CPQ Medicine (2024) 15:2
Case Control Study

Osteonecrosis of the Jaw Is Not Only Produced by Bisphosphonates. A Case Control Study Using Propensity Score Matching

Marlene García-Quintana[1*], Pedro Saavedra-Santana[2], Mario Vicente-Barrero[1,3], Sacramento Bocanegra-Pérez[3], Mª Pino Quintana-Montesdeoca[2] & Manuel Sosa-Henríquez[1,4]

[1]PhD. Research Group on Osteoporosis and Mineral Metabolism. Professor University of Las Palmas de Gran Canaria. Las Palmas de Gran Canaria (Spain)

[2]DMD. Professor Department of Mathematics. University of Las Palmas de Gran Canaria. Las Palmas de Gran Canaria (Spain).

[3]MD. Department Head. Service of Maxilo-Facial Surgery. Hospital University Insular. Las Palmas de Gran Canaria (Spain)

[4]DMD. Department Bone Metabolic Unit. Hospital University Insular. Professor Medicine University of Las Palmas de Gran Canaria. Las Palmas de Gran Canaria (Spain)

[*]Correspondence to: Dr. Marlene García Quintana, Department of Medical and Surgical Sciences, University Las Palmas de Gran Canaria (ULPGC), Las Palmas.

Copyright

Received: 20 December 2023

Published: 15 January 2024

Keywords: *Osteonecrosis; Jaw; Bisphosphonates; Etiology; Propensity Score Matching*

Abstract

Introduction: Propensity score matching (PSM) is a statistical matching technique that attempts to estimate the effect of a treatment, or another intervention based on the covariates that predict whether the treatment will be received. PSM attempts to reduce bias due to confounding variables that can be found in an estimate of the treatment effect obtained from simply comparing the results between units that received the treatment versus those that did not.

Objective: 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.

Material and 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 bisbhosphonates are involved.

Abbreviations (if used)

Osteonecrosis of the Jaw (ONJ).

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 long-term 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 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, that is one 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^{th} - 75^{th} 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 dependent 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 tables 1 and 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 $ONJ \mid X!, \ldots, X!$, 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%.

Table 1: *Clinical characteristics of the populations before matching*

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

Data are medias ± SD, medians (IQR) and frequencies (%).
Source: self made

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

	Controls N = 874	**ONJ N = 24**	**P value**
TRAP (UI/l)	2.7 (2.3 ; 3.3)	3.2 (2.4 ; 3.9)	0.025
TSH (UI/l)	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/cm²)	0.865 ± 0.173	0.992 ± 0.225	< 0.001
Femoral neck (g/cm²)	0.685 ± 0.133	0.736 ± 0.177	0.065
Total femur (g/cm²)	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 (TBS)	1.257 ± 0.121	1.273 ± 0.146	0.678
TScore	-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

Data are medias ± SD, medians (IQR) and frequencies (%).
Source: self made

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

	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 ng/mL	-1.609 (0.378)	< 0.001	0.200 (0.095 ; 0.420)
Rheumatoid Arthritis	3.511 (0.660)	< 0.001	33.49 (9.18 ; 122.1)
Chemotherapy	3.543 (0.598)	< 0.001	34.57 (10.7 ; 111.5)

*The propensity score deduced from this model is:
PS =0.1×Age+2.977×log FATR-1.609×log Osteocalcin+3.511×Arthirits+3.543 ×Chemotherapy
Source: self made

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)2.

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/cm2. 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 oil-based 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 X (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® (Basel, Switzerland). For PTH, total coefficients of variation (TCVs) ranged from 1.6% to 10.9%, and for 25OHD 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 5β (TRAP5β, 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.

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 beta-crosslaps, 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.

Table 3 shows the propensity score obtained through multivariate logistic regression for ONJ. The values chosen were age, serum TRAP and osteocalcin values, the presence of rheumatoid arthritis, and having received chemotherapy. The propensity score deduced from this model is shown in graph 1 with its pairings. This dispersion shows that the propensity scores are virtually identical within the matched subjects.

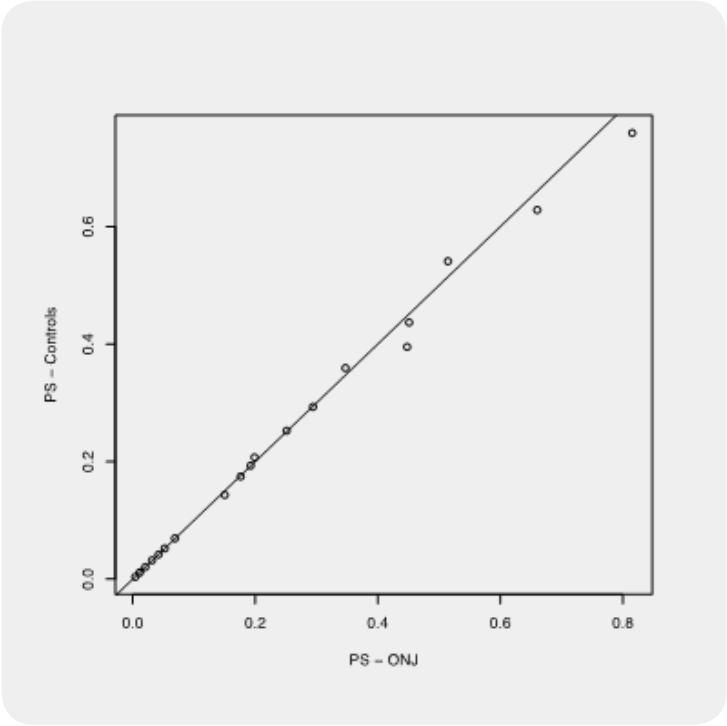

Figure 1: *Paired propensity scores.*
Source: self made

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 covariable.

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

	Controls N = 20	**ONJ N = 20**	**p value**	**% Standardized Difference**
Age, years	69.5 ± 8.6	69.8 ± 10.9	0.922	2.80
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)	0.850	-7.59
TSH (UI/L)	1.7 (1.3 ; 2.4)	2.6 (1.9 ; 3.2)	0.018	-53.47

Beta-crosslaps (pg/mL)	0.3 (0.2 ; 0.4)	0.3 (0.1 ; 0.4)	0.375	-28.40
Log-Osteocalcin (ng/mL)	2.7 (2.0 ; 3.0)	2.6 (2.2 ; 2.9)	0.659	-8.67
PTH (pg/mL)	43.8 (31.3 ; 67.6)	47.8 (36.1 ; 60.7)	0.478	26.01
P1NP (µg/mL)	42.7 (29.9 ; 52.7)	30.3 (19.1 ; 40.5)	0.089	-39.30
25-HCC (ng/mL)	22.0 (17.5 ; 27.7)	22.9 (17.8 ; 30.2)	0.623	44.02
Diabetes mellitus n (%)	5 (25.0)	4 (20.0)	1	-12.18
Chemotherapy n (%)	7 (35.0)	7 (35.0)	1	0
Rheumatoid Arthritis n (%)	5 (25.0)	5 (25.0)	1	0
T-Score < -2.5				
Lumbar n (%)	6 (33.3)	3 (15.0)	0.371	-
Femoral neck n (%)	2 (11.1)	4 (20.0)	1	-
Total hip n (%)	3 (16.7)	2 (10.0)	0.617	-
Five or more years with BFs n (%)	7 (35.0)	7 (35.0)	1	0

Data are medias ± SD, medians (IQR) and frequencies (%).
Source: self made

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 covariable.

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

Outcome	Covariables	p value	OR (95%CI)
Five or more years with BFs			
	ONJ	0.805	0.809 (0.151– 4.332)
	TSH	0.428	1.328 (0.659 – 2.675)

Source: self made

Discussions

The pathogenesis of ONJ caused by antiresorptive drugs remains to be elucidated and there are different theories, particularly for bisphosphonate-related ONJ. The most accepted hypothesis states that antiresorptive drugs reduce bone turnover in jaw resulting oversuppression which lead to ONJ (17–19). However, this hypothesis is based on a few animal studies [20]. There are also some inconsistencies in this theory. As ONJ does not manifest itself at other sites, the bone turnover of the jaw consequently has to be higher than that in any other bone in the body, which has not been proven. It is striking that these lesions appear exclusively

in the jaw and not in other bones of the body. It is believed that several factors would converge to do so. The first one would be that the oral cavity is the only region that exposes bone tissue to the external environment, via gingival sulcus. In addition, maxillary bones are subject to great stress functional constantly, which forces them physiologically at an accelerated rate of bone, superior to any other bone replacement, increased by odontogenic pathological processes or surgical acts [21].

Probably ONJ is a disease with a multifactorial etiology on which bisphosphonates are only a risk factor for its production [7,11,22,23], not the only one and, indeed, probably not the most important [24,25]. In fact, in some series, about 20% of the patients who have developed an ONJ were not receiving bisphosphonates [7,18,21,22,24,26-30]. It must be taken into account that ONJ is observed mainly and almost exclusively in patients suffering from cancer, whose receive as well as bisphosphonates many other drugs, chemotherapy and radiotherapy [5,7,10,11,18,19,22,23,26,32-34]. On the other hand, the pathogenesis of ONJ has been related to tooth extraction [30,35], the coexistence of osteoporosis [35], diabetes mellitus [36] rheumatoid arthritis [21] and vitamin D deficiency [37]. Another reason against the role of bisphosphonates in the etiology of ONJ is that ONJ has also been described in patients receiving denosumab and in other oncological treatments [33,34].

Our results of bone turnover markers confirm the hypothesis that there is no oversuppression in bone remodeling in the pathogenesis of ONJ, in agreement with the findings reported by some other authors [10,11,13,19,20,25-27]. We found similar vitamin D levels in both groups, cases and controls, and that was expected. So, vitamin D deficiency was not related to the presence of ONJ. Parathyroid hormone (PTH) levels were also similar in both groups without statistically significant differences ($p= 0.478$), so the presence of secondary hyperparathyroidism was not a factor related to the development of ONJ.

In our patient cases and controls, we studied bone quantity by DXA and bone quality bone by 2 different methods: trabecular bone score, who is a new method who assesses the integrity of trabeculae bone [38] and by quantitative ultrasounds measurements (QUS) measured at the heel, a method that some authors consider that it values the quality of bone [39,40]. Our results show that patients with ONJ have higher bone quantity than osteoporotic patients and similar bone quality. These findings are according with our results about bone turnover markers, all of which probably means that bone is normal in ONJ.

TSH values were the only statistically significant differences between cases and controls after the pairing match and it showed higher values in patients with ONJ compared to controls. Nevertheless, both figures are included in the normal range values of our laboratory and we value it as a casual finding without clinical signification. Indeed, we could not confirm any possible association between the presence of ONJ and the consumption of bisphosphonates for 5 years.

A limitation of our study was the number of patients included which was due, first, to the small number of cases we were able to obtain in which there was unequivocally a ONJ and second, to the difficulty of obtaining a perfect pairing match between cases and controls.

Conclusions

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.

Bibliography

1. Black, D. M. & Rosen, C. J. (2016). Postmenopausal Osteoporosis. *N Engl J Med., 374*(3), 254-262.

2. Cummings, S. R. & Melton, L. J. (2002). Epidemiology and outcomes of osteoporotic fractures. *Lancet, 359*(9319), 1761-1767.

3. González-Macías, J., Del Pino-Montes, J., Olmos, J. M. & Nogués, X. (2015). Guías de práctica clínica en la osteoporosis posmenopáusica, glucocorticoidea y del varón. Sociedad Española de Investigación Ósea y del Metabolismo Mineral (3.a versión actualizada 2014). *Rev Clin Esp., 215*(9), 515-526.

4. Tarantino, U., Iolascon, G., Cianferotti, L., Masi, L., Marcucci, G., Giusti, F., *et al*. (2017). Clinical guidelines for the prevention and treatment of osteoporosis: summary statements and recommendations from the Italian Society for Orthopaedics and Traumatology. *J Orthop Traumatol., 18*(Suppl 1), 3-36.

5. Eriksen, E. F., Díez-Pérez, A., Boonen, S. (2014). Update on long-term treatment with bisphosphonates for postmenopausal osteoporosis: A systematic review. *Bone, 58,* 126-135.

6. Watts, N. B. & Diab, D. L. (2010). Long-term use of bisphosphonates in osteoporosis. *J Clin Endocrinol Metab., 95*(4), 1555-1565.

7. Rizzoli, R., Burlet, N., Cahall, D., Delmas, P. D., Eriksen, E. F., Felsenberg, D., *et al*. (2008). Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis. *Bone, 42*(5), 841-847.

8. Selvi Sabater, P., Rizo Cerdá, A., Titos Arcos, J. & Espuny Miró, A. (2014). Posible denosumab-induced jaw osteonecrosis in the treatment of osteoporosis. A case report. *Farm Hosp., 38*(3), 248-256.

9. Diz, P., López-Cedrún, J. L., Arenaz, J. & Scully, C. (2012). Denosumab-related osteonecrosis of the jaw. *J Am Dent Assoc., 143*(9), 981-984.

10. Marx, R. E. (2003). Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis necrosis of the jaws. A growing epidemic. *J Oral Maxillofac Surg., 61*(9), 1115-1118.

11. Khan, A. A., Morrison, A., Hanley, D. A., Felsenberg, D., McCauley, L. K., O'Ryan, F., *et al*. (2015). Diagnosis and management of osteonecrosis of the jaw: A systematic review and international consensus. J Bone Miner Res., 30(1), 3-23.

12. Duboeuf, F., Braillon, P., Chapuy, M. C., Haond, P., Hardouin, C., Meary, M. F., *et al*. (1991). Bone mineral density of the hip measured with dual-energy X-ray absorptiometry in normal elderly women and in patients with hip fracture. *Osteoporos Int., 1*(4), 242-249.

13. Sosa, M., Hernández, D., Estévez, S., Rodríguez, M., Limiñana, J. M., Saavedra, P., *et al*. (1998). The range of bone mineral density in healthy Canarian women by dual X-ray absorptiometry radiography and quantitative computer tomography. *J Clin Densitom., 1*(4), 385-393.

14. Sosa, M., Saavedra, P., Muñoz-Torres, M., Alegre, J., Gómez, C., González-Macías, J., *et al*. (2002). Quantitative ultrasound calcaneus measurements: Normative data and precision in the Spanish population. *Osteoporos Int., 13*(6), 487-492.

15. Genant, H. K., Wu, C. Y., van Kuijk, C., Nevitt, M. C. (1993). Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res., 8*(9), 1137-1148.

16. Review, C., Communication, S. & Principles, G. (2004). World Medical Association. World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. *J Int Bioéthique., 15*(1), 124.

17. Orriss, I. R., Key, M. L., Colston, K. W. & Arnett, T. R. (2009). Inhibition of osteoblast function in vitro by aminobisphosphonates. *J Cell Biochem., 106*(1), 109-118.

18. Allen, M. R. & Burr, D. B. (2009). The pathogenesis of bisphosphonate-related osteonecrosis of the jaw: so many hypotheses, so few data. *J Oral Maxillofac Surg., 67*(5 suppl.), 61-70.

19. Rasmusson, L. & Abtahi, J. (2014). Bisphosphonate associated osteonecrosis of the jaw: An update on pathophysiology, risk factors, and treatment. *Int J Dent.,* 471035.

20. Huja, S. S., Fernandez, S. A. & Hill, K. J. & Li, Y. (2006). Remodeling dynamics in the alveolar process in skeletally mature dogs. *Anat Rec A Discov Mol Cell Evol Biol., 288*(12), 1243-1249.

21. Furuya, T., Maeda, S., Momohara, S., Taniguchi, A. & Yamanaka, H. (2016). Dental treatments, tooth extractions, and osteonecrosis of the jaw in Japanese patients with rheumatoid arthritis: results from the IORRA cohort study. *J Bone Miner Metab., 35*(3), 344-350.

22. Sosa Henríquez, M. (2009). Osteonecrosis de los maxilares: Documento de consenso SEIOMM. *Rev Osteoporos y Metab Miner, 1*(1), 41-51.

23. Ruggiero, S., Gralow, J., Marx, R. E., Hoff, A. O., Schubert, M. M., Huryn, J. M., *et al*. (2006). Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. *J Oncol Pract., 2*(1), 7-14.

24. Bocanegra-Pérez, M. S., Vicente-Barrero, M., Sosa-Henríquez, M., Rodríguez-Bocanegra, E., Limiña-na-Cañal, J. M., López-Márquez, A., *et al*. (2012). Bone metabolism and clinical study of 44 patients with bisphosphonate-related osteonecrosis of the jaws. *Med Oral Patol Oral Cir Bucal., 17*(6).

25. Sosa-Henríquez M, Vicente-Barrero M, Bocanegra-Pérez MS. (2011). Osteonecrosis de los maxilares: nuevas evidencias sobre su etiopatogenia. *Rev Osteoporos Metab Miner, 3*(1), 5-6.

26. Marx RE, Sawatari Y, Fortin M, Broumand V. (2005). bisphosphonate-induced exposed bone (osteone-crosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg., 63*(11), 1567-1575.

27. Raje, N., Woo, S. B., Hande, K., Yap, J. T., Richardson, P. G., Vallet, S., *et al*. (2008). Clinical, radiographic, and biochemical characterization of multiple myeloma patients with osteonecrosis of the jaw. *Clin Cancer Res., 14*(8), 2387-2395.

28. Assael, L. A. (2009). Oral bisphosphonates as a cause of bisphosphonate-related osteonecrosis of the jaws: clinical findings, assessment of risks, and preventive strategies. *J Oral Maxillofac Surg., 67*(5 suppl.), 35-43.

29. Otto, S., Hafner, S., Mast, G., Tischer, T., Volkmer, E., Schieker, M., *et al*. (2010). Bisphosphonate-related osteonecrosis of the jaw: is ph the missing part in the pathogenesis puzzle? *J Oral Maxillofac Surg., 68*(5), 1158-1161.

30. Gaudin, E., Seidel, L., Bacevic, M., Rompen, E. & Lambert, F. (2015). Occurrence and risk indicators of medication-related osteonecrosis of the jaw after dental extraction: A systematic review and meta-analysis. *J Clin Periodontol., 42*(10), 922-932.

31. Leizaola-Cardesa, I. O., Aguilar-Salvatierra, A., Gonzalez-Jaranay, M., Moreu, G., Sala-Romero, M. J. & Gómez-Moreno, G. (2016). Bisphosphonates, vitamin D, parathyroid hormone, and osteonecrosis of the jaw. Could there be a missing link? *Med Oral Patol Oral y Cir Bucal., 21*(2), e236-40.

32. Ristow, O., Gerngroß, C., Schwaiger, M., Hohlweg-Majert B, Kehl V, Jansen, H., *et al*. (2014). Effect of antiresorptive drugs on bony turnover in the jaw: Denosumab compared with bisphosphonates. *Br J Oral Maxillofac Surg., 52*(4), 308-313.

33. Troeltzsch, M., Woodlock, T., Kriegelstein, S., Steiner, T., Messlinger, K. & Troeltzsch, M. (2012). Physi-ology and pharmacology of nonbisphosphonate drugs implicated in osteonecrosis of the jaw. *J Can Dent Assoc (Tor)., 78*(1).

34. Ramírez, L., López-Pintor, R. M., Casañas, E., Arriba L de & Hernández, G. (2015). New non-bisphosphonate drugs that produce osteonecrosis of the jaws. *Oral Health Prev Dent., 13*(5), 385-393.

35. Huang, Y. F., Chang, C. T., Muo, C. H., Tsai, C. H., Shen, Y. F. & Wu, C. Z. (2015). Impact of bisphosphonate-related osteonecrosis of the jaw on osteoporotic patients after dental extraction: A population-based cohort study. *PLoS One., 10*(4), 1-13.

36. Peer, A. & Khamaisi, M. (2015). Diabetes as a risk factor for medication-related osteonecrosis of the jaw. *J Dent Res., 94*(2), 252-260.

34. Ramírez, L., López-Pintor, R. M., Casañas, E., Arriba L de & Hernández, G. (2015). New non-bisphosphonate drugs that produce osteonecrosis of the jaws. *Oral Health Prev Dent., 13*(5), 385-393.

35. Huang, Y. F., Chang, C. T., Muo, C. H., Tsai, C. H., Shen, Y. F. & Wu, C. Z. (2015). Impact of bisphosphonate-related osteonecrosis of the jaw on osteoporotic patients after dental extraction: A population-based cohort study. *PLoS One., 10*(4), 1-13.

36. Peer, A. & Khamaisi, M. (2015). Diabetes as a risk factor for medication-related osteonecrosis of the jaw. *J Dent Res., 94*(2), 252-260.

37. Heim, N., Warwas, F. B., Wilms, C. T., Reich, R. H. & Martini, M. (2017). Vitamin D (25-OHD) deficiency may increase the prevalence of medication-related osteonecrosis of the jaw. *J Craniomaxillofac Surg., 45*(12), 2068-2074.

38. Silva, B. C., Leslie, W. D., Resch, H., Lamy, O., Lesnyak, O., Binkley, N., *et al*. (2014). Trabecular bone score: A noninvasive analytical method based upon the DXA image. *J Bone Miner Res., 29*(3), 518-530.

39. Glüer, C. C. (2007). Quantitative Ultrasound-It is time to focus research efforts. *Bone, 40*(1), 9-13.

40. Raum, K., Grimal, Q., Varga, P., Barkmann, R., Glüer, C. C. & Laugier, P. (2014). Ultrasound to assess bone quality. *Curr Osteoporos Rep., 12*(2), 154-162.