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Risk factors for medication-related osteonecrosis of the jaws in menopausal women

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Aim: This study aimed to identify risk factors for medication-related osteonecrosis of the jaw (MRONJ) by carrying out clinical and radiographic evaluations of patients with osteopenia and osteoporosis using bisphosphonates (BFs). **Methods:** After approval by the CCS/UFES Ethics Committee (registration number 2,738,749), consultations were undertaken, and data were collected from medical records in cooperation with sectors from UFES and the University hospital. A total of 50 patients, 29 with osteoporosis and 21 with osteopenia were selected. Patients underwent a clinical and a panoramic dental x-ray examination to assess risk factors associated with oral health and dental interventions. **Results:** All patients had at least one local risk factor, the most frequent being tooth extraction (100%) and periodontal disease (50%) which, if associated with the use of BFs, could lead to MRONJ. Among the systemic risk factors, the most common were diabetes and corticosteroid therapy. The most used BF was alendronate, administered orally. **Conclusion:** The dental surgeon should evaluate all patients with osteopenia and osteoporosis using BFs to determine whether there are other risks. Whether there may be other potential risks, acknowledging upon key risks factors surrounding MRONJ are critical for early diagnosis and successful dental treatment.

Keywords: Osteoporosis. Bisphosphonate-associated osteonecrosis of the jaw. Risk factors. Jaw.

Introduction

Menopause, which usually starts around the age of 40, represents a gradual transition in which a woman moves from a reproductive to a non-reproductive phase. This period is characterized by a drop in the production of estrogen and progesterone hormones[1]. This leads to increased bone loss begins, which in turn contributes to the onset of osteoporosis. The decrease in bone matrix causes the individual to have greater mechanical fragility and, consequently, a higher incidence of fractures with minimal trauma, which makes it a public health problem[2].

Bisphosphonates (BFs) play an important role in the treatment of osteoporosis, since the use of these drugs increases bone density and bone strength, which results in a reduction in the risk of fractures[3]. Despite the benefits of a therapy with BFs, these drugs have been associated, since 2003, with a complication which exclusively affects the mandible and maxilla, called Medication-related osteonecrosis of the jaw (MRONJ)[4]. According to the American Association of Maxillofacial Surgeons (AAOMS), the definition of MRONJ involves three factors: previous or current treatment with BFs, exposure of necrotic bone in the jaws (persistent for more than eight weeks) and no history of radiotherapy in the region[4].

The identification of risk factors, which can be grouped into drug-related, demographic, systemic or local factors, is essential in preventing MRONJ. Thus, we carried out clinical and radiographic evaluations of patients with osteopenia and osteoporosis treated at the Menopause Clinic of the academic hospital of the Universidade Federal do Espirito Santo (HUCAM/UFES). Given that dental procedures or traumatic events can lead to osteonecrosis in individuals receiving bisphosphonate treatment, the objective of this study is to further investigate the risk factors associated with MRONJ, thereby aiding in the development of treatment protocols.

Materials and methods

This is a retrospective cross-sectional observational study, and it was approved by the Ethics Committee for Research with Human Beings of the CCS/UFES, registration number CAAE 89524718.0.0000.5060. Data were collected from the medical records of patients cared for by the extension project "Osteoporosis and Oral Health", which took place at the Ioufes Outpatient Unit 4 of in partnership with the Menopause Clinic at HUCAM/UFES. The patients involved in this project included those diagnosed with osteoporosis or osteopenia, referred by the HUCAM/UFES menopause clinician, or personally invited by extension project students.

Sample

Among the patients seen in the period between 2016 and 2019, those who met the inclusion/exclusion criteria defined for the research were selected. 50 patients agreed to participate. Inclusion criteria were as such: patients diagnosed with osteoporosis (densitometry less than or equal to -2.5 SD) and osteopenia (densitometry between -1.0 and -2.5 SD)[5] users of BFs. The exclusion criterion was: not being able to attend the dental clinic for a complementary radiographic examination.

Sociodemographic data, information on family and medical history, densitometric results, medications taken, history of tooth extractions were all collected. All patients underwent a radiographic examination. Additionally, due to the increased risk of developing MRONJ after the insertion of dental implants[6] six patients with dental implants were called for clinical reassessment. Clinical reassessment consisted of clinical and radiographic examination, including periapical radiographs.

Radiographic analysis

The patients underwent a panoramic radiographic examination using a PaX-400 equipment (Vatech) with a voltage of 40-90 kVp. The analysis of radiographs attempted to identify periodontal risk factors such as alveolar bone loss, presence of implants, extensive caries (large destruction with pulp involvement), or changes that could indicate the need for surgical intervention, such as root debris and intraosseous lesions. The evaluation was carried out by two trained researchers.

In addition to clinical evaluation, alveolar bone loss was detected and assessed through panoramic radiographs[7]. In the radiographic evaluation, we carefully observed the severity and degrees of oral problems, which closely reflect disease progression[8]. However, teeth unable to receive a thorough evaluation were not considered in the analysis.

Alveolar bone loss was classified as mild - alveolar bone loss restricted to the cervical third of the root; moderate - alveolar bone loss involving the boundary between the cervical third and the middle third of the root; severe- alveolar bone loss reaching the apical third of the root.

The implants were initially evaluated by panoramic radiograph. When necessary, periapical radiograph was performed to assist in the evaluation.

The criterion for success was bone loss up to, on average, 1.5 mm, which results in an alveolar crest at the level of the first thread in the implants and the absence of peri-implant radiolucency[9].

Factors considered as possible indicators of the need for invasive intervention were: severe alveolar bone loss, residual tooth roots and fragments exposed in the oral cavity and intraosseous lesions. The tabulated data were processed by descriptive statistical analysis. Statistical data such as central tendency, dispersion, percentile values, and normality (Shapiro-Wilk) were evaluated using Jamovi software version 2.2.5.0.

Results

Among the 50 patients, according to the most recent bone densitometry, 29 had osteoporosis and 21 had osteopenia. Age ranged from 56 to 87 years, with a mean of 68.82 years, and a median of 68 years.

The most used BF was Alendronate sodium 70 mg (43 patients) followed by Risedronate sodium 35 mg (7 patients). The drug was orally administered weekly to all patients, and drug use varied from one month to 15 years (Figure 1).

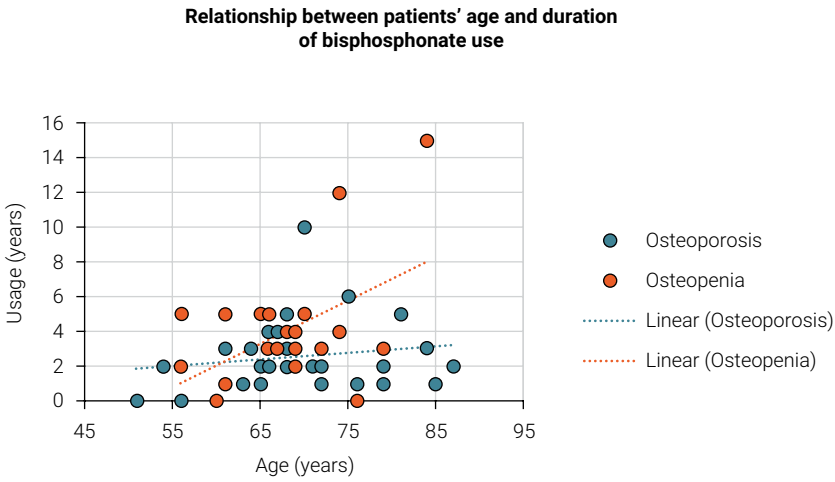

Figure 1. Relationship between patients' age and duration of bisphosphonate use.

The most frequent comorbidities were hypertension (62%) and diabetes (14%). As the utilization of BF is a crucial factor for the disease development, an assessment was conducted to examine the relationship between the duration of use and the type of medication employed. Patients were categorized based on the results of the bone densitometry examination (Table 1).

Table 1. Descriptive analysis of medication usage duration based on densitometric diagnosis

	Medication	Diagnostic classification by T-score	Usage (months)
N	Alendronate (70 mg)	osteopenia	20
		osteoporosis	23
	Risedronate (35 mg)	osteopenia	1
		osteoporosis	6
Mean	Alendronate (70 mg)	osteopenia	50.9
		osteoporosis	34.5
	Risedronate (35 mg)	osteopenia	8.00
		osteoporosis	22.0
Median	Alendronate (70 mg)	osteopenia	42.0
		osteoporosis	24
	Risedronate (35 mg)	osteopenia	8
		osteoporosis	24.0
Standard deviation	Alendronate (70 mg)	osteopenia	42.3
		osteoporosis	26.5
	Risedronate (35 mg)	osteopenia	NaN
		osteoporosis	9.03

Continue

Continuation

Minimum	Alendronate (70 mg)	osteopenia	3
		osteoporosis	1
	Risedronate (35 mg)	osteopenia	8
		osteoporosis	12
Maximum	Alendronate (70 mg)	osteopenia	180
		osteoporosis	120
	Risedronate (35 mg)	osteopenia	8
		osteoporosis	36
Shapiro-Wilk W	Alendronate (70 mg)	osteopenia	0.760
		osteoporosis	0.855
	Risedronate (35 mg)	osteopenia	NaN
		osteoporosis	0.866
Shapiro-Wilk p	Alendronate (70 mg)	osteopenia	< .001
		osteoporosis	0.003
	Risedronate (35 mg)	osteopenia	NaN
		osteoporosis	0.212

All patients had some type of alveolar bone loss and in 30 other bone alterations were observed, 11 with periapical lesions, eight with extensive caries, five with mineralization compatible with condensing osteitis, 11 with residual roots (seven exposed in the oral cavity and four buried roots).

Dental implants were identified in six patients. Twenty-seven implants were found, with an average of 4.5 implants/patient. Of these implants, twenty were rated successful and seven unsuccessful. In three patients, the implants were installed while using the drug, and three before starting the medication (Figure 2).

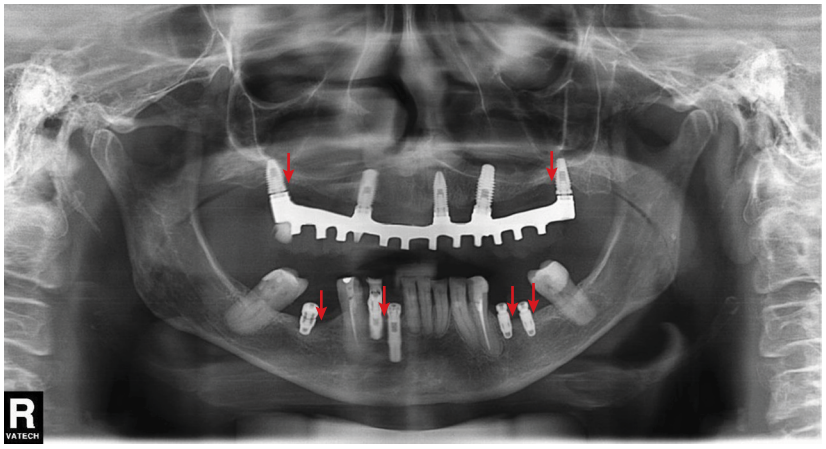

Figure 2. Panoramic radiograph showing five maxillary implants total denture over maxilla implant and five mandibular implants. Bone loss greater than 1.5 mm is observed (red arrows).

Regarding the systemic risk profile for MRONJ, the sample had seven patients with diabetes, seven were steroid users due to arthritis, arthrosis and systemic lupus erythematosus, one patient was HIV positive and five had a history of cancer.

Discussion

BFs have been widely used in patients to treat osteoporosis. Osteoporosis is a bone disease commonly related to age and hormonal imbalance, frequently observed in postmenopausal women[9]. The fact that MRONJ has been identified in a recent period[4], and the variety of potential risk factors that can trigger it, demonstrate a need for additional studies to complement those already published. With the increasing prevalence of antiresorptive drug use, understanding the risk factors for MRONJ is of utmost importance to ensure the safe implementation of dental interventions.

Diabetes is generally associated with microvascular bone ischemia, endothelial cell dysfunction and decreased bone remodeling, as well as induced apoptosis of osteoblasts and osteocytes. Bone neoformation is altered in uncompensated diabetics, leading to inadequate bone regeneration after injury. Furthermore, diabetes is associated with delayed wound healing. BFs can further exacerbate these states[10]. Thus, uncontrolled diabetes has been associated by some studies[10,11], with an increased risk of MRONJ. In our study, of the seven patients diagnosed with diabetes, three were uncontrolled.

Only one patient reported being HIV positive. The presence of the virus is not reported as a risk factor for MRONJ. Osteoporosis and osteopenia are among the so-called "non-infectious morbidities related to HIV and AIDS[12] and dentists should be aware that these patients are potential users of BFs.

A history of cancer was observed in five patients, three of the skin, two of which were treated with radiotherapy five years before (one in the hand and one in the forehead) and one by surgical excision three years before (in the hand), one of the breast treated for five years with radiotherapy and one bowel for 15 years treated with chemotherapy for six months. Radiation therapy in the head and neck region can lead to a condition called osteoradionecrosis, which differs from MRONJ. According to the American Association of Maxillofacial Surgeons (AAOMS) to distinguish MRONJ from other bone pathologies, the definition of MRONJ requires the three elements: previous or current treatment with BFs, exposure of necrotic bone in the jaws, persistent for more than 8 weeks and no history of radiotherapy in the region[13]. Therefore, such information is critical to exclude other pathologies in the diagnosis. A number of studies[11,14,15] have reported the appearance of bone necrosis in patients undergoing chemotherapy and intravenous therapy with BFs.

The risk for MRONJ of diseases such as arthritis/arthrosis and lupus due to the frequent use of corticosteroid therapy[16] has been discussed in the literature. Pazianas et al.[17] (2007) have reviewed 26 cases of osteonecrosis of the mandible in patients with osteoporosis treated with oral BFs and only two cases of MRONJ found an association of BFs with corticosteroids. In our sample, seven patients were using corticosteroid therapy associated with BFs and MRONJ was not observed among them.

The 31 hypertensive patients with hypertension reported to have their condition under control by medication and dietary strategies. However, hypertension is not usually described as a risk factor. This is also the case for hypothyroidism, Parkinson's disease, hypoparathyroidism, Sjogren's syndrome and hypercholesterolemia, systemic alterations found in our sample of six patients.

The type of medication, the administration route, the dosage and the duration of the treatment with BFs play a fundamental role in the emergence of MRONJ[18]. The drug most used by patients in our study was Alendronate 70 mg followed by Risedronate 35 mg, both taken orally. Alendronate belongs to the first generation, being a 1000-fold more potent anti-resorptive, and having great affinity for the bone matrix, since approximately 50% of the absorbed dose remains fixed to the bone. It is slowly eliminated and has an elimination half-life of up to ten years[19]. Risedronate is a third-generation drug, and a 5000-fold more potent anti-resorptive, has greater "desorption", which explains the better distribution throughout the bone tissue and the multisite effect. Thus, it is indicated when one wants speed of action, and multisite action[20]. Risedronate, after oral administration, has a concentration-time profile with three phases of elimination and a terminal half-life of 480 hours[21]. In our study, 43 patients used 70mg Alendronate sodium and seven patients 35mg Risedronate sodium.

Yoneda et al.[22] (2010) have demonstrated that the incidence of MRONJ begins to increase one year after the use of intravenous BFs and two to three years after the administration of oral BFs. In the present study, the length of use was variable, but most used it for less than four years, and only eleven patients reported using it for more than five years.

Panoramic radiographs have been used in some cohort studies and clinical trials. These studies have been limited to the MRONJ areas[23,24]. MRONJ radiographic findings include: thick lamina dura, widening of the periodontal ligament space, areas of osteolysis, bone sequestration, osteosclerosis of the dura and poor healing or non-healing of alveoli after extraction[5]. In our study, our findings did not indicate the presence of MRONJ in the patients.

Radiographic analysis, in addition to identifying suspicious areas of MRONJ, may also be used in the search for risk factors[25]. The analysis assessed factors that may impact the onset of MRONJ, such as the presence of extensive caries and oral health status which may require tooth extraction, which would be considered an indirect risk factor for MRONJ[26]. In addition to extensive caries, periapical lesions, bone lesions and alveolar bone loss, which could reflect untreated periodontal disease, were included as risk factors. In our study, eight patients had extensive caries, eleven patients had periapical lesions and five patients had bone lesions compatible with condensing osteitis.

Regarding the analysis of the alveolar bone condition, most of the radiographs showed alveolar bone loss. Bone changes caused by osteoporosis seem to worsen periodontal disease, but the pathogenesis of this process has yet to be fully understood[27]. In addition, untreated periodontal disease in patients undergoing treatment with BFs can lead to an increased risk of MRONJ[27]. Oral conditions that predispose to tooth extraction, such as moderate to advanced periodontitis, are indirect risk factors

for MRONJ[26]. As such, monitored dental care is recommended in order to maintain a healthy periodontal condition[27].

The installation of dental implants during therapy with BF, either intravenous and oral, is considered a local risk factor for MRONJ. In the present study, seven implants were installed during the use of BFs (three patients), and only one implant was evaluated as unsatisfactory. The use of BFs in these patients was greater than/equal to four years (4-8 years), and only six implants were installed with more than one year of BF use (1-4 years).

According to the AAOMS, the contraindication of implants is necessarily aimed at patients using intravenous BFs[13], but the literature is controversial regarding the risks of installing dental implants in users of oral BFs. A study by Koka et al.[28] have compared 121 implants placed in 55 BFs users (approximately one-third over five years of use) with 166 implants placed in 82 non-users. No MRONJ was observed in either group and implants in both groups showed similar profiles with a success rate of 99.2% in BFs users and a 98.2% success rate in non-users. Liddelow and Klineberg[29] (2011) have argued that the risk for MRONJ in patients who received oral BFs after implant surgery was estimated to be one in every 2000 to 8000 patients evaluated, depending on time and dosage, with three years being considered a significant period for the onset of MRONJ.

The presence of an implant/prosthesis with marked bone loss and/or peri-implantitis may be a risk factor for MRONJ, highlighting the need for more regular dental follow-up in patients with implants and users of BFs.

The presence of osteoporosis may interfere with a satisfactory fixation of the implant to the bone due to the decrease in the number and function of osteoblasts and increased activity of osteoclasts that alter the osseointegration process[30]. Correct placement of the implant can reduce the risk of fractures, in addition to minimizing bone resorption around the implants[31]. Healing screws, when not properly sanitized, leads to the accumulation of bacterial plaque. This in turn may cause from mucositis and peri-implantitis. Situations in which an inflammatory reaction leads to surrounding bone loss of the implants[30], what can pose risks for of MRONJ.

Although the use of oral BFs is not a contraindication to implant placement, one should be aware of the increased risk of complications for patients, particularly when other risk factors for MRONJ are present. To reduce this risk, the least traumatic surgery possible, antibacterial prophylaxis and topical antiseptics, should be performed[30].

Extractions are considered the major risk factor for MRONJ[32]. Mavrokokki et al.[33] (2007) have investigated patients who received therapy with oral BFs for the treatment of osteoporosis, and found that the MRONJ frequency ranged from one in 2,260 (0.04%) to one in 8,470 (0.01%). However, when focusing on the population undergoing tooth extraction, it was observed that the frequency increased, ranging from one in 1,130 (0.09%) to one in 296 (0.34%)[34]. Similarly, and more recently, Lo et al.[23] (2010) have looked at the prevalence of MRONJ in patients with a history of chronic use of oral BFs. Their data indicated a prevalence of MRONJ in this population of 1 in 952 BF users, or approximately 0.10%.

In the assessment of the patients medical records, it was observed that all had a history of tooth extraction, but they were unable to inform how long before and whether they were using the drug, but there was no history of MRONJ. For patients with an indication for extraction, a systemic evaluation was suggested to determine the duration of drug and to design proper guidance and planning of the surgical approach, thus acknowledging the potential for the onset of MRONJ[9].

Concerning the buried residual roots observed, due to the risk of developing MRONJ, intervention was not indicated, since bone lesions that indicated a greater risk of the occurrence of MRONJ were not observed if they were maintained. After starting therapy with BFs, extractions should be avoided and performed when essential due to the risk of infection and progression to MRONJ[35].

In this cross-sectional observational study, a wide range of risk factors related to various dental specialties could be analyzed. Although the studied sample allowed for the evaluation of a wide range of clinical and radiographic factors, it was impossible to analyze the factors present in patients diagnosed with MRONJ, as this specific subset of patients was not included in our sample. In-depth exploration in future studies, aiming to ascertain the risk factors present in patients who have developed the condition, may aid in developing appropriate guidelines for professional conduct.

In conclusion, the assessment of risk factors for MRONJ in patients with osteopenia/osteoporosis using BFs, it was observed that all patients had at least one local risk factor, which, if associated with the use of BFs, could lead to MRONJ, with the most frequent local risk factor being extraction (100%), followed by periodontal disease (50%). Of the systemic risk factors, the most common were diabetes and corticosteroid therapy. Regarding the period of use, most were within the time range considered to be of less risky, that is, less than four years. The dental approach towards patients using BFs must be cautious and judicious, with an analysis of local and systemic risk factors for the onset of MRONJ. Greater or lesser risk for MRONJ has to be based on the analysis of risk factors found in each patient. Thus, invasive procedures must be carefully approached by the dental surgeon to determine their suitability across users with varying oral health status users. When they are indeed necessary, they require thorough surgical planning and less traumatic surgery choices should be always be considered.

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Conflict of interest

The authors have no conflict of interests to disclose.

Data availability

Datasets related to this article cannot be shared at this moment because they are part of an ongoing research.

Author Contribution

Jocarla Campos Serafim: conception, design of this work, analysis and interpretation of the data, writing and review of the manuscript, participated in the discussion of the manuscript's findings. **Gustavo Azevedo Pitol:** conception, design of this work, analysis and interpretation of the data, writing and review of the manuscript, participated in the discussion of the manuscript's findings. **Ester Victorino Coser:** conception and design of this work, analysis and interpretation of the data, writing and review of the manuscript, participated in the discussion of the manuscript's findings. **Ben-Hur Albergaria:** conception and design of this work, analysis and interpretation of the data, writing and review of the manuscript, participated in the discussion of the manuscript's findings. **Stefania Carvalho Kano:** conception and design of this work, analysis and interpretation of the data, writing and review of the manuscript, participated in the discussion of the manuscript's findings. **Tânia Regina Grão Velloso:** conception and design of this work, analysis and interpretation of the data, writing and review of the manuscript, participated in the discussion of the manuscript's findings. All authors actively participated in the manuscript's findings, have revised and approved the final version of the manuscript.

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