also found in other studies [61,63].

One of the main risk factors previously described in the literature, for the development of BRONJ, is the duration of BPs therapy, with a higher risk of patients exposed to periods greater than 3 years, with a substantial increase in risk after 5 years of use [9]. In our study, the mean duration of therapy until the onset of BRONJ was 5.23 years (2 months to >15 years), with a similar finding of some other studies [27,62,64]. Likewise, some reports found duration of therapy as shorter as 3 years [61,8] and even 2 years [48], which demonstrates that exposure to BPs for a short period of time is not always a protector factor related to the development of BRONJ, and therefore, the individualization of therapy and evaluation for the presence of other risk factors is important [61,8,48].

Another risk factor reported in the literature is immunosuppressive therapy such as the use of glucocorticoid therapy. This association is relatively frequent in patients who use chronic corticosteroids to control autoimmune and/or systemic inflammatory diseases. Chronic glucocorticoid therapy has adverse effects on bone metabolism, in addition to the immunosuppressive and antiangiogenic effect, which may play an important role in the development of BRONJ among these patients [62]. Studies have suggested that the use of

Table 5. Distribution of Patients on the type and e a dose of the bisphosphonates used

	Alendronate	Risendronate	Ibandronate	Associations
No of cases	244 (88.08%)	17 (6.14%)	10 (3.61%)	Alend + Risend – 2 (0.72%) Alend + Iband – 3 (1.08%) Alen + Risen + Iband – 1 (0.36%)
Dose	70 mg/week: 93.85% 10 mg/day: 3.69% 35 mg/week: 2.46%	35 mg/week: 76.47% 2.5 mg/day: 17.64% 5 mg/day: 5.89%	150 mg/month: 100%	---

Table 6. Distribution of patients as the duration of thetherapy with oral bisphosphonates.

Duration	General	Alendronate	Risendronate	Ibandronate
< 3 years	50 (25.78%)	36 (21.69%)	5 (35.71%)	7 (87.5%)
≥ 3 e < 5 years	69 (35.57%)	62 (37.35%)	5 (35.71%)	1 (12.5%)
≥ 5 e < 10 years	58 (29.89%)	52 (31.32%)	4 (28.58%)	0
≥ 10 years	17 (8.76%)	16 (9.64%)	0	0
Total	**194**	**166**	**14**	**8**
< 5 years	119 (61.3%)	98 (59.03%)	10 (71.43%)	8 (100%)
≥ 5 years	75 (38.7%)	68 (40.97%)	4 (28.57%)	0

corticosteroids contributes to an early presentation and a more severe BRONJ, in addition to altering the prognosis of the disease, with a lower probability of cure and delay in healing [19,62]. In the present study, 12.38% were in the use of corticosteroids at the diagnosis of BRONJ, and had more advanced stages of the disease (stages 2 and 3 - 78.3%). However, the mean duration of BPs therapy until the onset of osteonecrosis was similar to the overall mean (4.3 versus 5.23 years).

Table 7. Precipitating Factors for BRONJ

Trauma / Dental procedure	Cases (%)
Dental extraction	152 (53.52%)
Dental implant	20 (7.04%)
Prosthesis	20 (7.04%)
Trauma orsurgery	5 (1.76%)
Infection (Periodontitis)	5 (1.76%)
Extraction + Dental Implant	1 (0.35%)
Dental Extraction + Prosthesis	1 (0.35%)
Dental Implant + Prosthesis	1 (0.35%)
None (SpontaneousBRONJ)	50 (17.60%)
- Use of corticosteroids	11
- Without other risk factors	39
No description	29(10.21%)

Smoking has also been described to be a risk factor for BRONJ. Wessel et al. [65] and Yarom et al. [56] have suggested an increased risk and a possible association between tobacco use and BRONJ, however, in our study, only 32% of the cases had a smoking history, making it impossible to drawn such conclusion.

The presence of trauma or dental procedures preceding the development of BRONJ is frequent, varying in several studies from 50% to 95% [48,44,59,63]. In our study, such procedures were described in 205 patients, and occurred in 82% of them, with dental extraction (53.52%), implant placement (07.04%) and dentures (07.04%) being the most frequent ones. These procedures/trauma are considered to be BRONJ's triggering factors and it is believed that BPs, due to their anti-resorptive properties, inhibit bone remodelling that normally occurs in the oral cavity and is increased after orthodontic procedures, especially dental extraction, which, together with its antiangiogenic properties, would result in osteonecrosis [63].

Studies in cancer patients using injectable bisphosphonates have shown an increased risk of BRONJ from 5 to 21 times in those who submitted to dentoalveolar procedures when compared to those who did not undergo such procedures [9,66]. In addition to the increased risk, studies have suggested a worse prognosis for the disease, with refractory disease and reduction in the probability of cure in patients undergoing dental extraction [62]. Based on these complications, some experts have recommended to stop BPs prior to dental procedures. However, there is no data demonstrating that discontinuation of the drug will improve outcomes, since the drug persists in the bone matrix even after its cessation [48].

The treatment of BRONJ is complex and involves surgical and non-surgical approaches, aiming at relieving symptoms, resolving soft tissue and/or bone infections and reducing the progression of bone necrosis [9]. Non-surgical management, with analgesia and oral mouthwashes, should be reserved for BRONJ patients without obvious infection, in order to avoid the progression of the disease [9]. The use of broad-spectrum systemic antibiotics is recommended in patients with BRONJ and signs of infection (stages 2 and 3) and the surgical approach, in turn, involves the removal of necrotic bone and the creation of soft tissue coverage for the bone to remain healthy, and may be more radical in cases where there are large segments of necrotic bone or when there is associated pathological fracture (stage 3). A summary of the treatment strategies based on the BRONJ staging is presented in Table 8, based on the AAOMS 2014 consensus [9].

Bone markers (BTM) have been evaluated by some [59]. In a study involving 30 patients using oral alendronate, a risk stratification was reported, where CTX values below 100 pg/mL represented a high risk of developing BRONJ, values between 100 and 150 pg/mL a moderate risk and values above 150 pg/mL a low risk. In addition, CTX values above 150 pg/mL, after medication withdrawal, were associated with a better prognosis. However, since there is only one report on this subject, most guidelines do not recommend the routine use of BTM in the evaluation and management of BRONJ [67].

Finally, though the evaluation of the oral cavity prior to initiation of bisphosphonate therapy is a well-defined approach in cancer patients who will take monthly injectable BPs, there is no consensus for patients using oral BPs for osteoporosis[9].

Table 8. Medication-related osteonecrosis of the jaw (MRONJ), based on the recommendations of the American Association of Oral &Maxillo facial Surgeons (AAOMS, 2014)

Stage	Therapeutic strategies
Stage 0	Systemic therapy to relief of symptoms (analgesia) and antibiotics
Stage 1	Site therapy antiseptic + Quarterly Follow-up Evaluate the indications for the continuation of the bisphosphonates
Stage 2	Antibiotic therapy (systemic and site) and pain control Surface debriding to mitigate injuries of soft tissue.
Stage 3	Antibiotic therapy (systemic and site) and pain control Debriding and surgical resection

6. CONCLUSION

Bisphosphonate-related osteonecrosis of the jaw is a rare disease associated with dental procedures and systemic conditions, and may occur at any time during therapy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study was approved by the Ethics in Research Committee of the Agamenon Magalhães Hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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