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Mandibular Inferior Cortical Bone Thickness on Panoramic Radiographs in Patients using Bisphosphonates

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Abstract

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Objective—To detect dimensional changes in the mandibular cortical bone associated with bisphosphonate (BP) use and to correlate the measurements of the cortical bone with the cumulative dose of BP therapy.

Methods—Mandibular inferior cortical bone thickness (MICBT) was measured under the mental foramen from panoramic radiographs of subjects using BP with and without bisphosphonate related osteonecrosis of the jaws (BRONJ) and controls.

Results—The highest mean MICBT was observed in BRONJ subjects 6.81 ($\pm$ 1.35 mm), when compared to subjects using BP 5.44 ($\pm$ 1.09 mm) and controls 4.79 ($\pm$ 0.85 mm; $p < 0.01$). The mean MICBT of BRONJ subjects was significantly higher than that of subjects using BP without BRONJ. There was a correlation between MICBT and cumulative dose of zoledronate.

Conclusion—The MICBT on panoramic radiograph is a potentially useful tool for the detection of dimensional changes associated with BP therapy.

Keywords

bisphosphonate-related osteonecrosis of the jaw; bone mineralization; panoramic radiography

Introduction

Bisphosphonates have been shown to effectively reduce osteoclastic bone resorption by inactivating osteoclasts and are prescribed for a large number of diseases and conditions where bone resorption needs to be reduced or controlled. Oral bisphosphonates (BP) are generally prescribed for osteopenia/osteoporosis, while intravenous BPs are primarily utilized to reduce skeletally related events (SREs, fractures, bone pain, and hypercalcemia due to excessive bone resorption) associated with malignancies such as multiple myeloma (MM) and breast, prostate, lung, and renal cancers metastatic to bone.^{1–2} The use of BP has clearly improved the quality of life for osteoporosis and cancer patients. However, a well-recognized side effect of bisphosphonate therapy is bisphosphonate-related osteonecrosis of the jaws (BRONJ) in patients with both oral and intravenous BP. The risk for BRONJ has been estimated at 2–3% for intravenous and 0.02–0.4% for oral BP.^{3,4} The incidence of ONJ in patients prescribed oral BPs for the treatment of osteoporosis ranges from less than 0.001% to 0.15% person-years of exposure. In patients with cancer, the incidence of ONJ is approximately 1% to 2% and appears to be related to dose and duration of BP exposure.⁴ The jaws are the most vulnerable part of the body in terms of interventions, surgically and bacteriologically, and this may have a significant effect on BRONJ. Tooth extraction is known to be one of the most common risk factors for BRONJ in patients treated with bisphosphonates, and the crude risk ratio for BRONJ after tooth extraction for patients with BP administration compared to those without was estimated to be 122.6.⁵ Finding early radiographic signs of BP-related changes in bone may predict the development of BRONJ. Thus, in those cases which patients under BP treatment need to have tooth extractions or invasive dental procedures, the BP related bone changes detected on radiographs might guide the planning for dental treatment.

Patients treated with oral BP therapy appear to have a considerably lower risk for BRONJ than patients treated with intravenous BP.^{6–7} It has been estimated that less than 1% of

ingested oral dose is absorbed and available for incorporation into bone while upwards of 60% of infused BP doses are incorporated into bone. Besides the influence of route of administration, the potency and the duration of use of the BP are associated with increasing the risk for BRONJ.⁸ The average time of treatment with BP until the occurrence of first symptoms of BRONJ has been reported to be 12 months for intravenous and over three years for oral administration.⁸⁻⁹ Besides the effects on bone, BP may play a role in the vascularity of the oral mucosa of patients with BRONJ, with consequent failure of healing of soft tissue lesions.¹⁰

The diagnosis of BRONJ is based on recognition of clinical changes. In order to diagnose BRONJ a patient must present exposed bone in the oral cavity that has been present for more than eight weeks and with a history of treatment with BP, without a previous history of radiation therapy to the jaws.¹¹ There is currently no laboratory or imaging criteria that are considered diagnostic of this condition.

Management strategies for BRONJ have been documented in the literature and remain primarily empiric. Routine non-invasive management with both topical and systemic antibiotics is most commonly used. Initially, between 2003 and 2005, surgical approaches that utilized debridement with sequesterectomy/curettage with primary closure were found to not only be unsuccessful for resolving BRONJ, but actually seemed to frequently worsen the condition.^{6, 8} More recently, extensive surgical resection of involved bone utilizing block resection (osteotomy) is showing promising results.¹²⁻¹⁵ However, it is still not clear when a surgical approach to treatment should be used as the surgery will often require extensive bone removal and potential loss of teeth adjacent to the lesion site. Numerous case reports and small treatment series utilizing treatments such as hyperbaric oxygen therapy, parathyroid hormone, platelet rich plasma, and low level lasers, for example, have been reported, but lack the necessary level of scientific evidence to support their use.^{8, 16-20} It is important to note that in the United States, the use of parathyroid hormone (i.e., teriparatide) is banned from use in patients with cancer because of concerns that it could promote cancer growth.²¹ Conclusive evidence is still lacking and no satisfactory evidence-based therapy is available to successfully manage BRONJ.

Denosumab, an anti RANKL monoclonal antibody, has been introduced for the treatment of osteoporosis and cancer metastatic to bone; it interferes with the formation of osteoclasts and thus has similar benefits as seen with bisphosphonates. At the same time, denosumab-related osteonecrosis of the jaw (DRONJ) has been described.²² Clinically DRONJ appears to be very similar to BRONJ. It is becoming increasingly critical that we understand the basic mechanisms of osteonecrosis of the jaws. One of us (MMS) has anecdotally observed osseous changes in jaws for patients treated with denosumab that similar to those noted for patients treated with bisphosphonates, but clearly future carefully designed studies should be carried out to determine the radiographic changes occurring in the jaw associated with denosumab administration and ultimately their relationship to DRONJ.

Imaging of BRONJ cases has shown a wide variety of features.²³⁻²⁷ Bone changes can also be detected in patients taking bisphosphonates.²⁸⁻²⁹ Currently, radiographic changes are only supportive evidence for the risk and the clinical diagnosis of BRONJ. Quantitative

methods for the evaluation of radiographic images to identify osseous changes in BP patients could clearly be of benefit to avoid observer subjectivity in interpretation of radiographic images. Measurable bone data have been reported in patients taking BP through many techniques including bone density, architecture, and cortical bone thickness.^{30–33}

The assessment of cortical bone thickness has been used for different clinical situations, mainly for determining the risk of bone fractures, as an alternative test for osteoporosis diagnosis, or to monitor responses to bone treatments.^{34–37} The cortical thickness has been measured in many different bones (tibia, radius, femur, spine, hips, vertebrae, iliac and metacarpus) through radiographs, histomorphometry, densitometry, dual-energy x-ray absorptimetry, x-ray radiogrammetry, or in more sophisticated exams like peripheral quantitative computed tomography (pQCT).^{30–31, 36–39} In the mandible, the cortical thickness measured from panoramic radiographs has been associated with the bone mineral density.^{35, 40–45} In a previous study with cone beam computed tomography (CBCT) mandibular images, we reported that the cortical bone volume, area and height were significantly higher in cases of BRONJ than in controls.⁴⁶ These mandibular cortical bone measurements represent a potentially useful tool in the detection of bone alterations associated with bisphosphonate use and in patients specifically with BRONJ.⁴⁶

The aim of the present study was to determine if there were dimensional changes in the mandibular cortical bone associated with BP use, by comparing the mandibular inferior cortical bone thickness (MICBT) of subjects using BP to controls, on panoramic radiographs of the jaws. A second aim was to correlate the measurements of the cortical bone with the type, dose and duration of BP therapy within the groups of subjects using BP with and without BRONJ.

Material and methods

Patient population

Patients from the two centers: the Oral Radiology Division, University of Washington (UW) School of Dentistry, Department of Oral Medicine and the Oral Medicine Service at the Seattle Cancer Care Alliance (SCCA) were enrolled in the study. Subjects were recruited from one of the three groups: subjects using BP not presenting BRONJ, subjects with BRONJ, and controls not using BP. Subjects with and without a history of BP treatment were eligible for participation if they had available panoramic radiographic images. Subjects with BRONJ were recruited to participate in the study through mailed requests to previously diagnosed subjects registered in one of the two clinics or as previously undiagnosed patients presented to one of the clinics during the period from September 2011 to February 2012. Subjects treated with BP without a history of BRONJ were recruited as they presented to either of the two centers during the same time period and were diagnosed as having BRONJ. Controls were recruited by direct contact by study personnel as they walked in for routine radiographic exam at the UW Oral Radiology service, during the same period of time, if their age ranged from 40 to 80 years old (age range of subjects using BP), and they had no history of BP treatment. Controls were excluded if there was a history of metastatic cancer; thyroid surgery; radioactive iodine treatment; or any bone diseases/disorders. Subjects from

any group were excluded if the region of interest was not present on the panoramic radiograph.

The study was approved by the Fred Hutchinson Cancer Research Center Investigational Review Office, protocol number 884 and 2457. All individuals signed an informed consent form.

Data collection

All subjects were asked to complete a questionnaire on health related issues. Bisphosphonate history, including the type, dose, and duration of BP treatment was retrieved from questionnaires and confirmed through review of the subject's medical records.

Panoramic radiographs were retrieved for analysis, digital or film depending on when and where they were taken. Most recent digital panoramic radiographs were obtained at the Oral Radiology clinic at UW, by standardized methodology and taken with Orthophos XG3 (Sirona, New York, USA). Most of the subjects using BP had non-digital panoramic radiographs, which were performed with Sirona Orthophos (Sirona Dental Inc., Charlotte, USA) equipment, in the Oral Medicine Service at the SCCA and subsequently scanned on Epson Perfection V700 Photo (Epson America Inc., Long Beach, USA) scanner, at resolution 300 pixels/inch. The vertical magnifications from both devices were comparable. All the images of subjects in the study were anonymized for evaluation. In order to verify the reliability of the evaluation, 44 images (29 subjects using BP and 15 controls) were analyzed by two investigators (initials S.R.T and S.P.D.).

For the cortical bone analysis, the mandibular inferior cortical bone thickness (MICBT) was measured below the mental foramen, on the right side of the mandible, in the available panoramic radiographs. The measurement of the MICBT was based on a previously described technique,^{40-41, 47-48} with a line constructed tangential to the inferior border of mandible and another line perpendicular to this tangent intersecting the inferior border of mandible and the mental foramen, along which the thickness of mandibular cortex was measured. (Figures 1a and 1b)

The cortical bone measurements obtained in the panoramic radiographs of the three groups were compared. Among the subjects using BP with and without BRONJ, the MICBT was also compared regarding the dose and duration of BP treatment.

Statistical analysis

The software SPSS 19.0© (SPSS Inc., IBM Company Headquarters, Chicago, Illinois, US) was used for storing and analyzing data. Chi-squared or Fisher exact tests were used to analyze group differences related to categorical variables between the three groups. ANOVA was used to analyze quantitative data between groups. The inter-rater reliability was assessed by the intra-class correlation coefficient. The significance level value was set at 0.05. Pearson bivariate correlations were used to assess the associations between MICBT and the periods of medication usage and the cumulative dosages.

Results

There were 84 subjects enrolled in the study: 10 subjects presenting BRONJ and 27 subjects who had been treated with BPs without BRONJ and 47 controls. Nine of the 10 subjects with BRONJ were recruited by mail while one was a walk-in patient. The clinical characteristics of subjects enrolled in the study are listed in Table 1.

When bone medications were analyzed, there was no statistically difference in the use of calcium and vitamin D for all groups. There were no significant differences in the period of usage (data not shown) or the cumulative doses of calcium when the groups of patients with and without BRONJ were compared among themselves or to controls. (Table 2) Moreover, there were no significant differences in the period of usage (data not shown) or the cumulative doses of vitamin D between subjects using BP and controls. However, subjects with BRONJ were taking smaller doses of vitamin D than subjects using BP without BRONJ ($p=0.01$), and presented lower cumulative doses ($p=0.02$) and smaller period of taking the medication ($p=0.01$) than control subjects. (Table 2)

The reasons for taking BP were as part of bone treatment for multiple myeloma (64.9%), malignancies (18.9%), and osteoporosis (16.2%). Table 2 shows the type of bone medication taken by subjects in the study and the mean cumulative doses. Zolendronate alone was the BP used by 85.2% of the subjects using BP without BRONJ and 90% of those with BRONJ. From the BRONJ subjects, 8 were exclusively using zolendronate, one had been treated with ibandronate and zolendronate, and one had been treated only with alendronate.

When the 32 patients that used zolendronate were analyzed, the mean period of time in which subjects presenting BRONJ were using the medication was 26.10 months (± 25.17); and subjects using BP without BRONJ were using BP for mean 9.70 (± 12.09) months ($p=0.01$). The mean cumulative dose of zolendronate of subjects with BRONJ was 104.40 (± 100.69) and 32.85 (± 38.45) for subjects that did not develop BRONJ ($p=0.003$). (Table 2)

The mandibular inferior cortical bone thicknesses (MICBT) of the 84 patients in the study taken from panoramic radiographs are represented in Figure 2. The mean MICBT of subjects with BRONJ was 6.81 (± 1.35) mm, of subjects using BP without BRONJ was 5.44 (± 1.09) mm and the MICBT of controls 4.79 (± 0.85) mm. There was a significant difference in the MICBT of the subjects from the three groups ($p<0.001$). There were higher means MICBT for the groups of patients with BRONJ and without BRONJ when they were separately compared to controls ($p<0.0001$ and $p=0.006$, respectively). When the MICBT of subjects with BRONJ and without BRONJ were compared, there were also significant differences between them ($p=0.003$).

The intra-class correlation coefficient for the MICBT between two examiners was 0.82 (confidence interval 95%: 0.59–0.93)

There were no significant differences when the mean MICBT of subjects using zolendronate (5.89 ± 1.23) was compared to subjects using other types of BP (5.30 ± 1.78) ($p=0.37$). The correlation of the MICBT with the period of BP usage and the cumulative doses were evaluated only in patients using zolendronate, as the great majority of the patients in the

study groups were using this type of BP. The MICBT of the 32 subjects using zoledronate according to the cumulative doses was shown in Figure 3. A low but statistically significant correlation ($r=0.37$, $p=0.02$) was found between MICBT and the cumulative dose of zoledronate. The correlation between MICBT and the period of zoledronate usage was also small and not quite statistically significant ($r=0.31$, $p=0.06$). No correlation was found between the MICBT and the cumulative dose or the period of usage of the medication for calcium and vitamin D.

Discussion

In the present study dimensional differences were detected in the mandibular cortical bone thickness of patients using BP with and without BRONJ and controls, as measured in panoramic radiographs. The mean MICBT of the 37 subjects using BP was significantly higher than that of the controls. Moreover, significant differences were found when the mean MICBT of BRONJ subjects was compared to subjects using BP without BRONJ. We had previously reported that the mandibular inferior cortical volume, area, and height were higher in patients with BRONJ than in controls.⁴⁶ The present study shows that dimensional changes may be detected even in patients using BP who do not present BRONJ. The significant differences between subjects with BRONJ and subjects using BP without BRONJ, suggest the use of MICBT as a tool to detect BP dimensional changes in the cortical bone. Futures prospective studies are needed to verify if this tool may predict the risk of developing BRONJ.

The dimensional changes in the MICBT associated with BP were reported previously in a study with cone beam computer tomography (CBCT) images.⁴⁶ In the present study we measured these differences in panoramic radiographic images, which are easily available, utilize lower radiation doses, and cost less when compared to CBCT. Moreover, the detection of the BP related dimensional changes by MICBT is a simple tool, which may be easily used by any dentist, in most image software.

The correlation between cortical bone thickness and the dose, and duration of BP therapy were also verified in the present study and there was some correlation between the MICBT and the cumulative dose of zoledronate. This data corroborates the statement that there is higher risk for developing BRONJ in subjects with higher doses and extended usage of BP.

There are a number of factors that are related to the degree to which different bisphosphonates can alter normal bone metabolism and these have been well documented.⁴⁸ Bisphosphonates can vary in their ability to a) adhere to hydroxyapatite in bone, b) disrupt osteoclastic activity due to interference with the malevolent farnesyl diphosphate synthase (FFP) activity, and c) influence on osteoblastic (bone forming) activity.⁴⁹ Since it has been estimated that the duration of retention of BPs in bone can approach 10–15 years, the influence of the previously administered drug will likely go on much longer after the drug administration is discontinued.^{50–51} All of these factors need to be considered when considering the findings of this study. For instance, BPs administered intravenously will show much higher amounts of drug adhering to bone after each dose when compared to oral dosing (upwards of 60% for intravenous administration versus less than 1% for oral

dosing).⁵² Furthermore, the more frequent that a BP is administered, the amount of bisphosphonate that is accumulated in bone will be higher (e.g., intravenous once every 28 days versus one every 12 months).⁵³ Animal studies support that zoledronate more readily adheres to calcium in bone and is especially prone to be incorporated into newly formed bone (osteoid) and thus comparatively can apparently more effectively inhibit bone resorption when compared to other bisphosphonates.⁵⁴ Thus when considering the potential effects of a BP on bone metabolism, it is important to consider which drug administered at what dose and frequency, and over what period of time. Future research will need to determine if and how the radiographically induced changes seen in dental radiographs change over time after bisphosphonate therapy is discontinued. If the accumulation of BP-induced radiographic image changes indicated a risk for BRONJ, then disappearance of these changes may be an indicator of decreasing BRONJ risk over time.

The cortical bone increases in thickness with BP therapy because of the action of the drug which has been shown to suppress the endocortical and intracortical remodeling.^{55–58} The mineralized skeleton is defined externally by its periosteal surface and internally by the endosteal surface (endocortical, intracortical, and trabecular components).⁵⁹ The endocortical component is the compact bone on the inside surface of the cortex, facing the marrow compartment, and the intracortical component is the bone within the cortex.⁵⁹ Experimental studies have shown that BPs normalize endocortical osteoclast number, cortical thickness and bone strength in mice with a conditional Cx43 gene deletion in osteoblasts and osteocytes (cKO).⁶⁰ Clinical studies have also shown improved cortical bone thickness after BP therapy.^{31, 38–39}

It is known also that the drug distribution varies in different bones due to a number of different factors.^{61–63} Some studies in humans and large animals have suggested that remodeling is considerably higher in the jaws, specifically within the intracortical component, when compared with other skeletal sites.⁶⁴ Since BPs are especially prone to be incorporated into osteoid, this could lead to a higher concentration of BP for these areas of the jaws. The mechanism by which suppression of remodeling results in necrotic bone is still under investigation.

The period of treatment with BP is considered a risk factor for BRONJ.^{6–7} The minimum time of BP treatment before developing BRONJ in patients of the present study using intravenous zoledronate was six months. The only patient with BRONJ using oral BP developed the condition within 24 months of BP usage. For both routes, the times for BRONJ onset were smaller than those reported in the literature but well within the range of times reported for BRONJ occurrence relative to drug administration.^{8–9} Zoledronate is one of the most potent BP and had been used by the majority of the subjects in the present study. It was in fact observed that those subjects using zoledronate that presented BRONJ had been taking the medication for longer periods and had higher cumulative doses of the medication than those without BRONJ, which corroborates reports that the potency and the period of BP usage are associated with a higher risk for BRONJ.⁸ It is worth noting that results from phase III clinical trials for denosumab have indicated that the risk for BRONJ is similar for both drugs (2.0%, denosumab; 1.4%, zoledronic acid; $p = 0.39$).⁶⁵

Calcium supplementation is recommended generally for most of the patients taking bisphosphonates to prevent hypocalcemia.⁶⁶ Vitamin D is also important for bone health and supplementation is recommended for patients with either osteoporosis or on bisphosphonates.⁶⁶ Calcium and vitamin D levels should be checked in patients routinely and doses adjusted as needed. While the present study suggest a potential protective effect of vitamin D against the development of BRONJ, it has to be noted that actual vitamin D levels for subjects were not available for analysis and vitamin D administration data was by patient report. More studies are needed in order to confirm this association.

There are several factors to be considered when comparing digital images with scanned prints radiographs, but the magnification on both devices is around 35%. Small variations in focus to object and object to detector distance do not affect the vertical magnification significantly which in contrast could be the case for the horizontal magnification. Thus the inclusion of both digital and scanned plane films in our data set seems to be justified.

There are several limitations in this study, because there were only few patients using BPs other than zoledronate, definitive conclusions regarding the influence of different BPs on changes noted on radiographic image analysis relative to cortical bone thickness cannot be made. Also, cross-sectional studies have their own disadvantages compared with prospective studies, but they constitute a useful starting point to test a hypothesis in rare conditions or conditions with a long latency period between exposure and disease manifestation, like BRONJ.

Future studies should concentrate on measuring MICBT in homogenous populations, with cohorts of patients with the same underlying disease, using the same type and route of BP. Moreover, prospective studies should measure individual changes in MICBT, which may be a more reliable tool to detect BP associated changes in the mandibular cortical bone than comparisons of groups. Furthermore, patients may have multiple factors affecting bone density and thus make bone different and thus cause differences in radiographic changes. Other studies with larger sample size should be designed in order to adjust for other varieties.

Conclusion

The mean MICBT of BRONJ subjects was significantly higher than that of subjects using BP without BRONJ, and the MICBT of subjects using BP without BRONJ was higher than the MICBT of controls. Among subjects using zoledronate, there was a correlation between the MICBT and the cumulative dose.

The measurement of the mandibular cortical thickness on panoramic radiograph image is a promising tool for the detection of bone alterations associated with BP therapy.

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References

1. Gutta R, Louis P. Bisphosphonates and osteonecrosis of the jaws: Science and rationale. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007; 104:186–93. [PubMed: 17448709]
2. Petrut B, Trinkaus M, Simmons C, Clemons M. A primer of bone metastases management in breast cancer patients. *Curr Oncol.* 2008; 15:S50–S7. [PubMed: 18231649]
3. Tennis P, Rothman KJ, Bohn RL, Tan H, Zavras A, Laskarides C, Calingaert B, Anthony MS. Incidence of osteonecrosis of the jaw among users of bisphosphonates with selected cancers or osteoporosis. *Pharmacoepidemiol Drug Saf.* 2012; 21:810–7. [PubMed: 22711458]
4. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O’Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watts NB, Brandi ML, Peters E, Guise T, Eastell R, Cheung AM, Morin SN, Masri B, Cooper C, Morgan SL, Obermayer-Pietsch B, Langdahl BL, Al Dabagh R, Davison KS, Kendler DL, Sandor GK, Josse RG, Bhandari M, El Rabbany M, Pierroz DD, Sulimani R, Saunders DP, Brown JP, Compston J. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res.* 2015; 30:3–23. [PubMed: 25414052]
5. Yamazaki T, Yamori M, Ishizaki T, Asai K, Goto K, Takahashi K, Nakayama T, Bessho K. Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: a cohort study. *Int J Oral Maxillofac Surg.* 2012; 41:1397–403. [PubMed: 22840716]
6. Badros A, Weikel D, Salama A, Goloubeva O, Schneider A, Rapoport A, Fenton R, Gahres N, Sausville E, Ord R, Meiller T. Osteonecrosis of the jaw in multiple myeloma patients: Clinical features and risk factors. *J Clin Oncol.* 2006; 24:945–52. [PubMed: 16484704]
7. Miglioratti C, Schubert MM, Peterson DE, Seneda M. Associated osteonecrosis of mandibular and maxillary bone. An emerging oral complication of supportive cancer therapy. *Cancer.* 2005; 104:83–93. [PubMed: 15929121]
8. Dannemann C, Grätz K, Zwahlen R. Clinical experiences with bisphosphonate induced osteochemonecrosis of the jaws. *Swiss Med Wkly.* 2006; 136:504–9. [PubMed: 16947089]
9. Mavrokokki T, Cheng A, Stein B, Goss A. Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. *J Oral Maxillofac Surg.* 2007; 65:415–23. [PubMed: 17307586]
10. Mozzati M, Martinasso G, Maggiora M, Scoletta M, Zambelli M, Carossa S, Oraldi M, Muzio G, Canuto RA. Oral mucosa produces cytokines and factors influencing osteoclast activity and endothelial cell proliferation, in patients with osteonecrosis of jaw after treatment with zoledronic acid. *Clin Oral Investig.* 2013; 17:1259.
11. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo S, Shane E. Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the american society for bone and mineral research. *J Bone Miner Res.* 2007; 22:1479–91. [PubMed: 17663640]
12. Kademani D, Koka S, Lacy MQ, Rajkumar SV. Primary surgical therapy for osteonecrosis of the jaw secondary to bisphosphonate therapy. *Mayo Clin Proc.* 2006; 81:1100–3. [PubMed: 16901034]
13. Wutzl A, Biedermann E, Wanschitz F, Seemann R, Klug C, Baumann A, Watzinger F, Schicho K, Ewers R, Millesi G. Treatment results of bisphosphonate-related osteonecrosis of the jaws. *Head Neck.* 2008; 30:1224–30. [PubMed: 18642292]
14. Abu-Id MH, Warnke PH, Gottschalk J, Springer I, Wiltfang J, Acil Y, Russo PA, Kreusch T. “Bisphossy jaws” - high and low risk factors for bisphosphonate-induced osteonecrosis of the jaw. *J Craniomaxillofac Surg.* 2008; 36:95–103. [PubMed: 18234504]
15. Stockmann P, Vairaktaris E, Wehrhan F, Seiss M, Schwarz S, Spriewald B, Neukam FW, Nkenke E. Osteotomy and primary wound closure in bisphosphonate-associated osteonecrosis of the jaw: a prospective clinical study with 12 months follow-up. *Support Care Cancer.* 2010; 18:449–60. [PubMed: 19609572]

16. Adornato MC, Morcos I, Rozanski J. The treatment of bisphosphonate-associated osteonecrosis of the jaws with bone resection and autologous platelet-derived growth factors. *J Am Dent Assoc.* 2007; 138:971–7. [PubMed: 17606496]
17. Agrillo A, Ungari C, Filiaci F, Priore P, Iannetti G. Ozone therapy in the treatment of avascular bisphosphonate-related jaw osteonecrosis. *J Craniofac Surg.* 2007; 18:1071–5. [PubMed: 17912085]
18. Harper RP, Fung E. Resolution of bisphosphonate-associated osteonecrosis of the mandible: possible application for intermittent low-dose parathyroid hormone [rhPTH(1-34)]. *J Oral Maxillofac Surg.* 2007; 65:573–80. [PubMed: 17307613]
19. Rugani P, Acham S, Truschnegg A, Obermayer-Pietsch B, Jakse N. Bisphosphonate-associated osteonecrosis of the jaws: surgical treatment with ErCrYSGG-laser. Case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2010; 110:e1–e6. [PubMed: 21112522]
20. Vescovi P, Manfredi M, Merigo E, Meleti M, Fornaini C, Rocca JP, Nammour S. Surgical approach with Er:YAG laser on osteonecrosis of the jaws (ONJ) in patients under bisphosphonate therapy (BPT). *Lasers Med Sci.* 2010; 25:101–13. [PubMed: 19543768]
21. Miller CS. Teriparatide's potential role in jaw bone related diseases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2011; 112:703–5. [PubMed: 22099856]
22. Ristow O, Gerngross C, Schwaiger M, Hohlweg-Majert B, Kehl V, Jansen H, Hahnefeld L, Koerdt S, Otto S, Pautke C. Effect of antiresorptive drugs on bony turnover in the jaw: denosumab compared with bisphosphonates. *Br J Oral Maxillofac Surg.* 2014; 52:308–13. [PubMed: 24582013]
23. Arce K, Assael LA, Weissman JL, Markiewicz MR. Imaging findings in bisphosphonate-related osteonecrosis of jaws. *J Oral Maxillofac Surg.* 2009; 67:75–84. [PubMed: 19371818]
24. Bisdas S, Chambron Pinho N, Smolarz A, Sader R, Vogl TJ, Mack MG. Biposphonate-induced osteonecrosis of the jaws: CT and MRI spectrum of findings in 32 patients. *Clin Radiol.* 2008; 63:71–7. [PubMed: 18068792]
25. Phal PM, Myall RW, Assael LA, Weissman JL. Imaging findings of bisphosphonate-associated osteonecrosis of the jaws. *AJNR Am J Neuroradiol.* 2007; 28:1139–45. [PubMed: 17569974]
26. Chiandussi S, Biasotto M, Dore F, Cavalli F, Cova MA, Di Lenarda R. Clinical and diagnostic imaging of bisphosphonate-associated osteonecrosis of the jaws. *Dentomaxillofac Radiol.* 2006; 35:236–43. [PubMed: 16798918]
27. Fleisher KE, Welch G, Kottal S, Craig RG, Saxena D, Glickman RS. Predicting risk for bisphosphonate-related osteonecrosis of the jaws: CTX versus radiographic markers. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2010; 110:509–16. [PubMed: 20674404]
28. Zaman MU, Nakamoto T, Tanimoto K. A retrospective study of digital subtraction technique to detect sclerotic changes in alveolar bone on intraoral radiographs of bisphosphonate-treated patients. *Dentomaxillofac Radiol.* 2013; 42:20130242.
29. Olutayo J, Agbaje JO, Jacobs R, Verhaeghe V, Velde FV, Vinckier F. Bisphosphonate-related osteonecrosis of the jaw bone: Radiological pattern and the potential role of CBCT in early diagnosis. *J Oral Maxillofac Res.* 2010; 1:e3. [PubMed: 24421968]
30. Bravenboer N, Papapoulos SE, Holzmann P, Hamdy NA, Netelenbos JC, Lips P. Bone histomorphometric evaluation of pamidronate treatment in clinically manifest osteoporosis. *Osteoporos Int.* 1999; 9:489–93. [PubMed: 10624455]
31. Hyldstrup L, Jorgensen JT, Sorensen TK, Baeksgaard L. Response of cortical bone to antiresorptive treatment. *Calcif Tissue Int.* 2001; 68:135–9. [PubMed: 11351495]
32. Torres SR, Chen CSK, Leroux BG, Lee PP, Hollender LG, Schubert MM. Fractal dimension evaluation of cone beam computed tomography in patients with bisphosphonate-associated osteonecrosis. *Dentomaxillofac Radiol.* 2011; 40:501–5. [PubMed: 22065799]
33. Greenspan SL, Perera S, Recker R, Wagner JM, Greeley P, Gomberg BR, Seaman P, Kleerekoper M. Changes in trabecular microarchitecture in postmenopausal women on bisphosphonate therapy. *Bone.* 2010; 46:1006–10. [PubMed: 20051275]
34. Briot K, Benhamou CL, Roux C. Hip cortical thickness assessment in postmenopausal women with osteoporosis and strontium ranelate effect on hip geometry. *J Clin Densitom.* 2012; 15:176–85. [PubMed: 22321661]

35. Passos JS, Gomes Filho IS, Sarmiento VA, Sampaio DS, Goncalves FP, Coelho JM, Cruz SS, Trindade SC, Cerqueira EM. Women with low bone mineral density and dental panoramic radiography. *Menopause*. 2012; 19:704–9. [PubMed: 22334058]
36. Hyldstrup L, Conway GS, Racz K, Keller A, Chanson P, Zacharin M, Lysgaard AL, Andreasen AH, Kappelgaard AM. Growth hormone effects on cortical bone dimensions in young adults with childhood-onset growth hormone deficiency. *Osteoporos Int*. 2012; 23:2219–26. [PubMed: 22124576]
37. Koeppen VA, Schilcher J, Aspenberg P. Atypical fractures do not have a thicker cortex. *Osteoporos Int*. 2012; 23:2893–6. [PubMed: 23076682]
38. Bock O, Borst H, Beller G, Armbrrecht G, Degner C, Martus P, Roth HJ, Felsenberg D. Impact of oral ibandronate 150 mg once monthly on bone structure and density in post-menopausal osteoporosis or osteopenia derived from in vivo muCT. *Bone*. 2012; 50:317–24. [PubMed: 22067902]
39. Chapurlat RD, Laroche M, Thomas T, Rouanet S, Delmas PD, de Vernejoul MC. Effect of oral monthly ibandronate on bone microarchitecture in women with osteopenia-a randomized placebo-controlled trial. *Osteoporos Int*. 2013; 24:311–20. [PubMed: 22402673]
40. Devlin H, Horner K. Mandibular radiomorphometric indices in the diagnosis of reduced skeletal bone mineral density. *Osteoporos Int*. 2002; 13:373–8. [PubMed: 12086347]
41. Taguchi A, Suei Y, Sanada M, Ohtsuka M, Nakamoto T, Sumida H, Ohama K, Tanimoto K. Validation of dental panoramic radiography measures for identifying postmenopausal women with spinal osteoporosis. *AJR Am J Roentgenol*. 2004; 183:1755–60. [PubMed: 15547223]
42. Taguchi A, Ohtsuka M, Nakamoto T, Naito K, Tsuda M, Kudo Y, Motoyama E, Suei Y, Tanimoto K. Identification of post-menopausal women at risk of osteoporosis by trained general dental practitioners using panoramic radiographs. *Dentomaxillofac Radiol*. 2007; 36:149–54. [PubMed: 17463099]
43. Taguchi A, Ohtsuka M, Tsuda M, Nakamoto T, Kodama I, Inagaki K, Noguchi T, Kudo Y, Suei Y, Tanimoto K. Risk of vertebral osteoporosis in post-menopausal women with alterations of the mandible. *Dentomaxillofac Radiol*. 2007; 36:143–8. [PubMed: 17463098]
44. Lopez-Lopez J, Alvarez-Lopez JM, Jane-Salas E, Estrugo-Devesa A, Ayuso-Montero R, Velasco-Ortega E, Segura-Egea JJ. Computer-aided system for morphometric mandibular index computation. (Using dental panoramic radiographs). *Med Oral Patol Oral Cir Bucal*. 2012; 17:e624–32. [PubMed: 22322489]
45. Neves FS, Oliveira LS, Torres MG, Toralles MB, da Silva MC, Campos MI, Campos PS, Crusoe-Rebello I. Evaluation of panoramic radiomorphometric indices related to low bone density in sickle cell disease. *Osteoporos Int*. 2012; 23:2037–42. [PubMed: 22006042]
46. Torres SR, Chen CSK, Leroux BG, Lee PP, Hollender LG, Santos ECA, Drew PS, Hung KC, Schubert MM. Mandibular Cortical Bone Evaluation on Cone Beam Computed Tomography Images of Patients with Bisphosphonate Associated Osteonecrosis of the Jaws. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2012; 113:695–703.
47. Bollen AM, Taguchi A, Hujoel PP, Hollender LG. Case-control study on self-reported osteoporotic fractures and mandibular cortical bone. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2000; 90:518–24. [PubMed: 11027391]
48. Wical KE, Swoope CC. Studies of residual ridge resorption. I. Use of panoramic radiographs for evaluation and classification of mandibular resorption. *J Prosthet Dent*. 1974; 32:7–12. [PubMed: 4525507]
49. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc*. 2008; 83:1032–45. [PubMed: 18775204]
50. Ott SM. Debating the duration of bisphosphonate therapy. *JAAPA*. 2013; 26:64–5. [PubMed: 24049945]
51. Ott SM. What is the optimal duration of bisphosphonate therapy? *Cleve Clin J Med*. 2011; 78:619–30. [PubMed: 21885695]
52. Bock O, Felsenberg D. Bisphosphonates in the management of postmenopausal osteoporosis--optimizing efficacy in clinical practice. *Clin Interv Aging*. 2008; 3:279–97. [PubMed: 18686751]

53. Sunyecz J. Optimizing dosing frequencies for bisphosphonates in the management of postmenopausal osteoporosis: patient considerations. *Clin Interv Aging*. 2008; 3:611–27. [PubMed: 19281054]
54. Zhu ED, Louis L, Brooks DJ, Boussein ML, Demay MB. Effect of bisphosphonates on the rapidly growing male murine skeleton. *Endocrinology*. 2014; 155:1188–96. [PubMed: 24422540]
55. Allen MR, Burr DB. Bisphosphonate effects on bone turnover, microdamage, and mechanical properties: What we think we know and what we know that we don't know. *Bone*. 2011; 49:56–65. [PubMed: 20955825]
56. Feher A, Koivunemi A, Koivunemi M, Fuchs RK, Burr DB, Phipps RJ, Reinwald S, Allen MR. Bisphosphonates do not inhibit periosteal bone formation in estrogen deficient animals and allow enhanced bone modeling in response to mechanical loading. *Bone*. 2010; 46:203–7. [PubMed: 19857619]
57. Kubek DJ, Burr DB, Allen MR. Ovariectomy stimulates and bisphosphonates inhibit intracortical remodeling in the mouse mandible. *Orthod Craniofac Res*. 2010; 13:214–22. [PubMed: 21040464]
58. Recker RR, Delmas PD, Halse J, Reid IR, Boonen S, Garcia-Hernandez PA, Supronik J, Lewiecki EM, Ochoa L, Miller P, Hu H, Mesenbrink P, Hartl F, Gasser J, Eriksen EF. Effects of intravenous zoledronic acid once yearly on bone remodeling and bone structure. *J Bone Miner Res*. 2008; 23:6–16. [PubMed: 17892374]
59. Seeman E. Pathogenesis of bone fragility in women and men. *Lancet*. 2002; 359:1841–50. [PubMed: 12044392]
60. Watkins MP, Norris JY, Grimston SK, Zhang X, Phipps RJ, Ebetino FH, Civitelli R. Bisphosphonates improve trabecular bone mass and normalize cortical thickness in ovariectomized, osteoblast connexin43 deficient mice. *Bone*. 2012; 51:787–94. [PubMed: 22750450]
61. Kozloff KM, Volakis LI, Marini JC, Caird MS. Near-infrared fluorescent probe traces bisphosphonate delivery and retention in vivo. *J Bone Miner Res*. 2010; 25:1748–58. [PubMed: 20200982]
62. Turek J, Ebetino FH, Lundy MW, Sun S, Kashemirov BA, McKenna CE, Gallant MA, Plotkin LI, Bellido T, Duan X, Triffitt JT, Russell RG, Burr DB, Allen MR. Bisphosphonate binding affinity affects drug distribution in both intracortical and trabecular bone of rabbits. *Calcif Tissue Int*. 2012; 90:202–10. [PubMed: 22249525]
63. Roelofs AJ, Stewart CA, Sun S, Blazewska KM, Kashemirov BA, McKenna CE, Russell RG, Rogers MJ, Lundy MW, Ebetino FH, Coxon FP. Influence of bone affinity on the skeletal distribution of fluorescently labeled bisphosphonates in vivo. *J Bone Miner Res*. 2012; 27:835–47. [PubMed: 22228189]
64. Allen MR, Burr DB. The pathogenesis of bisphosphonate-related osteonecrosis of the jaw: so many hypotheses, so few data. *J Oral Maxillofac Surg*. 2009; 67:61–70. [PubMed: 19371816]
65. Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, Lichinitser M, Fujiwara Y, Yardley DA, Viniegra M, Fan M, Jiang Q, Dansey R, Jun S, Braun A. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol*. 2010; 28:5132–9. [PubMed: 21060033]
66. Paggiosi MA, Peel N, McCloskey E, Walsh JS, Eastell R. Comparison of the effects of three oral bisphosphonate therapies on the peripheral skeleton in postmenopausal osteoporosis: the TRIO study. *Osteoporos Int*. 2014; 25:2729–41. [PubMed: 25074351]

Statement of Clinical Relevance

The mandibular inferior cortical bone thickness (MICBT) of patients using bisphosphonate has been detected in panoramic radiographs, and represents a potentially useful tool for the detection of dimensional changes associated with BP therapy.

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Figure 1.

a) Mandibular inferior cortical bone thickness as measured from panoramic radiograph. **b)** Detail from the same panoramic radiograph with demonstration of the technique for measuring cortical bone thickness. The thickness is measured as highlighted in black and the measurement is revealed in the software menu bar.

Figure 2. Box-plot graph of the mandibular inferior cortical bone thickness (MICBT) of controls, subjects using bisphosphonate (BP) and those presenting bisphosphonate related osteonecrosis of the jaws (BRONJ)

Figure 3.

Scattered graph of the mandibular inferior cortical bone thickness (MICBT) according to the cumulative doses of zolendronate in the 84 subjects enrolled in the study.

Table 1

Clinical and demographic characteristics of the 74 subjects in the study

Characteristics	Controls		Subjects using BP without BRONJ		Subjects with BRONJ	
	N= 47	%	N = 27	%	N = 10	%
Gender						
Male	24	51.1	13	48.1	5	50.0
Female	23	48.9	14	51.9	5	50.0
Age (mean $\pm$ SD)	58.5 $\pm$ 12.0		62.1 $\pm$ 9.8		61.3 $\pm$ 10.1	
Medical conditions						
Multiple myeloma	-	-	18	66.7	6	60.0
Cardiovascular	18	38.3	12	44.4	4	40.0
Gastric	4	8.5	11	40.7	2	20.0
Neurological/psychological	10	21.3	11	40.7	2	20.0
Osteopenia/osteoporosis	4	8.6	9	33.3	3	30.0
Thyroid	7	14.9	6	22.1	1	10.0
Malignancies	-	-	4	14.8	3	30.0
Allergic	-	-	5	18.5	1	10.0
Diabetes	4	8.5	2	7.4	-	-
Arthritis	2	4.3	-	-	-	-
Other	10	21.3	7	25.9	2	20.0
Medications						
Cardiovascular	18	38.3	12	44.4	4	40.0
Antimicrobial	3	6.4	13	48.1	4	40.0

Characteristics	Controls		Subjects using BP without BRONJ		Subjects with BRONJ	
	N= 47	%	N = 27	%	N = 10	%
Tranquilizer	5	10.6	5	18.5	-	-
Antiplatelet/anticoagulant	11	23.4	7	25.9	3	30.0
Analgesic	6	12.8	9	33.3	4	40.0
Hormones	6	12.8	6	22.2	1	10.0
Antihistaminic	1	2.1	5	18.5	2	20.0
Corticosteroids	2	4.3	6	22.2	4	10.0
NSAID	3	6.4	3	11.1	-	-
Gastric	4	8.5	12	44.4	3	30.0
Antilipidic	8	17.0	3	11.1	3	30.0
Neuro/psychologic	14	29.8	14	51.9	3	30.0
Immunologic	2	4.3	5	18.5	-	-
Vitamins/supplements	20	42.6	17	63.0	6	60.0

SD – standard deviation

Number of subjects using bone medications and the cumulative doses in controls and cases using bisphosphonates with and without bisphosphonate related osteonecrosis of the jaws

Table 2

Medication	Number of subjects using medication			Cumulative doses of medication		
	Controls	Using BP	Without BP	Using BP	Without BP	BRONJ
Calcium ($\times 10^3$)	7	16	6	230 $\pm$ 553	386 $\pm$ 496	489 $\pm$ 547
Vitamin D ($\times 10^3$) [†]	18	15	7	371 $\pm$ 622	637 $\pm$ 117	131 $\pm$ 256
Bisphosphonates [*]						
Alendronate	-	5	1	-	651.11 $\pm$ 1932.05	720.00 $\pm$ 2276.83
Risedronate	-	2	-	-	2733.33 $\pm$ 9851.04	-
Zoledronate	-	23	9	-	32.85 $\pm$ 38.45	104.40 $\pm$ 100.69
Ibandronate	-	-	1	-	-	900.00

[†] International units; all the others in milligrams

^{*} Some patients had a history of using more than one type of BP

BP- bisphosphonates; BRONJ- bisphosphonate related osteonecrosis of the jaws