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# Osteonecrosis of the Jaw is not only Produced by Bisphosphonates: A Case Control Study using Propensity Score Matching

## Abstract

**Purpose:** To study the possible association between the development of osteonecrosis of the jaws and the use of bisphosphonates in patients diagnosed with osteonecrosis of the jaws and compared them with a control group using propensity score matching.

**Methods:** Case-control study carried out with 24 patients suffering from osteonecrosis of the jaws and 874 controls. Using propensity score matching 20 patients with osteonecrosis of the jaws and 20 controls were perfectly matched.

**Results:** After matching, there were no statistically significant differences in age, serum levels of beta-crosslaps, osteocalcin, procollagen I, tartrate-resistant acid phosphatase, Parathyroid hormone and Vitamin D or the presence of diabetes mellitus, chemotherapy, rheumatoid arthritis, bone mineral density, prevalence of osteoporosis, trabecular bone score, quantitative ultrasound measurements, or bisphosphonate use for 4 or 5 years.

**Conclusions:** Osteonecrosis of the jaws is a disease probably caused by a multifactorial etiology. Bisphosphonate use was not identified as its only main cause.

**Clinical relevance**: Our results show that the pathophysiology of osteonecrosis of the jaws is multifactorial and in its etiology, many factors apart from bisphosphonates are involved.

Keywords: Osteonecrosis; Jaw; Bisphosphonates; Etiology; Propensity score matching

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# Introduction

Osteoporosis is a very common disease, affecting mainly older people, with fragility fractures its clinical complication [1,2]. Bisphosphonates are the first choice drug in most clinical guidelines for treating osteoporosis [3,4] but there are no data published about its long-term security. So, in recent years, some diseases such as atypical fractures and osteonecrosis of the jaw (ONJ) have been published as possible complications of longterm treatment with bisphosphonates [5-7]. Nevertheless, these complications have also been described with denosumab, which is a potent antiresorptive with no pharmacological relationship with bisphosphonates [8,9].

ONJ is a new clinical entity first described in 2003 by Marx et al. who reported exposed maxillar bone without healing to infection and necrosis. Although from the outset, its etiology was related to the use of bisphosphonates this relationship has not been Marlene García-Quintana<sup>1\*</sup>, Pedro Saavedra-Santana<sup>2</sup>, Mario Vicente-Barrero<sup>1,3</sup>, Sacramento Bocanegra-Pérez<sup>3</sup>, Ma Pino Quintana-Montesdeoca<sup>2</sup> and Manuel Sosa-Henríquez<sup>1,4</sup>

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completely stated, because most ONJ cases have been described in oncology patients receiving bisphosphonates in very high dose, not used in the treatment of osteoporosis, in addition to other drugs, chemotherapy and radiotherapy [10].

Although ONJ is a feared complication, its current incidence is very low and the studies performed to establish a direct relationship

with bisphosphonates treatment sometimes have shown contradictory results. Although ONJ is a feared complication, its current incidence is very low and the studies performed to establish a direct relationship with bisphosphonates treatment sometimes have shown contradictory results. We have not find any of these studies performed with propensity score test, which is one of the interpretation of the concept of probability, in which there is a perfect matching between cases and controls.

# **Materials and Methods**

This is a case-control study in which cases were the patients presented ONJ and controls patients suffering from osteoporosis. 24 patients were diagnosed of ONJ following the criteria of The International Task Force on Osteonecrosis of the Jaw [11] and were attended at the Maxillofacial Service at the Hospital University Insular. We included as controls 874 patients suffering from osteoporosis who were attended at the bone metabolic unit at the Hospital University Insular. Taking into account the clinical and biochemical data, propensity score matching was applied and only 20 cases (from 24 patients with ONJ) were perfectly matched to 20 controls from 874 patients of control group.

### **Statistical analysis**

**Univariate analysis:** Categorical variables are expressed as frequencies and percentages and continuous as mean and standard deviation (SD) when data followed a normal distribution, or as median and interquartile range (IQR=25<sup>th</sup>-75<sup>th</sup> percentile) when distribution departed from normality. For independent data, the percentages were compared, as appropriate, using the Chi-square ( $\chi^2$ ) test or the exact Fisher test, the means by the t-test and the medians by the Wilcoxon test for independent data. For dependent data, the percentages were compared using the McNemar test, the means by the t-test for paired data and the medians by the Wilcoxon test for data.

**Propensity score:** After performing an initial comparison between both groups, patients and controls, we observed some statistically significant differences in some variables, as shown in **Table 1** and **Table 2**. Because of this, we made a matching process with "propensity score", selecting the variables by the multivariant logistic regression. The resulting model, presented in **Table 3** included the following variables: age, TRAP, osteocalcin, rheumatoid arthritis and chemotherapy. To obtain a perfect pairing, we lost 4 patients and only 20 cases and 20 patients could be finally included.

To determine the association between the use of the bisphosphonates and the osteonecrosis of jaw, we selected for each case a similar control (matching). This process was based on a propensity score obtained by means of the logistic regression. More concretely, we consider as propensity score the probability:

Pr *ONJ* | *X*!, . . . , *X*!, which was defined by the logistic model:

logit Pr  $ONJ \mid X!, \ldots, X! = \beta! + \beta!$ 

Age, bone metabolism markers that showed significant association with the ONJ in univariate analysis, cancer, chemotherapy and rheumatoid arthritis were entered into the multivariate analysis. Selection of variables based on complete enumeration algorithm and Bayes information criterion (BIC) was then performed. The model was summarized as coefficients (SE), p-values (likelihood ratio test) and odds-ratios, which were estimated by confidence intervals at 95%.

**Matching:** We then carried out a 1-to-1 matched analysis without replacement on the basis of each patient's estimated propensity score. After propensity score matching, baseline characteristics were compared with the McNemar tests for binary variables and the t-tests for Wilcoxon test, as appropriate, for continuous variables. In addition, we assessed the success of propensity score matching to balance covariates in the 2 groups using standardized differences. Standardized differences of less than 10% support the assumption of balance between the 2 groups.

**Conditional logistic regression:** The endpoint was the rate of subjects treated with bisphosphonates for five or more years. For each one of them, a logistic model having the binary variable presence/absence of ONJ as covariable was considered. These models were estimated by means of the conditional likelihood. From the models were obtained the corresponding odds-ratios, which were estimated by means of 95% confidence intervals. Statistical significance was set at p<0.05.

### **Physical examination**

A complete physical examination was carried out of every patient included in the study. Height was measured without shoes, and weight with light clothes was estimated on a balance scale. Body mass index (BMI) was derived from the formula: BMI=weight (kg)/height (m)<sup>2</sup>.

## **Dual-energy X-ray Absorptiometry (DXA)**

Bone mineral density (BMD) was measured by a DXA Hologic QDR 4500 Discovery (Hologic, Spain). The area of interest at the lumbar spine measurement was L2-L4. At the femoral site, two regions were measured: femoral neck and total hip. The software provided by the manufacturer allowed anatomical separations [12]. The results were expressed in g/cm<sup>2</sup>. Precision of the system (coefficient of variation) was 0.5% in vitro (standard bone phantom) and 0.9% in vivo (12 patients measured twice in the same day). All the determinations were measured by the same operator, so no inter-observer variation existed. T-scores were calculated from the reference values previously obtained from Canary Islands population [13].

## **Trabecular Bone Score (TBS)**

All TBS measurements were performed using TBS iNsight Software, version 2.0.0.1 (Med-Imaps, Pessac, France). This software uses the raw DXA image of the anteroposterior spine for the same region of interest as the BMD measurement. The densitometer was calibrated using anthropomorphic phantoms.

### **Quantitative Ultrasound (QUS) measurements**

All subjects underwent calcaneus measurement by QUS. This was carried out using the Sahara Clinical sonometer (Hologic Inc., Bedford, MA). The system consists of 2 unfocused transducers mounted co-axially on a monitor caliper. One transducer acts as the transmitter and the other as the receiver. The transducers are

acoustically coupled to the heel using soft rubber pads and an oilbased coupling gel. The Sahara device measures both broadband ultrasound attenuation (BUA) and speed of sound (SOS) at a fixed region of interest in the midcalcaneus, and the BUA and SOS results are combined to provide an estimate of the quantitative ultrasound index (QUI) using the formula:

#### $QUI=0.41 \times (BUA+SOS)-571$

For all QUS measurements, the corresponding T-scores and Z-scores were calculated according the normative data for the Spanish population, previously established by our working group [14].

#### **Biochemical measurements**

Serum specimens were obtained after an overnight fast. Blood was collected without additives between 8:00 and 9:00 a.m. After centrifugation at 1 500 g for 10 min, serum was aliquoted and frozen at -20°C within 1 h from phlebotomy until the biochemical analyses were performed. Serum parathyroid hormone (PTH) and 25-hydroxy-vitamin D (25-OHD) were measured by electrochemiluminescence with Elecsys 170 PP (Modular Analytics) of Roche Diagnostic<sup>®</sup> (Basel, Switzerland). For PTH, total coefficients of variation (TCVs) ranged from 1.6% to 10.9%, and for 25 OHD TCVs was 4.9% using blinded quality control samples in our laboratory.

The measured remodeling bone markers for formation were Osteocalcin (OC) (electrochemiluminescence immunoassay, analyser Elecsys, Roche Diagnostics, IN), and N-terminal propeptide of type 1 collagen (PINP) (electrochemiluminescence immunoassay Roche Diagnostics). The markers for resorption were tartrate-resistant acid phosphatase 5 $\beta$  (TRAP5 $\beta$ , colourimetry, Hitachi 704 Boehringer Manheim GmbH) and carboxy-terminal telopeptide of type I collagen (CTX, enzymatic immunoassay, analyser Elecsys CrossLaps, Roche Diagnostics SL, Barcelona, Spain).

#### **Fractures assessment**

Prevalent vertebral fractures were assessed on standard lateral spine radiographs in all subjects. Vertebral fractures were defined following the radiological semiquantitative criteria of Genant [15]. The presence of nonvertebral fractures was documented firstly by a self-reported history with later confirmation in medical hospital records or X-ray films.

## Results

**Table 1** shows the characteristics of the studied populations before the performed matching by the propensity score method. Patients with ONJ had a higher age than controls and also had a higher prevalence of cancer, chemotherapy treatment, rheumatoid arthritis, oral steroids therapy and a higher use of bisphosphonates for more than 5 years, while controls showed a higher prevalence of fragility fractures and maternal hip fractures.

	Controls	ONJ	p value
	N=874	N=24	
Age (years)	62.4 ± 11.2	69.0 ± 11.0	0.005
Sex (male)	111 (12.7)	4 (16.7)	0.535
Diabetes	134 (15.3)	5 (20.8)	0.401
mellitus			
Cancer	94 (10.8)	11 (45.8)	< 0.001
Chemotherapy	40 (4.6)	11 (45.8)	< 0.001
Rheumatoid	18 (2.1)	9 (37.5)	< 0.001
Arthritis			
Oral steroids	77 (8.8)	7 (29.2)	0.005
Fragility	281 (32.3)	7 (29.2)	< 0.001
fractures			
Mother with hip	100 (11.5)	2 (8.3)	< 0.001
fracture			
Five or more	117 (13.4)	8 (33.3)	0.012
years with BFs			
Note: Data are modias + SD modians (IOP) and frequencies $(\%)$			

Note: Data are medias ± SD, medians (IQR) and frequencies (%)

**Table 1:** Characteristics of the populations before the matching: Clinical features.

**Table 2** shows biochemical, densitometric and ultrasonographic values of the populations studied before the matching. Patients with ONJ had higher values of TRAP, and lower values of betacrosslaps, P1NP and osteocalcin than controls. Bone mineral density was higher in cases than controls, but only significantly at L2-L4 (p<0.001). There was a lower prevalence of osteoporosis densitometric values in patients with ONJ (T-score<-2.5 at any of the measured sites: lumbar spine, femoral neck or total hip). There were no statistical differences in trabecular bone score (TBS) and quantitative ultrasound parameters measured at the calcaneus between both groups of patients.

	Controls	ONJ	p value	
	N=874	N=24	-	
TRAP (UI/I)	2.7 (2.3; 3.3)	3.2 (2.4; 3.9)	0.025	
TSH (UI/I)	2.0 (1.3; 2.7)	2.4 (1.7; 3.2)	0.098	
Beta-crosslaps (pg/mL)	0.4 (0.2; 0.6)	0.3 (0.2; 0.4)	0.001	
Osteocalcin (ng/mL)	20.3 (13.7; 30.2)	13.4 (9.5; 19.4)	0.003	
PTH (pg/mL)	49.3 (36.5; 78.5)	49.3 (36.1; 82.0)	0.793	
P1NP (µg/mL)	42.7 (29.3; 60.3)	31.3 (20.1; 39.0)	0.001	
25-HCC (ng/mL)	22.4 (16.0; 30.1)	21.6 (16.0; 30.2)	0.877	
DXA				
L2-L4 (g/cm <sup>2</sup> )	0.865 ± 0.173	0.992 ± 0.225	< 0.001	
Femoral neck (g/cm <sup>2</sup> )	0.685 ± 0.133	0.736 ± 0.177	0.065	
Total femur (g/cm <sup>2</sup> )	0.816 ± 0.159	0.880 ± 0.169	0.054	
T-Score<-2.5	Number (%)	Number (%)		
Lumbar	299 (34.5)	3 (12.5)	0.025	
Femoral neck	147 (17.0)	4 (16.7)	1	
Total hip	152 (17.6)	2 (8.3)	0.409	
Trabecular bone score	$1.257 \pm 0.121$	$1.273 \pm 0.146$	0.678	
(TBS)				
T-Score	-2.375 ± 1.518	-2.163 ± 1.823	0.671	
QUS				
QUI	79.4 ± 21.3	83.3 ± 25.3	0.422	
SOS (m/s)	1516.2 ± 101.5	1529.4 ± 40.5	0.562	
BUA (dB/mHz)	63.2 ± 19.7	64.8 ± 23.1	0.721	
Note: Data are medias ± SD, medians (IQR) and frequencies (%)				

**Table 2:** Comparison of biochemical markers of bone remodeling, hormones and densitometry between controls and patients with osteonecrosis of the jaws.

**Table 3** shows the propensity-score obtained by means of the multivariate logistic regression for ONJ. Chosen values were age, serum values of TRAP and osteocalcin, the presence of rheumatoid arthritis, and having received chemotherapy. The propensity score deduced from this model is:

	Coefficient (SE)	p value	OR (95% CI)	
Age, per year	0.100 (0.027)	<0.001	1.105 (1.049; 1.164)	
Log-TRAP, UI/L	2.967 (0.927)	0.001	19.43 (3.16; 119.4)	
Log-Osteocalcin, per	-1.609 (0.378)	< 0.001	0.200 (0.095; 0.420)	
ng/mL				
Rheumatoid	3.511 (0.660)	< 0.001	33.49 (9.18; 122.1)	
Arthritis				
Chemotherapy 3.543 (0.598) <0.001 34.57 (10.7; 111.5)				
Note: The propensity score deduced from this model is: PS=0.1 $\times$				
Age+2.977 × logFATR-1.609 × log Osteocalcin+3.511 × Arthirits+3.543				

 Table 3: Variables included in the model for calculation of propensity score.

× Chemotherapy

**Figure 1** shows the paired propensity scores. This scatter shows that propensity scores are practically identical within the paired subjects.



**Table 4** shows obtained data when cases and controls were compared after the matching performed by the paired propensity scores. There are no statistically significant differences between both groups with the exception of serum TSH levels, which were into the normal range. Nevertheless, we performed the next logistic regression using this hormone as co-variable.

	Controls	ONJ	p value	%
	N=20	N=20		Standardized
				Difference
Age, years	69.5 ± 8.6	69.8 ± 10.9	0.922	2.8
Sex male n (%)	3 (15.0)	3 (15.0)	1	0
Log-FATR	1.1 (0.9; 1.4)	1.1 (0.9; 1.3)	0.85	-7.59
TSH (UI/L)	1.7 (1.3; 2.4)	2.6 (1.9; 3.2)	0.018	-53.47
Beta-crosslaps	0.3 (0.2; 0.4)	0.3 (0.1; 0.4)	0.375	-28.4
(pg/mL)				
Log-Osteocalcin	2.7 (2.0; 3.0)	2.6 (2.2; 2.9)	0.659	-8.67
(ng/mL)				
PTH (pg/mL)	43.8 (31.3;	47.8 (36.1;	0.478	26.01
	67.6)	60.7)		
P1NP (µg/mL)	42.7 (29.9;	30.3 (19.1;	0.089	-39.3
	52.7)	40.5)		
25-HCC ( ng/	22.0 (17.5;	22.9 (17.8;	0.623	44.02
mL)	27.7)	30.2)		
Diabetes	5 (25.0)	4 (20.0)	1	-12.18
mellitus n (%)				
Chemotherapy	7 (35.0)	7 (35.0)	1	0
n (%)				

Rheumatoid	5 (25.0)	5 (25.0)	1	0
	- ( /	- ( /		_
Arthritis n (%)				
T-Score<-2.5	3.543 (0.598)	3.543 (0.598)	3.543	3.543 (0.598)
			(0.598)	
Lumbar n (%)	6 (33.3)	3 (15.0)	0.371	-
Femoral neck	2 (11.1)	4 (20.0)	1	-
n (%)				
Total hip n (%)	3 (16.7)	2 (10.0)	0.617	-
Five or more	7 (35.0)	7 (35.0)	1	0
years with BFs				
n (%)				

**Note:** Data are medias ± SD, medians (IQR) and frequencies (%)

 Table 4: Comparison of the variables studied after matching by propensity score.

**Table 5** shows the results of the conditional logistic regression for the exposure to bisphosphonates for 5 years. In both cases, there was no statistical association between the use of bisphosphonates and the presence of ONJ, either alone or analyzing them using TSH value as a co-variable.

Outcome	<b>Co-variables</b>	p value	OR (95%CI)
Five or more	ONJ	0.805	0.809 (0.151-4.332)
years with BFs	TSH	0.428	1.328 (0.659-2.675)

**Table 5:** Conditional logistic regression for the exposure tobisphosphonates for 5 years.

# Conclusion

In conclusion, our results confirm that there is not a direct casual association between the use of bisphosphonates after 5 years and the development of ONJ. This is probably due to the fact that in the pathogenesis of this disease can exist a number of clinical factors in addition to the use of bisphosphonates, such as the presence of a cancer and the chemotherapy used in its treatment, poor oral and dental health, corticoids, diabetes and teeth extractions.

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