

Anatomic Factors Related to Bisphosphonate Osteonecrosis of the Jaws: a Portuguese Retrospective Study



Factores Anatômicos Relacionados com a Osteonecrose dos Maxilares por Bisfosfonatos: Um Estudo Retrospectivo Realizado em Portugal

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ABSTRACT

Aims: The objectives of this study of bisphosphonate-related osteonecrosis of the jaws (BRONJ) were to determine local distribution, possible anatomically associated or determinant factors and other bone involvement of the disease, contributing with this new data towards the establishment of its prevalence in Portugal.

Material and methods: The authors made a retrospective study of patients presenting BRONJ, at the Department of Stomatology of Santa Maria University Hospital, in Lisbon (42 cases) from 1st January 2004, to April 30th, 2011. SPSS Statistics was implemented.

Results: There was a higher prevalence of lesions in the lower jaw (66.7%), compared to the upper jaw (26.19%) and a significantly higher occurrence in alveolar bone (95.24%). The molars and premolars were the most affected areas (highest value at 6th sextant = 35.29%). In all cases, the onset of injury occurred after a medication period of up to 90 days, spontaneously in 14.29% of patients.

Conclusions: For severity, BRONJ was a significant anatomoclinical entity in all 42 new cases in this study, and for discomfort (pain) in 81.1% of them. There was an anatomic correlation between the occurrence of the disease and its location in the jaws. There was a clinical association with trauma and type, route and length of administration of the bisphosphonate, with Zoledronate being administered intravenously in 76.19% of the cases. The jaws were the unique place where the disease occurred. Preventive measures should be implemented, avoiding trauma, and performing surgical procedures within 90 days after prescription.

RESUMO

Objectivos: São objectivos deste estudo sobre osteonecrose dos maxilares por bisfosfonatos (BRONJ), conhecer a distribuição local da doença, saber se existem factores anatómicos associados ou determinantes, se há outros ossos atingidos, e contribuir com novos dados para o estabelecimento da sua prevalência em Portugal.

Materiais e métodos: Os autores fizeram um estudo retrospectivo dos doentes com osteonecrose dos maxilares por bisfosfonatos, do Serviço de Estomatologia do Hospital Universitário de Santa Maria em Lisboa (42 casos), de 1 de Janeiro de 2004 a 30 de Abril de 2011. Utilizaram o programa estatístico SPSS Vs.19.

Resultados: Há uma maior prevalência de lesões na mandíbula (66,7%), quando comparada com a do maxilar superior (26,19%). É significativamente superior no osso alveolar (95,24%). A área de molares e pré-molares é a mais atingida (valor mais elevado no 6º sextante = 35,29%). Em todos os casos a lesão ocorreu após um período de medicação superior a noventa dias, espontaneamente em 14,29% dos doentes.

Conclusões: A osteonecrose dos maxilares por bisfosfonatos é uma entidade anátomo-clínica relevante (42 novos casos neste estudo), pela gravidade e desconforto (dor em 81,1%). Existe correlação anatómica. Há associação ao trauma, tipo de bisfosfonato, via e tempo de administração. O Zoledronato foi administrado por via endovenosa em 76,19% dos doentes. Os maxilares foram o único local em que a doença ocorreu em todos os casos. Recomendam-se medidas preventivas, evitando o trauma e utilizando a janela de intervenção de 90 dias, após a prescrição.

INTRODUCTION

Similar in structure to pyrophosphates, bisphosphonates are synthetic drugs which act as potent inhibitors of osteoclast-mediated bone resorption. They are also important in the inhibition of angiogenesis.^{1,2}

The first cases of bisphosphonate-related osteonecrosis of the jaws (BRONJ) as a potential complication in the treatment of osteoporosis and bone metabolism disorders related with cancer were reported in 2003 by Marx³ and Migliorati.⁴

The risk of the occurrence of the disease in these circumstances is now estimated to be between 0.00007% – 0.04% when these drugs are orally administered, and 1% – 10% if administered intravenously.⁵

From on-going scientific study, a perspective has emerged of BRONJ. Notable aspects of the phenomena include: the dose-dependent reduction of bone resorption, the inhibition of recruitment and promotion of apoptosis of osteoclasts; the stimulation of osteoblastic activity, and the decrease in the formation of capillary tubes, and consequent reduction of blood vessels which can lead to avascular osteonecrosis. Important also is the triggering or aggravation of BRONJ by traumatic factors, including dental extraction procedures. The occurrence of spontaneous BRONJ has long been noted. It is also clear that for a drug to influence bone turnover in jaws (a site having one of the slowest rates) has to be taken in high doses and for long

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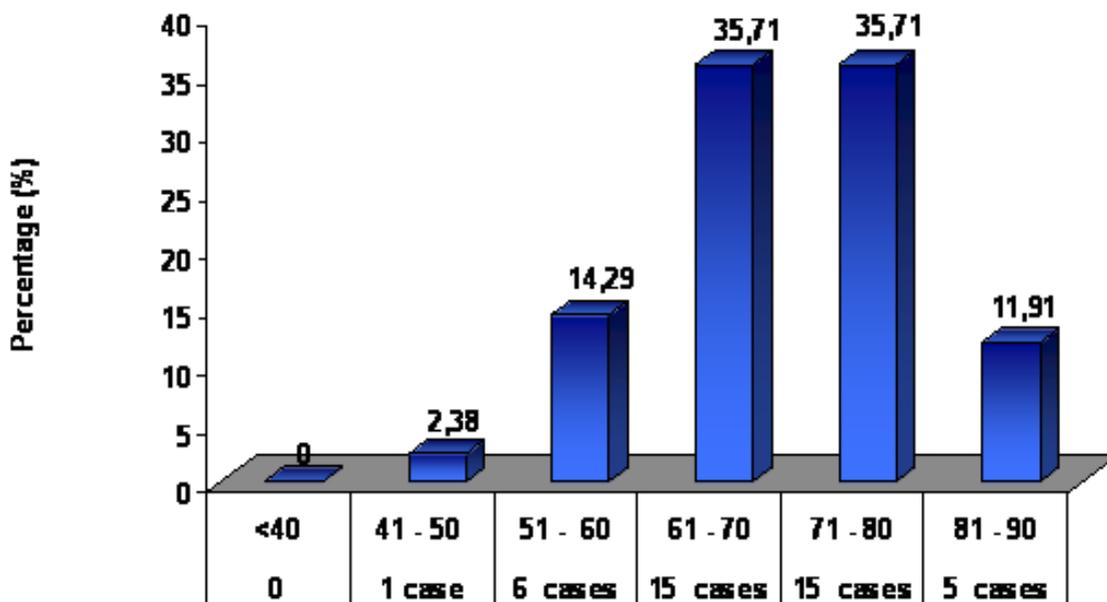


Fig. 1 – Distribution of cases by age groups

periods; this factor implicates risk of BRONJ involvement.⁶

Given that resorptive properties of bisphosphonates have increased about tenfold² from the first generation (etidronate), through the second group of amino-bisphosphonates (alendronate and pamidronate), to the third (risedronate and zoledronate) and there has been ever-increasing concern⁷ amongst dentists for information regarding the most effective procedures for dental extractions; and further, based on clinical evidence, the best time for intervention.

The authors considered as a working hypotheses that there are also anatomical and systemic⁷ conditioning factors for BRONJ: namely, the slow turnover of the basal bone of the jaws, the increased blood supply and more rapid bone remodeling related to periodontal vasculature that causes a higher local drug concentration; the thin mucous coating of

the bone, and local predisposition to operative trauma.

The main objective of this study therefore was to assess the local distribution of the disease, the presence of any anatomically associated or determinant factors, and the occurrence of other bone involvement for a group of patients presenting BRONJ. They also sought to contribute data towards determining the prevalence of BRONJ in Portugal.

MATERIAL AND METHODS

The authors made a retrospective study of forty-two patients presenting with BRONJ at the Department of Stomatology of Santa Maria University Hospital, in Lisbon, from 1st January 2004, to April 30th, 2011, attended by the Special Care Stomatological Consultation for Patients with Cancer, and the Oral Surgery Unit.

Figure 1 shows the age distribution of patients of both gender, who appeared during the period of time under study. There was a predominance of females (male=38.1%; female=61.9%).

A structured protocol governing each patient's clinical history relevant to the underlying disease included: the type of bisphosphonate, route and time of its administration; the anatomical location (by sextant) and associated factors; and the imaging (panoramic radiography and CT) and analyses (serum CTX) results.

Statistical analysis was performed: SPSS Statistics Vs.19 was the implemented program. Cochran's Q-test and McNemar were the non-parametric methods elected for which $p < 0.05$ was considered significant.

RESULTS

The classic macroscopic appearance of a lesion in the oral cavity consisting of a secondarily infected, round ulcer on the alveolar ridge, yellow greyish in appearance, with



Fig. 2 – Macroscopic aspect of the classic lesion of BRONJ

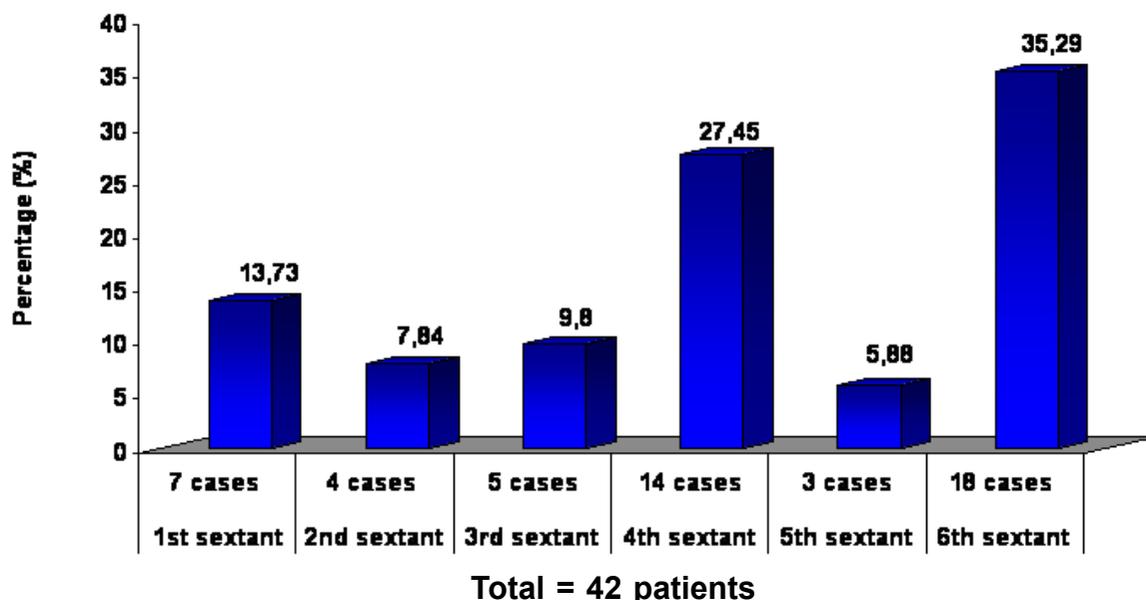


Fig. 3 – Occurrence in the involved sextants

diameter between 2 mm and 80 mm, was found (Fig. 2).

The initial lesion was imperceptible, radiolucent, and often accompanied by pain, which was present in 37 patients (88.1%).

Both single and multiple lesions were seen, in some cases accompanied by severe bone destruction that sometimes resulted in fractures.

The lower jaw was involved in 28 cases (66.7%) and the upper jaw in 11 cases (26.19%); in the remaining 3 cases (7.14%) there was involvement of both jaws.

All the sextants were involved, mainly the 6th (35.29% = 18 cases) and the 4th (27.45% = 14 cases) (Fig. 3).

Although other areas of both jaws were affected, the hard palate (2.38% = 1 case), the tuberosity (2.38% = 1 case), predominantly, it was the alveolar portion of the oral cavity that developed necrosis (95.24% = 40 cases).

The basal bone was involved in 8 cases (19.05%), the lingual wall in 10 (23.8%), the buccal wall in 5 (11.9%), with involvement of both walls in 2 (4.76%). Mylohyoid ridge involvement occurred in two patients (4.76%) (Table 1).

Underlying diseases were, in decreasing order: prostate neoplasm (30.95% = 13 patients), breast neoplasm (26.1%

= 11 cases), multiple myeloma (16.67% = 7 cases), osteoporosis (14.29% = 6 cases) and other underlying diseases (11.90% = 5 patients).

Zoledronate was the drug most administered, intravenously, in 32 patients (76.19%). Alendronate and Ibandronate were orally taken, respectively by 8 patients (19.05%) and 1 patient (2.38%). In 1 patient (2.38%), oral intake of Alendronate and Ibandronate were associated.

The patients had taken medication for a period ranging from 3 months to 9 years, with the largest number of patients (13 = 30.95%) receiving treatment for 2 years.

A large number of patients has experienced some type of trauma before the onset of BRONJ: surgically associated, 32 patients (76.19%), dental direct trauma, 1 patient (2.38%), prosthetic trauma, 1 patient (2.38%). Others had presented with related acute inflammatory episodes: 2 patients (4.76%). Six patients (14.29%), had no identified associated factor and so were deemed as suffering from a spontaneous occurrence of necrosis.

The jaws were the unique site where the disease occurred in all cases.

Table 1 – Anatomoclinical correlation of bone involvement.

Bone involved	Number of cases	Percentage (%)
Basal bone	8	19.05
Lingual wall	10	23.8
Buccal wall	5	11.9
Both walls	2	4.76
Mylohyoid ridge	2	4.76

DISCUSSION

The authors compared their results with those of other researchers, ranging from Marx's (2003)³ and Ruggiero, et al. (2004).⁸ to Marcin, et al. (2010).⁹ The lower jaw was the most affected in all studies, although in the latest, there was less discrepancy in the results taken separately for each jaw, or both when simultaneously affected by disease (Table 2). In our study, statistical analysis by Cochran's Q-test did not show that the proportion of individuals with BRONJ in the lower jaw was significantly higher than the upper jaw ($p = 0.210$). We conclude that the anatomic structure of the bone cannot be a determining or conditioning factor for the existing sectorial differences of prevalence in each jaw.

Statistical analysis confirmed the existence of significant differences in the proportions obtained for the various sextants ($Q = 23.861, p < 0.05$), with a higher proportion of individuals having involvement of the 4th and 6th. The greater occurrence of the disease in the posterior sextants of the lower jaw (18 cases at 6th sextant = 35.29% and 14 cases in the 4th sextant = 27.45%), can be explained by masticatory trauma prevalent in this area.

The application of the McNemar test showed that differences in the proportions of BRONJ patients with basal or alveolar bone involvement (the latter being higher) were significant ($p < 0.05$). The slow bone turnover in the basal

bone of the jaws, can explain the lower occurrence of the disease (19.05%) in this location. On the other hand, in the alveolar bone, the increased blood supply, and more rapid bone remodeling related to periodontal vasculature which invites higher local drug concentration may explain the higher prevalence of BRONJ in this area (95.24%).

Statistical results did not allow us to conclude that the predominance of women in our group of patients with BRONJ was significant in relation to the proportion of men who had the same problem ($p = 0.165$). Thus, we assumed that the occurrence of the disease could result from the therapies used for the treatment of the patient's systemic underlying diseases, some of them gender dependent (ie breast cancer).

The authors considered the causes of trauma associated with the occurrence of the disease, and found a relation with surgical trauma in 32 patients (76.19%), one case directly attributable to an injury of dental origin (2.38%) and another with prosthetic trauma (2.38%). The sum of patients who suffered trauma (34 = 80.95%), approached the results obtained by Marx (78%) and Ruggiero, et al. (54 = 86%), but was lower than those obtained by Marcin, et al., 31 patients = 91.18%. The association with acute inflammatory episode, found in 2 patients (4.76%), however, may be included in "traumatic factors" and so raising the percentage

Table 2 – Comparative results of local distribution of BRONJ, with other researchers.

Investigators/Study	Total number of cases	Percentage distribution (number of patients)		
		Upper jaw	Lower jaw	Both jaws
Marx (2003)	36	14% (...)	80% (...)	6% (...)
Ruggiero, et al. (2004)	63	37% (23)	62% (39)	1% (1)
Marcin, et al. (2010)	34	35.29% (12)	64.71% (22)	11.77% (4)
Present study	42	26.19% (11)	66.7% (28)	7.14% (3)

Table 3 – Comparative table of correlate factors with other researchers

Authors/Study	Total number of cases	Percentage (number of patients)				
		Cases of trauma			Inflammatory episode	Spontaneous occurrence
		Surgical	Dental direct trauma	Prosthetic		
Marx (2003)	36	78% (...)	22% (...)
Ruggiero, et al. (2004)	63	86% (54)	14% (9)
Marcin, et al. (2010)	34		91.18% (31)		...	8.82% (3)
Present study	42	76.19% (32)	2.38% (1)	2.38% (1)	4.76% (2)	14.29% (6)

of this study to 85.71%, bringing it closer to the values obtained by Marcin. The spontaneous appearance of BRONJ in 6 patients (14.29%), is a value close to that of Ruggiero, *et al.* (9 patients = 14%), and slightly higher than that of Marcin, *et al.* (3 patients = 8.82%) but lower to the result presented by Marx, 22% (Table 3).

Clear evidence of direct relationship with dental trauma was identified in 2.38% of patients of the present study.

Given that recently Lowes (2010)¹⁰ has referred the possible relationship between the administration of Bisphosphonates and increased risk of two types of hip fractures (subtrochanteric and diaphyseal – in both cases with a prevalence below 1%), it should be noted that in patients of this study, there was no involvement of other bones.

CONCLUSIONS

Given that:

- For severity, BRONJ was a significant anatomoclinical entity in all 42 new cases in this study, and for discomfort

(pain) in 81.1% of them.

- There was an anatomic correlation between the occurrence of the disease and its location in the jaws.

- There was a clinical association with trauma and type, route and length of administration of the bisphosphonate, Zoledronate being administered intravenously in 76.19% of the cases.

- The jaws were the unique place where the disease occurred.

Authors finally concluded that to prevent disease avoiding trauma, surgical measures should be implemented within 90 days after prescription.

CONFLICTS OF INTEREST

None stated.

FUNDING SOURCES

None stated.

REFERENCES

1. Silva MB. Osteonecrose dos ossos maxilares e bifosfonatos. www.marcosbrito.com [Access on June 14th, 2011].
2. Aderson G, Karen C, Figueiredo Maria A Z, Yurgel L S, Azambuja A A. Bisphosphonates and maxillary osteonecrosis: literature review and two case reports. *Revista Brasileira de Cancerologia* 2006;52(1):25-31.
3. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003;61(9):1115–1117.
4. Migliorati CA. Bisphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol* 2003;21(22):4253–4254.
5. Mariotti A. Bisphosphonates and Osteonecrosis of the Jaws. *J Dent Educ* 2008;72(8):919-929.
6. Consolaro A. Controvérsias na Ortodontia. Medicamentos versus Ortodontia. *R Clin Orton Dental Press* 2003;2(2):100.
7. Campisi G, Fede OD, Musciotto A, Casto AL, Muzio LL, Fulfaro F, *et al.* Bisphosphonate-related osteonecrosis of the jaw (BRONJ): run dental management designs and issues in diagnosis. *Ann Oncol* 2007;18(Suppl 6):vi168–vi172.
8. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004;62(5):527–534.
9. Kos M, Kuebler JF, Luczak K, Engelke W. Bisphosphonate-related osteonecrosis of the jaws: A review of 34 cases and evaluation of risk. *J Craniomaxillofac Surg* 2010;38(4):255-259.
10. Lowes R. FDA Adds Femur Fracture Warning to Bisphosphonate Labels. *Medscape Medical News* © 2010WebMD, LLC.